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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients

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ABSTRACT

Objective

To determine the ideal conditions for use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in elderly outpatients with chronic pulmonary diseases.

Design

Prospective cohort study

Participants

A total of 1,378 outpatients with chronic pulmonary diseases ≥60 years of age

Intervention

Participants were educated about PPV23, and those who responded affirmatively were vaccinated between August and November 2002. The participants who chose no intervention served as controls. The pre-vaccine period was defined as August 2001 to August 2002. Participants were followed from December 2002 to the end of study in November 2004 (for 2 years) or until death.

Main outcome measures

Events of interest included the first episode of bacterial (including pneumococcal) pulmonary infection and death of any cause.

Results

Frequent episodes of pulmonary infection during the pre-vaccine period significantly increased the event rate during the 2-year observation period ($p < 0.001$). Chronic respiratory failure was associated with an increased number of events only when the pulmonary infection episode did not occur in the pre-vaccine period ($p < 0.001$). No significant differences in survival probability were observed between the vaccinated and unvaccinated group during analysis of the entire cohort. In the Cox proportional hazards

regression model, the event rate increased significantly when pulmonary infection occurred in the pre-vaccine period or when a patient had chronic respiratory failure. In the subgroup analysis, PPV23 significantly reduced event rates only in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period ($p = 0.019$).

Conclusion

The efficacy of PPV23 against pulmonary infection and death of any cause might be unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs to be given to elderly patients with chronic pulmonary disease at an earlier time in which infectious complications in the lung have not yet occurred.

Summary

● Article focus (hypothesis):

The efficacy of PPV23 might be compromised by an episode of pulmonary infection in the pre-vaccine period or chronic respiratory failure in elderly patients with chronic pulmonary disease.

● Key messages:

1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the pre-vaccine period.

2. The event rate could be reduced by PPV23 in patients with noninfectious complications such as chronic respiratory failure.

3. Elderly patients with chronic pulmonary disease need to receive the PPV23 vaccination at an earlier time in which infectious complications in the lung have not yet occurred.

- Strengths and limitations of this study:

1. Only participants who responded affirmatively received PPV23. They were not assigned randomly to a group.

2. The diagnosis of pulmonary disease was not made in the majority of patients who had pulmonary infection during the study period. The microbiological diagnosis in the lower respiratory tract, which is not normally sterile, is ambiguous.

INTRODUCTION

Streptococcus pneumoniae continues to be one of the main causative pathogens in community-acquired pneumonia and meningitis.[1-2] Due to the high mortality rate of *S. pneumoniae* infections, especially in elderly and very young patients, prophylactic use of 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for people at an increased risk of pneumococcal disease in developed countries.[3-7] The efficacy of PPV23, however, remains controversial. Despite the fact that the results of pre- and post-licensed trials in immunocompetent people were supportive of regulatory approval of vaccine use, clinical studies in elderly or young adults with comorbidities in developed countries produced little convincing evidence of effectiveness against a common manifestation of pneumococcal infections such as pneumonia.[8-10] A retrospective study conducted in 1999 suggested that PPV23 was associated with significant reductions in hospitalisation and mortality rates of elderly patients with chronic lung disease and contributed to medical care cost savings, although meta-analytical reviews published thereafter failed to show statistically significant evidence of the protective effects of PPV23 against the development of pneumonia in elderly patients with chronic illnesses.[11-13]

We previously reported a 2-year cohort clinical study of elderly outpatients with chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial and pneumococcal pulmonary infection onset and outcome.[14] Analysis of the comparison between the vaccinated and unvaccinated group showed a decline in the incidence of bacterial pulmonary infection only in the vaccinated group. This result might be associated with PPV23 effectiveness, although detailed background information regarding underlying pulmonary conditions was not provided. Subgroup analysis needs to be carried out since chronic pulmonary disease includes various clinical and pathophysiological pictures. Underlying pulmonary diseases could cause chronic respiratory failure if repeatedly complicated by lung infections, and such heterogeneity may generate different outcomes after vaccination.[15] We decided to reanalyse the data to study the influence of clinical background during the pre-vaccine period on PPV23 efficacy in elderly patients with chronic pulmonary disease.

METHODS

Study population

A total of 1,378 outpatients ≥60 years of age (data at the start of the study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory Diseases Centre were informed of the prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic pulmonary diseases in this study included bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous mycobacteria, and others (Table 1). Home oxygen therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS) Guidelines for 97 participants with chronic respiratory failure upon study initiation (Table 1), but no

patients were newly prescribed HOT during the observation period.

Study design

We did not adopt a randomised controlled study design since the PPV23 vaccination is considered a part of standard care in many developed countries. Additionally, some elderly participants with chronic pulmonary disease were in an immunocompromised status; therefore, a randomised controlled study of vaccine effectiveness may violate ethical principles and human rights. Written informed consent forms were obtained from all participants. To avoid selection bias, doctors and other medical staffs were not allowed to assign patients to the vaccine or non-vaccine group; instead, individual patients decided whether or not to be vaccinated. A total of 647 patients were injected with PPV23 (Pneumovax, Merck, NJ, USA) intramuscularly into their non-dominant upper arm with between August and November 2002.

Data collection

Participants were followed from December 2002 to the end of the study in November 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as clinical status remained stable. A diagnosis of pulmonary infection was made by respiratory physicians according to the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults. In brief, patients were diagnosed with an infectious lung complication when they presented with fever (≥38 °C), cough, yellow sputum, or chest pain and blood testing revealed marked inflammatory responses such as elevated levels of neutrophils and serum C-reactive protein. Chest radiography was performed when an infective inflammatory process in

the lung was suspected to distinguish pneumonia from acute bronchitis or infectious exacerbation of chronic bronchitis. In addition to a urinary pneumococcal antigen test, Gram staining and sputum culture were conducted when a diagnosis of bacterial pulmonary infection was made to determine the causative microorganisms and the pattern of antibiotic susceptibility. Empirical antibiotic therapy was started promptly after diagnosis of infection in the lung was made. The initial treatment was replaced by second-line therapy of antibiotics chosen according to the sensitivity results.

Event of interest

We hypothesised that repeated pulmonary infection and concomitant gradual loss of lung function might be related to a reduced PPV23 efficacy. Participants were grouped based on these factors: frequency of infectious (including pneumococcal) pulmonary infection episode within 1 year prior to the PPV23 vaccination (0 episodes, 1 episode, and >1 episode), and chronic respiratory failure represented by HOT usage. Events of interest included the first episode of bacterial or pneumococcal pulmonary infection (pneumonia, acute bronchitis, or exacerbation of chronic bronchitis) where antibiotic treatment was required, and death of any cause. The case of death with missing values was not counted as an event of interest but was included in the mortality rate.

Statistical analysis

Differences in event rates were depicted with Kaplan-Meier curves, and the log-rank test was applied for analysis. Cross-tabulated data were compared by the Wilcoxon test or the Pearson's chi-square test. Relative risks for the events were estimated using the Cox proportional hazards regression model. The PASW statistics 18 (SPSS Inc. IL,

USA) and SAS software (SAS Institute Inc. NC, USA) were used for the statistical analysis.

RESULTS

A total of 1,378 patients ≥60 years old with chronic pulmonary disease were enrolled in this study between August and November 2002. The pre-vaccine period was defined as 1 year prior to PPV23 vaccination (August 2001 to August 2002). Patient characteristics are shown in Table 1. In the group without pulmonary infection during the pre-vaccine period, significant reductions in vaccination rate, age, and frequency of chronic respiratory failure were observed compared with the other 2 groups with at least 1 episode of infectious lung complications. No significant gender difference was seen among groups.

The effects of underlying pulmonary conditions on event occurrences were analysed before PPV23 effectiveness were evaluated. The survival rate in the Kaplan-Meier method dropped significantly as the frequency of pulmonary infection in the pre-vaccine period increased (Figure 1). Chronic respiratory failure was associated with a significant event rate increase only in the absence of pulmonary infection in the pre-vaccine period (Table 2). A higher mortality rate was seen in patients with pulmonary infection during the pre-vaccine period and in chronic pulmonary failure ($p < 0.001$).

Participants were not randomly assigned to groups; vaccination was chosen or declined by each individual. As a result, the number of vaccinated patients was significantly higher than the number of unvaccinated patients when pulmonary infection occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness

was seen between the vaccinated and unvaccinated group in the Kaplan-Meier method (log rank test, p = 0.391). The mortality rate was, however, significantly high in the vaccinated group (log-rank test, p = 0.008). This result may be misleading due to the vaccination imbalance among groups. The Cox proportional hazards regression model applied for covariate adjustment showed that the episodes of pulmonary infection and chronic respiratory failure in the pre-vaccine period were associated with an increased risk of pulmonary infection and death after PPV23 vaccination (Table 3). No significant effects of PPV23 on mortality rate were observed (Table 3). These results suggested the following: PPV23 efficacy might be compromised by some factors such as pulmonary infection in the pre-vaccine period or chronic respiratory failure; and imbalance of PPV23 distribution among the groups may be associated with an increased mortality rate in the vaccinated group.

A subgroup analysis was performed to find the ideal condition for PPV23 use in elderly patients with chronic pulmonary disease. There are no significant differences between vaccinated and unvaccinated patients when grouped only by frequency of pulmonary infection in the pre-vaccine period (not shown). The event rate was somewhat reduced when patients with chronic respiratory failure were vaccinated (p = 0.071). This effectiveness became significant when patients who had an episode of pulmonary infection in the pre-vaccine period were excluded (Figure 2). Of note, the final event-free survival rate was 0.755, which was close to the levels observed in patients who had not had an episode of pulmonary infection and chronic respiratory failure during the pre-vaccine period (Table 4). These results suggest that PPV23 might provide beneficial effects in elderly patients with chronic respiratory failure if episodes of pulmonary infection during the pre-vaccine period did not occur.

There were only 29 pneumococcal events during the observation period (pneumococcal pulmonary infection, 22; death, 7). The probability of pneumococcal events increased significantly in the presence of pulmonary infection during the pre-vaccine period (log-rank test, $p < 0.001$). No effects of chronic respiratory failure on survival rate were observed. PPV23 vaccination did not show significant protective effects against the development of pneumococcal events even after subgroup analysis (data not shown).

DISCUSSION

The effects of the PPV23 vaccination on elderly patients with chronic pulmonary disease varied in accordance with the frequency of lung infection episodes and the presence of chronic respiratory failure during the pre-vaccine period. Our findings suggest the following: PPV23 vaccination might work effectively unless previous lung infection episodes had occurred; and subgroup analysis of the underlying disease associated with pneumococcal complications might be useful for finding the possible ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the presence of pulmonary infection episodes prior to vaccination or chronic pulmonary failure in elderly patients with chronic pulmonary disease.

Comparison with other studies

Previous pulmonary infection was highly associated with poor clinical prognosis. This finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly people with chronic pulmonary disease in the presence of infectious complications

during the pre-vaccine period. In a multicentre double-blind controlled study conducted in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly non-immunocompromised individuals who had been treated for community-acquired pneumonia.[16] In that study, the survival rate calculated by the Kaplan-Meier method was still >80% in both vaccinated and unvaccinated populations after 2-year observation, while our results showed that the survival rate was <60% if episodes of pulmonary infection had occurred within 1 year prior to vaccination. These results are consistent with previous suggestions that chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that protective effects of PPV23 could not be obtained.[17-19] Conflicting results were shown in some other reports in which the beneficial effects of PPV23 in patients with COPD were indicated, although previous episodes of pneumonia prior to vaccination were not considered and participants were not limited to the elderly.[11, 20] Alfageme et al showed PPV23 effectiveness in patients <65 years of age with COPD in a randomised controlled study in 596 patients.[21] These results and our data indicate that PPV23 might be inefficacious on the elderly population with chronic pulmonary disease especially when complicated by lung infection prior to the vaccination. Despite the strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD), altered immune response, disruption of a physical barrier in the airways due to progressive chronic pulmonary disease, and repeated pulmonary infection could compromise the benefits.[1, 22] PPV23 vaccination should be given to patients with chronic pulmonary disease at an earlier stage in which infectious complications have not yet occurred.

The probability of survival was significantly increased by PPV23 in the presence of

chronic respiratory failure in patients without episodes of pulmonary infection prior to vaccination. The survival rate was 75.5% when PPV23 was given. Without PPV23, survival was reduced to 45.0%, almost the same level as that in the case where infectious lung complications had occurred during the pre-vaccine period. This result indicates that pulmonary infection or death due to chronic respiratory failure could be prevented by the PPV23 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be administered in COPD patients when airflow is severe and chronic respiratory failure is present, but these treatments were suggested to be risk factors for community-acquired pneumonia.[23-25] Additionally, bacterial colonisation of the distal airway may occur due to the altered pulmonary defense.[22] We suggest that patients receive the PPV23 vaccination soon after the diagnosis of chronic respiratory disease such as COPD, especially when maintenance treatments for impaired lung function are expected to be risk factors for pneumonia. In this study, the number of participants with chronic respiratory failure who were free of lung infections during the pre-vaccine period was only 70. Thus, a large scale study is warranted.

Strengths and limitations of the study

When informed consents were obtained prior to the study initiation, PPV23 vaccine recommendations were made and only participants who responded affirmatively received the vaccination. This method may be associated with these results: the vaccination rate increased significantly in high-risk patients who had at least 1 episode of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory failure; and the mortality rate was higher in vaccinated patients, although the presence of adverse effects of PPV23 is unlikely because PPV23 had generally been considered

safe based on clinical experience since 1977.[7] In the Cox proportional hazards model, PPV23 was not a risk factor for the events. All of the participants in this study were elderly patients with chronic pulmonary disease, and all of them could be categorised into groups for which PPV23 vaccination is recommended in the United States and some European countries.[3, 7, 12] In Japan, no vaccine recommendations against pneumococcal infection are issued by the Japanese Ministry of Health, Labor and Welfare.[26] Japanese participants need to accept some risks for the public benefit and not for their own if selected for the unvaccinated group. This condition is different from that in some developed countries where unvaccinated control subjects in clinical trials of the PPV23 vaccine could still be protected by previous vaccination and indirect immunity from other people, including children.[27-29] Pneumococcal infection was associated with increasing mortality rates, while the beneficial effects of PPV23 without any severe adverse events were suggested in some previous clinical trials.[1, 8, 13, 30-31] Therefore, we decided to conduct a nonrandomised clinical study to ensure that participants were treated with respect and dignity.

The diagnosis of pneumococcal disease was not made in the majority of patients who had pulmonary infections during the observation period. Identification of *S. pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However, compared to IPD defined as any condition in which *S. pneumonia* is identified in a normally sterile body site, microbiological diagnosis in the lower respiratory tract is ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for pneumococcal identification might be unreliable due to the technical difficulties in obtaining good-quality sputum and in distinguishing causative specimens from colonisation.[19, 32] The positive results in urine antigen testing might be related to

previous infection or colonisation. It might be difficult to assess PPV23 effectiveness on pneumococcal pulmonary infection using these procedures. Blood cultures are recommended for patients hospitalised after a diagnosis of community-acquired pneumonia, although its cost-effectiveness has been questioned in several studies.[33] Less expensive, novel techniques for accurate diagnosis of pneumonia need to be developed.

Conclusions and policy implications

Our data demonstrated that the beneficial effects of the PPV23 vaccination may not be obtainable if an episode of pulmonary infection occurred during the pre-vaccine period in elderly patients with chronic pulmonary disease. We suggest that PPV23 needs to be given soon after chronic pulmonary disease is diagnosed. In developed countries, including Japan, elderly populations with chronic pulmonary disease are growing in number. The Japanese Ministry of Health, Labor and Welfare should introduce the PPV23 vaccination for patients with chronic pulmonary disease and in routine vaccination of children along with pneumococcal conjugate vaccine that could provide indirect beneficial effects to the population in whom PPV23 efficacy may not be expected.

Table 1: Baseline characteristics of 1378 outpatients with chronic pulmonary disease

	Frequency of pulmonary infection during the pre-vaccine period			P Value†
	0 (n = 1164)	1 (n = 167)	>1 (n = 43)	
Age				
Mean ± SD	71.3 ± 7.0	73.3 ± 6.9	73.0 ± 7.0	< 0.001
Median	71	73	73	
Male	626 (53.8%)	98 (58.7%)	27 (62.8%)	0.272
Female	538 (46.2%)	69 (41.3%)	16 (37.2%)	
Chronic respiratory disease*				
Bronchial asthma	517	59	16	
Chronic pulmonary emphysema	197	40	14	
Old tuberculosis	157	33	10	
Chronic bronchitis	106	18	5	
Interstitial pneumonia	100	9	0	
Non-tuberculous mycobacteria	84	10	2	
Bronchioectasis	31	13	5	
Others	103	15	4	
PPV23-vaccinated	512 (44.0%)	109 (65.3%)	25 (58.1%)	< 0.001
PPV23-unvaccinated	652 (56.0%)	58 (34.7%)	18 (41.9%)	
Chronic respiratory failure				
+	70 (6.0%)	20 (12.0%)	7 (16.3%)	< 0.001
-	1094 (94.0%)	147 (88.0%)	36 (83.7%)	

*Some patients were diagnosed as having more than one chronic respiratory disease.

†Data was analyzed using the Wilcoxon test or the Pearson's test.

Table 2: The effects of pulmonary infection and chronic respiratory failure during the pre-vaccine period on the event-free survival rate

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	Survival rate at the end of the study*	P value*
0	(−)	0.843	<0.001
0	(+)	0.689	
1	(−)	0.527	0.506
1	(+)	0.450	
>1	(−)	0.275	0.348
>1	(+)	0.143	

*Data was analyzed using the log-rank test.

Table 3: Association of the frequency of pulmonary infection during the pre-vaccine period, chronic respiratory failure and the PPV23 vaccination with the development of the events or death of any cause

	Hazard ratio	95% CI	P Value
Covariates for the risk of the events			
Pulmonary infection during the pre-vaccine period			
1 episode	3.243*	2.435 - 4.319	<0.001
>1 episode	6.437*	4.368 - 9.487	<0.001
Chronic respiratory failure	1.779	1.240 - 2.554	0.002
PPV23 vaccination	0.900	0.707 - 1.147	0.396
Covariates for the risk of death			
Pulmonary infection during the pre-vaccine period			
1 episode	2.393*	1.442 - 3.972	0.001
>1 episode	1.866*	0.800 - 4.351	0.149
Chronic respiratory failure	2.761	1.580 - 4.827	<0.001
PPV23 vaccination	1.473	0.932 - 2.328	0.097

*Hazard ratio was estimated in relative to the case of outpatients with no episode of pulmonary infection during the pre-vaccine period.

Table 4: The influence of pulmonary infection and chronic respiratory failure during the pre-vaccine period on the PPV23 vaccine efficacy

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	Vaccinated*	Unvaccinated*	P Value†
(−)	(−)	0.846 (465)	0.836 (629)	0.931
	(+)	0.755 (47)	0.450 (23)	0.019
1 episode	(−)	0.557 (92)	0.490 (55)	0.665
	(+)	0.431 (17)	0.333 (3)	0.876
>1 episode	(−)	0.317 (22)	0.214 (13)	0.200
	(+)	0.000 (3)	0.250 (4)	0.093

*Data represented the survival rate at the end of the study (2 years after the PPV23 vaccination). Numbers in parenthesis indicate numbers of patients.

†Data was analyzed using the log-rank test.

Contributions: SI analysed the data, and drafted and revised the paper. YW designed the whole study, and collected the data from the clinical records of the participants. TK wrote the statistical analysis plan, and analysed the data. TS, NM, TK and YI interpreted the findings, and revised the draft paper. SM, YN and SM supervised data analysis and assessment.

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Competing interests: None declared.

Ethical approval: Full approval of Institutional Review Board in the Kanagawa Cardiovascular and Respiratory Diseases Centre was obtained prior to the study initiation.

Data sharing: No additional data available.

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The material (clinical data) that had been used for ref. 14 is modified and printed with the permission of the ©European Respiratory Society.

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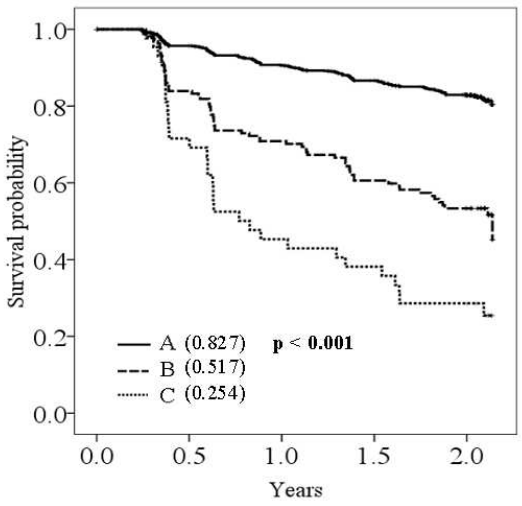
STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6,7,16
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7,8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,16
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,16
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11,16,17,19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11,17,18
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11,19
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



Kaplan-Meier survival curves of patients with/without episodes of pulmonary infection during the pre-vaccine period: A, 0 episodes; B, 1 episode; C, > 1 episode
Numbers in parenthesis indicate the survival rate at the end of the study.

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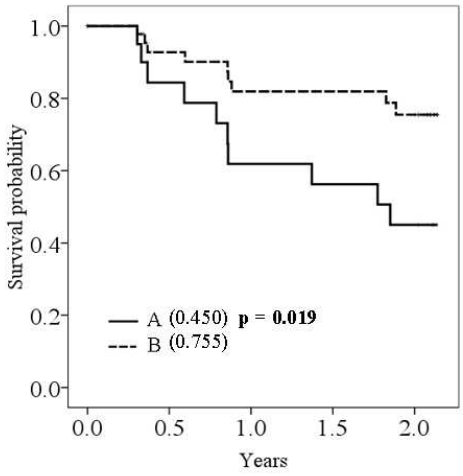

Kaplan-Meier survival curves of patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period: A, unvaccinated; B, vaccinated
Numbers in parenthesis indicate the survival rate at the end of the study.

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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients

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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients

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Key word: PPV23, chronic pulmonary disease, elderly patient, respiratory infection

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ABSTRACT

Objective

To determine the ideal conditions for use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in elderly outpatients with chronic pulmonary diseases.

Design

Prospective cohort study

Participants

A total of 1,378 outpatients with chronic pulmonary diseases ≥60 years of age

Intervention

Participants were educated about PPV23, and those who responded affirmatively were vaccinated between August and November 2002. The participants who chose no intervention served as controls. The pre-vaccine period was defined as August 2001 to August 2002. Participants were followed for 2 years from December 2002 or until death.

Main outcome measures

Events of interest included the first episode of bacterial (including pneumococcal) pulmonary infection (primary endpoint) and death of any cause (secondary endpoint).

Results

Frequent episodes of pulmonary infection during the pre-vaccine period significantly decreased event-free survival during the 2-year observation period ($p < 0.001$). Chronic respiratory failure was associated with a decreased event-free survival only when the pulmonary infection episode did not occur in the pre-vaccine period ($p < 0.001$). No significant differences in event-free survival were observed between the vaccinated and unvaccinated group during analysis of the entire cohort. In the Cox proportional hazards

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regression model, event-free survival decreased significantly when pulmonary infection occurred in the pre-vaccine period. In the subgroup analysis, the first episode of bacterial pulmonary infection (but not death of any cause) was reduced significantly by PPV23 only in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period (p = 0.019).

Conclusion

The efficacy of PPV23 against pulmonary infection and death of any cause might be unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs to be given to elderly patients with chronic pulmonary disease at an earlier time in which infectious complications in the lung have not yet occurred.

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Summary

● Article focus (hypothesis):

The efficacy of PPV23 might be compromised by an episode of pulmonary infection in the pre-vaccine period or chronic respiratory failure in elderly patients with chronic pulmonary disease.

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● Key messages:

1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the pre-vaccine period.

2. The episode of pulmonary infection could be prevented by PPV23 in elderly patients with noninfectious complications such as chronic respiratory failure.

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3. Elderly patients with chronic pulmonary disease need to receive the PPV23 vaccination at an earlier time in which infectious complications in the lung have not yet occurred.

● Strengths and limitations of this study:

1. Only participants who responded affirmatively received PPV23. They were not assigned randomly to a group.

2. The diagnosis of pneumococcal pulmonary disease was not made in the majority of patients who had pulmonary infection during the study period. The microbiological diagnosis in the lower respiratory tract, which is not normally sterile, is ambiguous.

INTRODUCTION

Streptococcus pneumoniae continues to be one of the main causative pathogens in community-acquired pneumonia and meningitis.[1-2] Due to the high mortality rate of *S. pneumoniae* infections, especially in elderly and very young patients, prophylactic use of 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for people at an increased risk of pneumococcal disease in developed countries.[3-7] The efficacy of PPV23, however, remains controversial. Despite the fact that the results of pre- and post-licensed trials in immunocompetent people were supportive of regulatory approval of vaccine use, clinical studies in elderly or young adults with comorbidities in developed countries produced little convincing evidence of effectiveness against a common manifestation of pneumococcal infections such as pneumonia.[8-12] A retrospective study conducted in 1999 suggested that PPV23 was associated with significant reductions in hospitalisation and mortality rates of elderly patients with chronic lung disease and contributed to medical care cost savings, although meta-analytical reviews published thereafter failed to show statistically significant evidence of the protective effects of PPV23 against the development of pneumonia in elderly patients with chronic illnesses.[13-15]

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We previously reported a 2-year cohort clinical study of elderly outpatients with chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial and pneumococcal pulmonary infection onset and outcome.[16] Analysis of the comparison between the vaccinated and unvaccinated group showed a decline in the incidence of bacterial pulmonary infection only in the vaccinated group. This result might be associated with PPV23 effectiveness, although detailed background information regarding underlying pulmonary conditions was not provided. Subgroup analysis needs to be carried out since chronic pulmonary disease includes various clinical and pathophysiological pictures. Underlying pulmonary diseases could cause chronic respiratory failure if repeatedly complicated by lung infections, and such heterogeneity may generate different outcomes after vaccination.[17] We decided to reanalyse the data to study the influence of clinical background during the pre-vaccine period on PPV23 efficacy in elderly patients with chronic pulmonary disease.

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METHODS

Study population

All the outpatients ≥60 years of age (a total of 1,378 participants at the start of the study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory Diseases Centre were included in this study. These patients were informed of the prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic pulmonary diseases in this study included bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous mycobacteria, and others (Table 1). Patients who presented with a fever (≥37.5 °C) were excluded from the study according to the Preventive Vaccination Law issued by the

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Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these patients became stable, they were invited to participate in the study. Home oxygen therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS) Guidelines for 97 participants with chronic respiratory failure upon study initiation (Table 1), but no patients were newly prescribed HOT during the observation period.

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Study design

We did not adopt a randomised controlled study design since the PPV23 vaccination is considered a part of standard care in many developed countries. Additionally, some elderly participants with chronic pulmonary disease were in an immunocompromised status; therefore, a randomised controlled study of vaccine effectiveness may violate ethical principles and human rights. Written informed consent forms were obtained from all participants. To avoid selection bias, doctors and other medical staffs were not allowed to assign patients to the vaccine or non-vaccine group; instead, individual patients decided whether or not to be vaccinated. The same form, which included an explanation of the study, was provided to all the participants. A total of 647 patients were injected with PPV23 (Pneumovax, Merck, NJ, USA) intramuscularly into their non-dominant upper arm with between August and November 2002. The pre-vaccine period was defined as 1 year prior to PPV23 vaccination (August 2001 to July 2002).

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Data collection

Participants were followed from December 2002 to the end of the study in November 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as clinical status remained stable. A diagnosis of pulmonary infection was made by

respiratory physicians according to the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults. In brief, pulmonary infection was suspected if more than 2 of the following criteria were present: temperature ≥ 37.0 °C, white blood cell count > 8,000/mm^3, and C-reactive protein > 0.7 mg/dl. A diagnosis of pneumonia was made when chest radiographs revealed alveolar opacities. If a cough with yellow sputum production was observed in the absence of the alveolar opacities on the chest radiograph, the patients were diagnosed with acute bronchitis or exacerbation of chronic bronchitis. It was very difficult to clearly distinguish pneumonia from acute bronchitis or an acute exacerbation of chronic bronchitis in some patients since there were considerable clinical overlaps between these illnesses including the symptoms, blood test results, causative pathogens, and antibiotic treatment. Hence, pulmonary infection was expressed as a dichotomous variable.

A diagnosis of pneumococcal pulmonary infection was made if *Streptococcus pneumoniae* was the dominant organism stained with Gram stain in the sputum smear or if the sputum culture was positive (> 10^7 colony forming units/ml). When *S. pneumoniae* was not identified, patients were diagnosed with a pulmonary infection caused by an identified pathogen or with a bacterial pulmonary infection if no possible causative pathogen was detected but if the clinical data were highly suggestive of bacterial infection in the lung. Empirical antibiotic therapy was started in all the patients promptly once clinical data sufficient to satisfy the definition of pulmonary infection were obtained. The initial treatment was replaced by second-line therapy of antibiotics chosen according to the sensitivity results.

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Deleted: In brief, patients were diagnosed with an infectious lung complication when they presented with fever (≥38 °C), cough, yellow sputum, or chest pain and blood testing revealed marked inflammatory responses such as elevated levels of neutrophils and serum C-reactive protein. Chest radiography was performed when an infective inflammatory process in the lung was suspected to distinguish pneumonia from acute bronchitis or infectious exacerbation of chronic bronchitis.

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Event of interest

We hypothesised that repeated pulmonary infection and concomitant gradual loss of lung function might be related to a reduced PPV23 efficacy. Participants were grouped based on these factors: frequency of infectious (including pneumococcal) pulmonary infection episode within 1 year prior to the PPV23 vaccination (0 episodes, 1 episode, and >1 episode), and chronic respiratory failure represented by HOT usage. Events of interest included the first episode of bacterial or pneumococcal pulmonary infection (pneumonia, acute bronchitis, or exacerbation of chronic bronchitis) where antibiotic treatment was required (primary endpoint), and death of any cause (secondary endpoint). The case of death with missing values was not counted as an event of interest but was included in the mortality rate.

Statistical analysis

Differences in event-free survival were depicted with Kaplan-Meier curves, and the log-rank test was applied for analysis. The primary and secondary endpoints (the first episode of pulmonary infection and death of any cause, respectively) were analysed separately. Cross-tabulated data were compared by the Wilcoxon test or the Pearson's chi-square test. Relative risks for the events were estimated using the Cox proportional hazards regression model. The covariates used in the analysis were: (1) pulmonary infection during the pre-vaccine period, (2) chronic respiratory failure, and (3) PPV23 vaccination. For further analysis, gender and age were added as covariates and the data were analyzed. No any other variables were regarded as covariates in relation to event-free survival. The PASW statistics 18 (SPSS Inc. IL, USA) and SAS software (SAS Institute Inc. NC, USA) were used for the statistical analysis.

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RESULTS

Participant characteristics are shown in Table 1. Significant reductions in vaccination rate, age, and frequency of chronic respiratory failure were observed in the group without pulmonary infection during the pre-vaccine period compared with the other 2 groups with at least 1 episode of infectious lung complications. No significant gender difference was seen among groups.

The effects of underlying pulmonary conditions on event occurrences were analysed before PPV23 effectiveness were evaluated. Event-free survival in the Kaplan-Meier method dropped significantly as the frequency of pulmonary infection in the pre-vaccine period increased: the first episode of pulmonary infection, Figure 1; death of any cause, Supplemental Figure A. Chronic respiratory failure was associated with a significant decrease in event-free survival only in the absence of pulmonary infection in the pre-vaccine period: the first episode of pulmonary infection, Supplemental Figure B, Table 2; death of any cause, Supplemental Figure C, Supplemental Table A.

Participants were not randomly assigned to groups; vaccination was chosen or declined by each individual. As a result, the number of vaccinated patients was significantly higher than the number of unvaccinated patients when pulmonary infection occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness against the development of first episode of pulmonary infection during the observation period was seen between the vaccinated and unvaccinated group in the Kaplan-Meier method (Supplemental Figure D). The mortality rate was, however, significantly high in the vaccinated group (Supplemental Figure E). This result may be misleading due to the vaccination imbalance among groups. In the Cox proportional hazards regression model

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applied for covariate adjustment, no hazardous effects of PPV23 on the incidence or timing of the first episode of pulmonary infection or death of any cause were observed. The hazard ratio for the first episode of pulmonary infection or death of any cause increased significantly due to some covariates such as pulmonary infection during the pre-vaccine period and chronic respiratory failure. Other covariates including gender, and age were not associated with the first episode of pulmonary infection but were associated with death of any cause (Table 3). The cause of death (n = 85) among all the participants during the observation period was shown in Supplemental Table B.

A subgroup analysis was performed to find the ideal condition for PPV23 use in elderly patients with chronic pulmonary disease. There are no significant differences in pulmonary infection-free survival between vaccinated and unvaccinated patients when grouped only by frequency of pulmonary infection in the pre-vaccine period (not shown). Pulmonary infection-free survival was somewhat improved when patients with chronic respiratory failure were vaccinated (p = 0.078). This effectiveness became significant when patients who had at least 1 episode of pulmonary infection in the pre-vaccine period were excluded (Figure 2) (Table 4). The mortality was not reduced by PPV23 in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period (Supplemental Figure F). The cause of death (n = 9) among patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period was as follows: chronic respiratory failure, 2; cerebrovascular disease, 2; and unknown, 1 in vaccinated patients and chronic respiratory failure, 2; lung cancer, 1; and unknown, 1 in unvaccinated patients. In this group, PPV23 was shown to have an effect on the first episode of pulmonary infection but it did not reduce the number of deaths due to any cause.

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There were only 29 pneumococcal pulmonary infection during the observation period (pneumococcal pulmonary infection, 22; death, 7; Supplemental Table C). The pneumococcal pneumonia-free survival decreased significantly in the presence of pulmonary infection during the pre-vaccine period ($p < 0.001$; Supplemental Figure G). No effects of chronic respiratory failure on pneumococcal pneumonia-free survival were observed ($p = 0.196$). PPV23 vaccination did not show significant protective effects against the development of pneumococcal pneumonia (Supplemental Figure H).

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DISCUSSION

The effects of the PPV23 vaccination on elderly patients with chronic pulmonary disease varied in accordance with the frequency of lung infection episodes and the presence of chronic respiratory failure during the pre-vaccine period. Our findings suggest the following: PPV23 vaccination might work effectively unless previous lung infection episodes had occurred; and subgroup analysis of the underlying disease associated with pneumococcal complications might be useful for finding the possible ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the presence of pulmonary infection episodes prior to vaccination or chronic pulmonary failure in elderly patients with chronic pulmonary disease.

Comparison with other studies

Previous pulmonary infection was highly associated with poor clinical prognosis. This finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly people with chronic pulmonary disease in the presence of infectious complications

during the pre-vaccine period. In a multicentre double-blind controlled study conducted in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly non-immunocompromised individuals who had been treated for community-acquired pneumonia.[18] In that study, the survival rate calculated by the Kaplan-Meier method was still >80% in both vaccinated and unvaccinated populations after 2-year observation, while our results showed that the survival rate was <60% if episodes of pulmonary infection had occurred within 1 year prior to vaccination. These results are consistent with previous suggestions that chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that protective effects of PPV23 could not be obtained.[19-21] Conflicting results were shown in some other reports in which the beneficial effects of PPV23 in patients with COPD were indicated, although previous episodes of pneumonia prior to vaccination were not considered and participants were not limited to the elderly.[13, 22] Alfageme et al showed PPV23 effectiveness in patients <65 years of age with COPD in a randomised controlled study in 596 patients.[23] These results and our data indicate that PPV23 might be inefficacious on the elderly population with chronic pulmonary disease especially when complicated by lung infection prior to the vaccination. Despite the strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD), altered immune response, disruption of a physical barrier in the airways due to progressive chronic pulmonary disease, and repeated pulmonary infection could compromise the benefits.[1, 24] PPV23 vaccination should be given to patients with chronic pulmonary disease at an earlier stage in which infectious complications have not yet occurred.

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The probability of survival was significantly increased by PPV23 in the presence of

chronic respiratory failure in patients without episodes of pulmonary infection during the pre-vaccine period. The pulmonary infection-free survival rate was 75.5% at the end of the observation period when PPV23 was given. Without PPV23, survival was reduced to 45.0%, almost the same level as that in the case where infectious lung complications had occurred during the pre-vaccine period. This result indicates that pulmonary infection due to chronic respiratory failure could be prevented by the PPV23 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be administered in COPD patients when airflow is severe and chronic respiratory failure is present, but these treatments were suggested to be risk factors for community-acquired pneumonia.[25-27] Additionally, bacterial colonisation of the distal airway may occur due to the altered pulmonary defense.[24] We suggest that patients receive the PPV23 vaccination soon after the diagnosis of chronic respiratory disease such as COPD, especially when maintenance treatments for impaired lung function are expected to be risk factors for pneumonia. In this study, the number of participants with chronic respiratory failure who were free of lung infections during the pre-vaccine period was only 70. Thus, a large scale study is warranted.

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Strengths and limitations of the study

When informed consents were obtained prior to the study initiation, PPV23 vaccine recommendations were made and only participants who responded affirmatively received the vaccination. This method may be associated with these results: the vaccination rate increased significantly in high-risk patients who had at least 1 episode of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory failure; and the mortality rate was higher in vaccinated patients, although the presence

of adverse effects of PPV23 is unlikely because PPV23 had generally been considered safe based on clinical experience since 1977.[7] In the Cox proportional hazards model, PPV23 was not a risk factor for the events. All of the participants in this study were elderly patients with chronic pulmonary disease, and all of them could be categorised into groups for which PPV23 vaccination is recommended in the United States and some European countries.[3, 7, 14] In Japan, no vaccine recommendations against pneumococcal infection are issued by the Japanese Ministry of Health, Labour and Welfare.[11] Japanese participants need to accept some risks for the public benefit and not for their own if selected for the unvaccinated group. This condition is different from that in some developed countries where unvaccinated control subjects in clinical trials of the PPV23 vaccine could still be protected by previous vaccination and indirect immunity from other people, including children.[28-30] Pneumococcal infection was associated with increasing mortality rates, while the beneficial effects of PPV23 without any severe adverse events were suggested in some previous clinical trials.[1, 8, 15, 31-32] Therefore, we decided to conduct a nonrandomised clinical study to ensure that participants were treated with respect and dignity.

The doctors had access to the patients' vaccination record during the observation period. However, at the time of this study, PPV23 had already been approved by the Japanese Ministry of Health, Labour and Welfare, and there were no conflicts of interest with pharmaceutical companies. All the treatments were supported by the public health care system funded by the Japanese government; no specific grants were provided from any funding agencies. Diagnosis of pulmonary infection was made according to the same diagnostic criteria. Therefore it is unlikely that treatment bias occurred during the observation period.

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The diagnosis of pneumococcal disease was not made in the majority of patients who had pulmonary infections during the observation period. Identification of *S. pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However, compared to IPD defined as any condition in which *S. pneumonia* is identified in a normally sterile body site, microbiological diagnosis in the lower respiratory tract is ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for pneumococcal identification might be unreliable due to the technical difficulties in obtaining good-quality sputum and in distinguishing causative specimens from colonisation.[21] The positive results in urine antigen testing might be related to previous infection or colonisation.[33] It might be difficult to assess PPV23 effectiveness on pneumococcal pulmonary infection using these procedures. Blood cultures are recommended for patients hospitalised after a diagnosis of community-acquired pneumonia, although its cost-effectiveness has been questioned in several studies.[34] Less expensive, novel techniques for accurate diagnosis of pneumonia need to be developed.

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Conclusions and policy implications

Our data demonstrated that the beneficial effects of the PPV23 vaccination may not be obtainable if an episode of pulmonary infection occurred during the pre-vaccine period in elderly patients with chronic pulmonary disease. We suggest that PPV23 needs to be given soon after chronic pulmonary disease is diagnosed. In developed countries, including Japan, elderly populations with chronic pulmonary disease are growing in number. The Japanese Ministry of Health, Labour and Welfare should introduce the PPV23 vaccination for patients with chronic pulmonary disease and in routine

vaccination of children along with pneumococcal conjugate vaccine that could provide indirect beneficial effects to the population in whom PPV23 efficacy may not be expected.

Table 1: Baseline characteristics of 1378 outpatients with chronic pulmonary disease

	Frequency of pulmonary infection during the pre-vaccine period			P Value†
	0 (n = 1164)	1 (n = 167)	>1 (n = 43)	
Age				
Mean ± SD	71.3 ± 7.0	73.3 ± 6.9	73.0 ± 7.0	< 0.001
Median	71	73	73	
Male	626 (53.8%)	98 (58.7%)	27 (62.8%)	0.272
Female	538 (46.2%)	69 (41.3%)	16 (37.2%)	
Chronic respiratory disease*				
Bronchial asthma	517	59	16	
Chronic pulmonary emphysema	197	40	14	
Old tuberculosis	157	33	10	
Chronic bronchitis	106	18	5	
Interstitial pneumonia	100	9	0	
Non-tuberculous mycobacteria	84	10	2	
Bronchioectasis	31	13	5	
Others	103	15	4	
PPV23-vaccinated	512 (44.0%)	109 (65.3%)	25 (58.1%)	< 0.001
PPV23-unvaccinated	652 (56.0%)	58 (34.7%)	18 (41.9%)	
Chronic respiratory failure				
+	70 (6.0%)	20 (12.0%)	7 (16.3%)	< 0.001
-	1094 (94.0%)	147 (88.0%)	36 (83.7%)	

*Some patients were diagnosed as having more than one chronic respiratory disease.

†Data was analyzed using the Wilcoxon test or the Pearson's test.

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Table 2: The effects of pulmonary infection during the pre-vaccine period and chronic respiratory failure on pulmonary infection-free survival after PPV23 vaccination

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	N	event*	Pulmonary infection-free survival at the end of the study*	95%CI	P value†
0	(−)	1094	154	0.840	0.816 – 0.864	<0.001
0	(+)	70	19	0.653	0.525 – 0.781	
1	(−)	147	59	0.550	0.462 – 0.638	0.506
1	(+)	20	10	0.409	0.168 – 0.649	
>1	(−)	36	25	0.315	0.161 – 0.469	0.348
>1	(+)	7	6	0.143	0.000 – 0.402	

*Event represented the number of patients who were diagnosed with pulmonary infection during the observation period.

†Data was analyzed using the log-rank test.

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Table 3: Association of the frequency of pulmonary infection during the pre-vaccine period, chronic respiratory failure, PPV23, gender and age with the first episode of pulmonary infection or death of any cause

	Hazard ratio	95% CI	P Value
Covariates for the risk of the first episode of pulmonary infection			
Pulmonary infection during the pre-vaccine period			
1 episode	3.251*	2.436 – 4.338	<0.001
>1 episode	6.480*	4.380 – 9.589	<0.001
Chronic respiratory failure	1.767	1.227 – 2.546	0.002
PPV23 vaccination	1.096	0.848 – 1.416	0.396
Gender	0.911	0.712 – 1.166	0.457
Age	0.994	0.976 – 1.013	0.553
Covariates for the risk of death of any cause			
Pulmonary infection during the pre-vaccine period			
1 episode	2.289*	1.380 – 3.797	0.001
>1 episode	3.134*	1.486 – 6.612	0.003
Chronic respiratory failure	2.152	1.234 – 3.752	0.007
PPV23 vaccination	0.795	0.499 – 1.264	0.332
Gender	0.340	0.199 – 0.580	<0.001
Age	1.040	1.008 – 1.072	0.014

*Hazard ratio was estimated in relative to the case of outpatients with no episode of pulmonary infection during the pre-vaccine period.

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Table 4: The influence of pulmonary infection during the pre-vaccine period and chronic respiratory failure on the PPV23 vaccine efficacy

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	Vaccinated*	Unvaccinated*	P Value†
(−)	(−)	0.846 (465)	0.836 (629)	0.931
	(+)	0.755 (47)	0.450 (23)	0.019
1 episode	(−)	0.557 (92)	0.490 (55)	0.665
	(+)	0.431 (17)	0.333 (3)	0.876
>1 episode	(−)	0.317 (22)	0.214 (13)	0.200
	(+)	0.000 (3)	0.250 (4)	0.093

*Data represented the pulmonary infection-free survival (%) at the end of the study (2 years after PPV23 vaccination). Numbers in parenthesis indicate numbers of patients.

†Data was analyzed using the log-rank test.

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Contributions: SI analysed the data, and drafted and revised the paper. YW designed the whole study, and collected the data from the clinical records of the participants. TK wrote the statistical analysis plan, and analysed the data. TS, NM, TK and YI interpreted the findings, and revised the draft paper. SM, YN and SM supervised data analysis and assessment.

Funding: This research received no specific grants from any funding agencies in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Ethical approval: Full approval of Institutional Review Board in the Kanagawa Cardiovascular and Respiratory Diseases Centre was obtained prior to the study initiation.

Data sharing: No additional data available.

Acknowledgement

The material (clinical data) that had been used for ref. 14 is modified and printed with the permission of the ©European Respiratory Society.

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Of note, the final event-free survival rate was 0.755, which was close to the levels observed in patients who had not had an episode of pulmonary infection and chronic respiratory failure during the pre-vaccine period (Table 4). These results suggest that PPV23 might provide beneficial effects in elderly patients with chronic respiratory failure if episodes of pulmonary infection during the pre-vaccine period did not occur.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*)For matched studies, give matching criteria and number of exposed and unexposed	6,7,18
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10
		(*b*) Describe any methods used to examine subgroups and interactions	9,10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10,18
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,18
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-12,18-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12,19,20
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients: Prospective cohort study

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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients: Prospective cohort study

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Key word: PPV23, chronic pulmonary disease, elderly patient, respiratory infection

Word count: 3262

ABSTRACT

Objective

To determine the ideal conditions for use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in elderly outpatients with chronic pulmonary diseases.

Design

Prospective cohort study

Participants

A total of 1,378 outpatients with chronic pulmonary diseases ≥60 years of age

Intervention

Participants were educated about PPV23, and those who responded affirmatively were vaccinated between August and November 2002. The participants who chose no intervention served as controls. The pre-vaccine period was defined as August 2001 to August 2002. Participants were followed for 2 years from December 2002 or until death.

Main outcome measures

Events of interest included the first episode of bacterial (including pneumococcal) pulmonary infection (primary endpoint) and death of any cause (secondary endpoint).

Results

Frequent episodes of pulmonary infection during the pre-vaccine period significantly decreased event-free survival during the 2-year observation period ($p < 0.001$). Chronic respiratory failure was associated with a decreased event-free survival only when the pulmonary infection episode did not occur in the pre-vaccine period ($p < 0.001$). No significant differences in event-free survival were observed between the vaccinated and unvaccinated group during analysis of the entire cohort. In the Cox proportional hazards

regression model, event-free survival decreased significantly when pulmonary infection occurred in the pre-vaccine period. In the subgroup analysis, the first episode of bacterial pulmonary infection (but not death of any cause) was reduced significantly by PPV23 only in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period ($p = 0.019$).

Conclusion

The efficacy of PPV23 against pulmonary infection and death of any cause might be unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs to be given to elderly patients with chronic pulmonary disease at an earlier time in which infectious complications in the lung have not yet occurred.

Summary

● Article focus (hypothesis):

The efficacy of PPV23 might be compromised by an episode of pulmonary infection in the pre-vaccine period or chronic respiratory failure in elderly patients with chronic pulmonary disease.

● Key messages:

1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the pre-vaccine period.

2. The episode of pulmonary infection could be prevented by PPV23 in elderly patients with noninfectious complications such as chronic respiratory failure.

3. Elderly patients with chronic pulmonary disease need to receive the PPV23 vaccination at an earlier time in which infectious complications in the lung have not yet occurred.

- Strengths and limitations of this study:

1. Only participants who responded affirmatively received PPV23. They were not assigned randomly to a group.

2. The diagnosis of pneumococcal pulmonary disease was not made in the majority of patients who had pulmonary infection during the study period. The microbiological diagnosis in the lower respiratory tract, which is not normally sterile, is ambiguous.

INTRODUCTION

Streptococcus pneumoniae continues to be one of the main causative pathogens in community-acquired pneumonia and meningitis.[1-2] Due to the high mortality rate of *S. pneumoniae* infections, especially in elderly and very young patients, prophylactic use of 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for people at an increased risk of pneumococcal disease in developed countries.[3-7] The efficacy of PPV23, however, remains controversial. Despite the fact that the results of pre- and post-licensed trials in immunocompetent people were supportive of regulatory approval of vaccine use, clinical studies in elderly or young adults with comorbidities in developed countries produced little convincing evidence of effectiveness against a common manifestation of pneumococcal infections such as pneumonia.[8-12] A retrospective study conducted in 1999 suggested that PPV23 was associated with significant reductions in hospitalisation and mortality rates of elderly patients with chronic lung disease and contributed to medical care cost savings, although meta-analytical reviews published thereafter failed to show statistically significant evidence of the protective effects of PPV23 against the development of pneumonia in elderly patients with chronic illnesses.[13-15]

We previously reported a 2-year cohort clinical study of elderly outpatients with chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial and pneumococcal pulmonary infection onset and outcome.[16] Analysis of the comparison between the vaccinated and unvaccinated group showed a decline in the incidence of bacterial pulmonary infection only in the vaccinated group. This result might be associated with PPV23 effectiveness, although detailed background information regarding underlying pulmonary conditions was not provided. Subgroup analysis needs to be carried out since chronic pulmonary disease includes various clinical and pathophysiological pictures. Underlying pulmonary diseases could cause chronic respiratory failure if repeatedly complicated by lung infections, and such heterogeneity may generate different outcomes after vaccination.[17] We decided to reanalyse the data to study the influence of clinical background during the pre-vaccine period on PPV23 efficacy in elderly patients with chronic pulmonary disease.

METHODS

Study population

All the outpatients ≥60 years of age (a total of 1,378 participants at the start of the study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory Diseases Centre were included in this study. These patients were informed of the prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic pulmonary diseases in this study included bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous mycobacteria, and others (Table 1). Patients who presented with a fever (≥37.5 °C) were excluded from the study according to the Preventive Vaccination Law issued by the

Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these patients became stable, they were invited to participate in the study. Home oxygen therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS) Guidelines for 97 participants with chronic respiratory failure upon study initiation (Table 1), but no patients were newly prescribed HOT during the observation period.

Study design

We did not adopt a randomised controlled study design since the PPV23 vaccination is considered a part of standard care in many developed countries. Additionally, some elderly participants with chronic pulmonary disease were in an immunocompromised status; therefore, a randomised controlled study of vaccine effectiveness may violate ethical principles and human rights. Written informed consent forms were obtained from all participants. To avoid selection bias, doctors and other medical staffs were not allowed to assign patients to the vaccine or non-vaccine group; instead, individual patients decided whether or not to be vaccinated. The same form, which included an explanation of the study, was provided to all the participants. A total of 647 patients were injected with PPV23 (Pneumovax, Merck, NJ, USA) intramuscularly into their non-dominant upper arm with between August and November 2002. The pre-vaccine period was defined as 1 year prior to PPV23 vaccination (August 2001 to July 2002).

Data collection

Participants were followed from December 2002 to the end of the study in November 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as clinical status remained stable. A diagnosis of pulmonary infection was made by

respiratory physicians according to the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults. In brief, pulmonary infection was suspected if more than 2 of the following criteria were present: temperature ≥ 37.0 °C, white blood cell count > 8,000/mm^3, and C-reactive protein > 0.7 mg/dl. A diagnosis of pneumonia was made when chest radiographs revealed alveolar opacities. If a cough with yellow sputum production was observed in the absence of the alveolar opacities on the chest radiograph, the patients were diagnosed with acute bronchitis or exacerbation of chronic bronchitis. It was very difficult to clearly distinguish pneumonia from acute bronchitis or an acute exacerbation of chronic bronchitis in some patients since there were considerable clinical overlaps between these illnesses including the symptoms, blood test results, causative pathogens, and antibiotic treatment. Hence, pulmonary infection was expressed as a dichotomous variable.

A diagnosis of pneumococcal pulmonary infection was made if *Streptococcus pneumoniae* was the dominant organism stained with Gram stain in the sputum smear or if the sputum culture was positive (> 10^7 colony forming units/ml). When *S. pneumoniae* was not identified, patients were diagnosed with a pulmonary infection caused by an identified pathogen or with a bacterial pulmonary infection if no possible causative pathogen was detected but if the clinical data were highly suggestive of bacterial infection in the lung. Empirical antibiotic therapy was started in all the patients promptly once clinical data sufficient to satisfy the definition of pulmonary infection were obtained. The initial treatment was replaced by second-line therapy of antibiotics chosen according to the sensitivity results.

Event of interest

We hypothesised that repeated pulmonary infection and concomitant gradual loss of lung function might be related to a reduced PPV23 efficacy. Participants were grouped based on these factors: frequency of infectious (including pneumococcal) pulmonary infection episode within 1 year prior to the PPV23 vaccination (0 episodes, 1 episode, and >1 episode), and chronic respiratory failure represented by HOT usage. Events of interest included the first episode of bacterial or pneumococcal pulmonary infection (pneumonia, acute bronchitis, or exacerbation of chronic bronchitis) where antibiotic treatment was required (primary endpoint), and death of any cause (secondary endpoint). The case of death with missing values was not counted as an event of interest but was included in the mortality rate.

Statistical analysis

Differences in event-free survival were depicted with Kaplan-Meier curves, and the log-rank test was applied for analysis. The primary and secondary endpoints (the first episode of pulmonary infection and death of any cause, respectively) were analysed separately. Cross-tabulated data were compared by the Wilcoxon test or the Pearson's chi-square test. Relative risks for the events were estimated using the Cox proportional hazards regression model. The covariates used in the analysis were: (1) pulmonary infection during the pre-vaccine period, (2) chronic respiratory failure, and (3) PPV23 vaccination. For further analysis, gender and age were added as covariates and the data were analyzed. No any other variables were regarded as covariates in relation to event-free survival. The PASW statistics 18 (SPSS Inc. IL, USA) and SAS software (SAS Institute Inc. NC, USA) were used for the statistical analysis.

RESULTS

Participant characteristics are shown in Table 1. Significant reductions in vaccination rate, age, and frequency of chronic respiratory failure were observed in the group without pulmonary infection during the pre-vaccine period compared with the other 2 groups with at least 1 episode of infectious lung complications. No significant gender difference was seen among groups.

The effects of underlying pulmonary conditions on event occurrences were analysed before PPV23 effectiveness were evaluated. Event-free survival in the Kaplan-Meier method dropped significantly as the frequency of pulmonary infection in the pre-vaccine period increased: the first episode of pulmonary infection, Figure 1; death of any cause, Supplemental Figure A. Chronic respiratory failure was associated with a significant decrease in event-free survival only in the absence of pulmonary infection in the pre-vaccine period: the first episode of pulmonary infection, Supplemental Figure B, Table 2; death of any cause, Supplemental Figure C, Supplemental Table A.

Participants were not randomly assigned to groups; vaccination was chosen or declined by each individual. As a result, the number of vaccinated patients was significantly higher than the number of unvaccinated patients when pulmonary infection occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness against the development of first episode of pulmonary infection during the observation period was seen between the vaccinated and unvaccinated group in the Kaplan-Meier method (Supplemental Figure D). The mortality rate was, however, significantly high in the vaccinated group (Supplemental Figure E). This result may be misleading due to the vaccination imbalance among groups. In the Cox proportional hazards regression model

applied for covariate adjustment, no hazardous effects of PPV23 on the incidence or timing of the first episode of pulmonary infection or death of any cause were observed. The hazard ratio for the first episode of pulmonary infection or death of any cause increased significantly due to some covariates such as pulmonary infection during the pre-vaccine period and chronic respiratory failure. Other covariates including gender, and age were not associated with the first episode of pulmonary infection but were associated with death of any cause (Table 3). The cause of death (n = 85) among all the participants during the observation period was shown in Supplemental Table B.

A subgroup analysis was performed to find the ideal condition for PPV23 use in elderly patients with chronic pulmonary disease. There are no significant differences in pulmonary infection-free survival between vaccinated and unvaccinated patients when grouped only by frequency of pulmonary infection in the pre-vaccine period (not shown). Pulmonary infection-free survival was somewhat improved when patients with chronic respiratory failure were vaccinated ($p = 0.078$). This effectiveness became significant when patients who had at least 1 episode of pulmonary infection in the pre-vaccine period were excluded (Figure 2) (Table 4). The mortality was not reduced by PPV23 in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period (Supplemental Figure F). The cause of death (n = 9) among patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period was as follows: chronic respiratory failure, 2; cerebrovascular disease, 2; and unknown, 1 in vaccinated patients and chronic respiratory failure, 2; lung cancer, 1; and unknown, 1 in unvaccinated patients. In this group, PPV23 was shown to have an effect on the first episode of pulmonary infection but it did not reduce the number of deaths due to any cause.

There were only 29 pneumococcal pulmonary infection during the observation period (pneumococcal pulmonary infection, 22; death, 7; Supplemental Table C). The pneumococcal pneumonia-free survival decreased significantly in the presence of pulmonary infection during the pre-vaccine period ($p < 0.001$; Supplemental Figure G). No effects of chronic respiratory failure on pneumococcal pneumonia-free survival were observed ($p = 0.196$). PPV23 vaccination did not show significant protective effects against the development of pneumococcal pneumonia (Supplemental Figure H).

DISCUSSION

The effects of the PPV23 vaccination on elderly patients with chronic pulmonary disease varied in accordance with the frequency of lung infection episodes and the presence of chronic respiratory failure during the pre-vaccine period. Our findings suggest the following: PPV23 vaccination might work effectively unless previous lung infection episodes had occurred; and subgroup analysis of the underlying disease associated with pneumococcal complications might be useful for finding the possible ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the presence of pulmonary infection episodes prior to vaccination or chronic pulmonary failure in elderly patients with chronic pulmonary disease.

Comparison with other studies

Previous pulmonary infection was highly associated with poor clinical prognosis. This finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly people with chronic pulmonary disease in the presence of infectious complications

during the pre-vaccine period. In a multicentre double-blind controlled study conducted in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly non-immunocompromised individuals who had been treated for community-acquired pneumonia.[18] In that study, the survival rate calculated by the Kaplan-Meier method was still >80% in both vaccinated and unvaccinated populations after 2-year observation, while our results showed that the survival rate was <60% if episodes of pulmonary infection had occurred within 1 year prior to vaccination. These results are consistent with previous suggestions that chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that protective effects of PPV23 could not be obtained.[19-21] Conflicting results were shown in some other reports in which the beneficial effects of PPV23 in patients with COPD were indicated, although previous episodes of pneumonia prior to vaccination were not considered and participants were not limited to the elderly.[13, 22] Alfageme et al showed PPV23 effectiveness in patients <65 years of age with COPD in a randomised controlled study in 596 patients.[23] These results and our data indicate that PPV23 might be inefficacious on the elderly population with chronic pulmonary disease especially when complicated by lung infection prior to the vaccination. Despite the strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD), altered immune response, disruption of a physical barrier in the airways due to progressive chronic pulmonary disease, and repeated pulmonary infection could compromise the benefits.[1, 24] PPV23 vaccination should be given to patients with chronic pulmonary disease at an earlier stage in which infectious complications have not yet occurred.

The probability of survival was significantly increased by PPV23 in the presence of

chronic respiratory failure in patients without episodes of pulmonary infection during the pre-vaccine period. The pulmonary infection-free survival rate was 75.5% at the end of the observation period when PPV23 was given. Without PPV23, survival was reduced to 45.0%, almost the same level as that in the case where infectious lung complications had occurred during the pre-vaccine period. This result indicates that pulmonary infection due to chronic respiratory failure could be prevented by the PPV23 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be administered in COPD patients when airflow is severe and chronic respiratory failure is present, but these treatments were suggested to be risk factors for community-acquired pneumonia.[25-27] Additionally, bacterial colonisation of the distal airway may occur due to the altered pulmonary defense.[24] We suggest that patients receive the PPV23 vaccination soon after the diagnosis of chronic respiratory disease such as COPD, especially when maintenance treatments for impaired lung function are expected to be risk factors for pneumonia. In this study, the number of participants with chronic respiratory failure who were free of lung infections during the pre-vaccine period was only 70. Thus, a large scale study is warranted.

Strengths and limitations of the study

When informed consents were obtained prior to the study initiation, PPV23 vaccine recommendations were made and only participants who responded affirmatively received the vaccination. This method may be associated with these results: the vaccination rate increased significantly in high-risk patients who had at least 1 episode of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory failure; and the mortality rate was higher in vaccinated patients, although the presence

of adverse effects of PPV23 is unlikely because PPV23 had generally been considered safe based on clinical experience since 1977.[7] In the Cox proportional hazards model, PPV23 was not a risk factor for the events. All of the participants in this study were elderly patients with chronic pulmonary disease, and all of them could be categorised into groups for which PPV23 vaccination is recommended in the United States and some European countries.[3, 7, 14] In Japan, no vaccine recommendations against pneumococcal infection are issued by the Japanese Ministry of Health, Labour and Welfare.[11] Japanese participants need to accept some risks for the public benefit and not for their own if selected for the unvaccinated group. This condition is different from that in some developed countries where unvaccinated control subjects in clinical trials of the PPV23 vaccine could still be protected by previous vaccination and indirect immunity from other people, including children.[28-30] Pneumococcal infection was associated with increasing mortality rates, while the beneficial effects of PPV23 without any severe adverse events were suggested in some previous clinical trials.[1, 8, 15, 31-32] Therefore, we decided to conduct a nonrandomised clinical study to ensure that participants were treated with respect and dignity.

The doctors had access to the patients' vaccination record during the observation period. However, at the time of this study, PPV23 had already been approved by the Japanese Ministry of Health, Labour and Welfare, and there were no conflicts of interest with pharmaceutical companies. All the treatments were supported by the public health care system funded by the Japanese government; no specific grants were provided from any funding agencies. Diagnosis of pulmonary infection was made according to the same diagnostic criteria. Therefore it is unlikely that treatment bias occurred during the observation period.

The diagnosis of pneumococcal disease was not made in the majority of patients who had pulmonary infections during the observation period. Identification of *S. pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However, compared to IPD defined as any condition in which *S. pneumonia* is identified in a normally sterile body site, microbiological diagnosis in the lower respiratory tract is ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for pneumococcal identification might be unreliable due to the technical difficulties in obtaining good-quality sputum and in distinguishing causative specimens from colonisation.[21] The positive results in urine antigen testing might be related to previous infection or colonisation.[33] It might be difficult to assess PPV23 effectiveness on pneumococcal pulmonary infection using these procedures. Blood cultures are recommended for patients hospitalised after a diagnosis of community-acquired pneumonia, although its cost-effectiveness has been questioned in several studies.[34] Less expensive, novel techniques for accurate diagnosis of pneumonia need to be developed.

Conclusions and policy implications

Our data demonstrated that the beneficial effects of the PPV23 vaccination may not be obtainable if an episode of pulmonary infection occurred during the pre-vaccine period in elderly patients with chronic pulmonary disease. We suggest that PPV23 needs to be given soon after chronic pulmonary disease is diagnosed. In developed countries, including Japan, elderly populations with chronic pulmonary disease are growing in number. The Japanese Ministry of Health, Labour and Welfare should introduce the PPV23 vaccination for patients with chronic pulmonary disease and in routine

vaccination of children along with pneumococcal conjugate vaccine that could provide indirect beneficial effects to the population in whom PPV23 efficacy may not be expected.

Table 1: Baseline characteristics of 1378 outpatients with chronic pulmonary disease

	Frequency of pulmonary infection during the pre-vaccine period			P Value†
	0 (n = 1164)	1 (n = 167)	>1 (n = 43)	
Age				
Mean ± SD	71.3 ± 7.0	73.3 ± 6.9	73.0 ± 7.0	< 0.001
Median	71	73	73	
Male	626 (53.8%)	98 (58.7%)	27 (62.8%)	0.272
Female	538 (46.2%)	69 (41.3%)	16 (37.2%)	
Chronic respiratory disease*				
Bronchial asthma	517	59	16	
Chronic pulmonary emphysema	197	40	14	
Old tuberculosis	157	33	10	
Chronic bronchitis	106	18	5	
Interstitial pneumonia	100	9	0	
Non-tuberculous mycobacteria	84	10	2	
Bronchioectasis	31	13	5	
Others	103	15	4	
PPV23-vaccinated	512 (44.0%)	109 (65.3%)	25 (58.1%)	< 0.001
PPV23-unvaccinated	652 (56.0%)	58 (34.7%)	18 (41.9%)	
Chronic respiratory failure				
+	70 (6.0%)	20 (12.0%)	7 (16.3%)	< 0.001
-	1094 (94.0%)	147 (88.0%)	36 (83.7%)	

*Some patients were diagnosed as having more than one chronic respiratory disease.

†Data was analyzed using the Wilcoxon test or the Pearson's test.

Table 2: The effects of pulmonary infection during the pre-vaccine period and chronic respiratory failure on pulmonary infection-free survival after PPV23 vaccination

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	N	event*	Pulmonary infection-free survival at the end of the study*	95%CI	P value †
0	(−)	1094	154	0.840	0.816 – 0.864	<0.001
0	(+)	70	19	0.653	0.525 – 0.781	
1	(−)	147	59	0.550	0.462 – 0.638	0.506
1	(+)	20	10	0.409	0.168 – 0.649	
>1	(−)	36	25	0.315	0.161 – 0.469	0.348
>1	(+)	7	6	0.143	0.000 – 0.402	

*Event represented the number of patients who were diagnosed with pulmonary infection during the observation period.

† Data was analyzed using the log-rank test.

Table 3: Association of the frequency of pulmonary infection during the pre-vaccine period, chronic respiratory failure, PPV23, gender and age with the first episode of pulmonary infection or death of any cause

	Hazard ratio	95% CI	P Value
Covariates for the risk of the first episode of pulmonary infection			
Pulmonary infection during the pre-vaccine period			
1 episode	3.251*	2.436 – 4.338	<0.001
>1 episode	6.480*	4.380 – 9.589	<0.001
Chronic respiratory failure	1.767	1.227 – 2.546	0.002
PPV23 vaccination	1.096	0.848 – 1.416	0.396
Gender	0.911	0.712 – 1.166	0.457
Age	0.994	0.976 – 1.013	0.553
Covariates for the risk of death of any cause			
Pulmonary infection during the pre-vaccine period			
1 episode	2.289*	1.380 – 3.797	0.001
>1 episode	3.134*	1.486 – 6.612	0.003
Chronic respiratory failure	2.152	1.234 – 3.752	0.007
PPV23 vaccination	0.795	0.499 – 1.264	0.332
Gender	0.340	0.199 – 0.580	<0.001
Age	1.040	1.008 – 1.072	0.014

*Hazard ratio was estimated in relative to the case of outpatients with no episode of pulmonary infection during the pre-vaccine period.

Table 4: The influence of pulmonary infection during the pre-vaccine period and chronic respiratory failure on the PPV23 vaccine efficacy

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	Vaccinated*	Unvaccinated*	P Value†
(−)	(−)	0.846 (465)	0.836 (629)	0.931
	(+)	0.755 (47)	0.450 (23)	0.019
1 episode	(−)	0.557 (92)	0.490 (55)	0.665
	(+)	0.431 (17)	0.333 (3)	0.876
>1 episode	(−)	0.317 (22)	0.214 (13)	0.200
	(+)	0.000 (3)	0.250 (4)	0.093

*Data represented the pulmonary infection-free survival (%) at the end of the study (2 years after PPV23 vaccination). Numbers in parenthesis indicate numbers of patients.

†Data was analyzed using the log-rank test.

Contributions: SI was responsible for interpretation of the data, and drafted, revised the manuscript. YW was responsible for study design, collection and interpretation of the data. TK and SM provided statistical support including analysis of the data and training in the use of statistical software. TK and SM also drafted the statistical analysis part in the manuscript. TS, NM, TK and YI helped interpreting the findings and contributed to critical revision of the drafted manuscript, particularly regarding pulmonary infection issues. YN and SM helped interpreting the data, provided very useful suggestion regarding immunization and public health policy, and revised the drafted manuscript. All authors approved the final version of the manuscript.

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Competing interests: None declared.

Ethical approval: Full approval of Institutional Review Board in the Kanagawa Cardiovascular and Respiratory Diseases Centre was obtained prior to the study initiation.

Data sharing: No additional data available.

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The material (clinical data) that had been used for ref. 14 is modified and printed with the permission of the ©European Respiratory Society.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

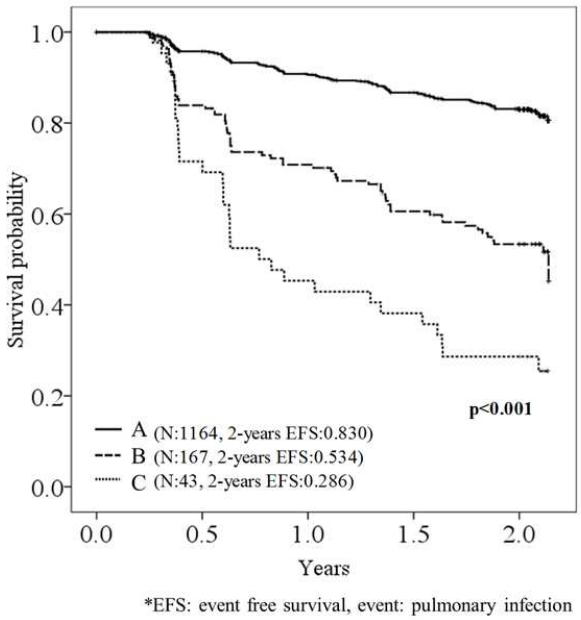
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*)For matched studies, give matching criteria and number of exposed and unexposed	6,7,18
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10
		(*b*) Describe any methods used to examine subgroups and interactions	9,10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10,18
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,18
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-12,18-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12,19,20
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

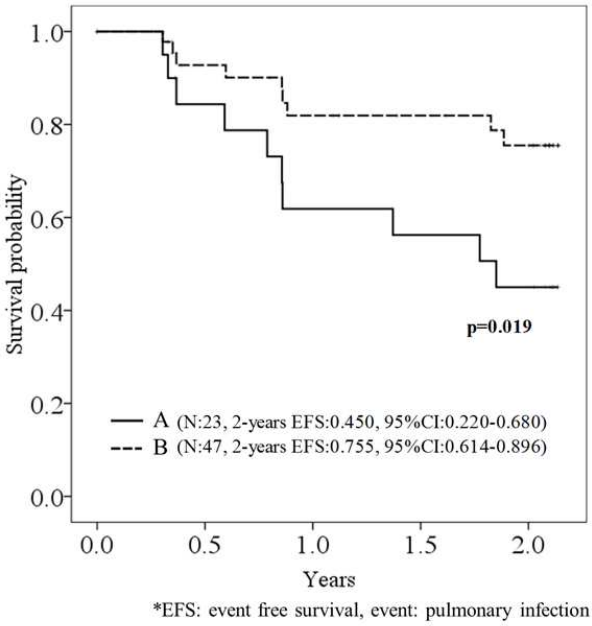
Figure 1



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Frequency of pulmonary infection during the pre-vaccine period: zero episodes, A; one episode, B; more than 1 episode, C

254x190mm (96 x 96 DPI)

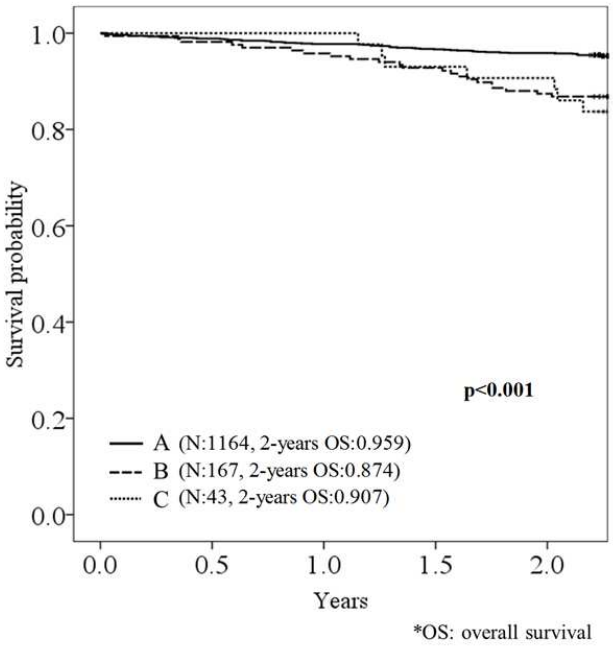
Figure 2



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

254x190mm (96 x 96 DPI)

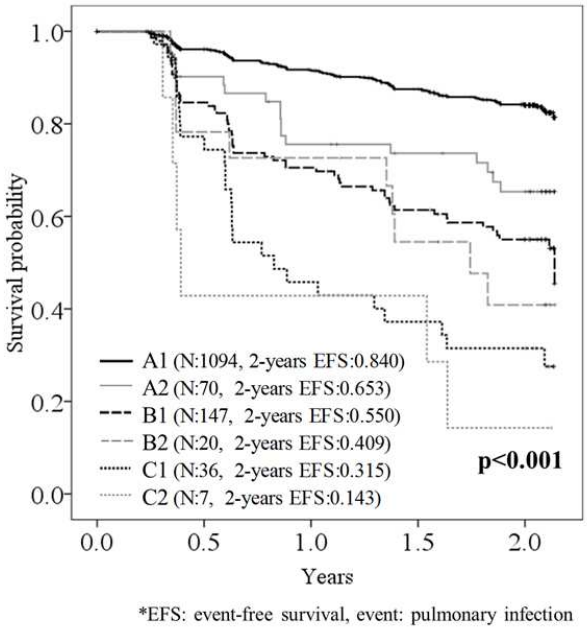
Figure A



Kaplan-Meier curves showing the proportion of patients free of death during the observation period Frequency of pulmonary infection during the pre-vaccine period: 0 episodes, A; one episode, B; more than one episode, C

254x190mm (96 x 96 DPI)

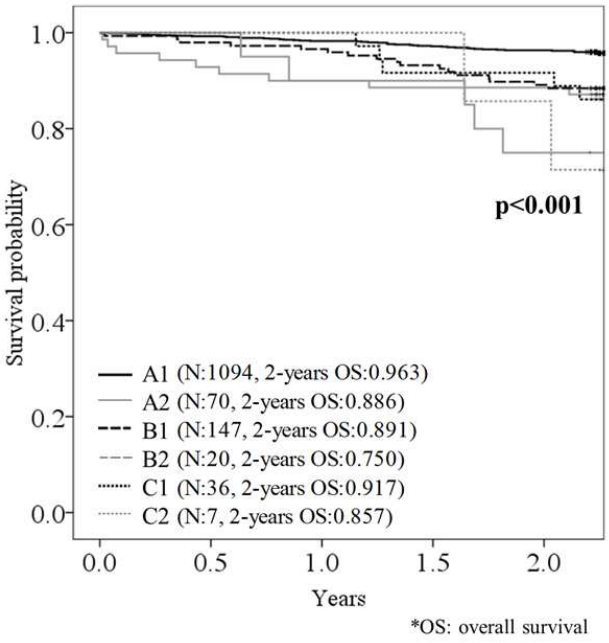
Figure B



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2
One episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, B1; with chronic respiratory failure, B2
More than 1 episode of pulmonary infection during the pre-vaccine period without chronic respiratory failure, C1; with chronic respiratory failure, C2

254x190mm (96 x 96 DPI)

Figure C



Kaplan-Meier curves showing the proportion of patients free of death during the observation period
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2
One episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, B1; with chronic respiratory failure, B2
More than 1 episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, C1; with chronic respiratory failure, C2

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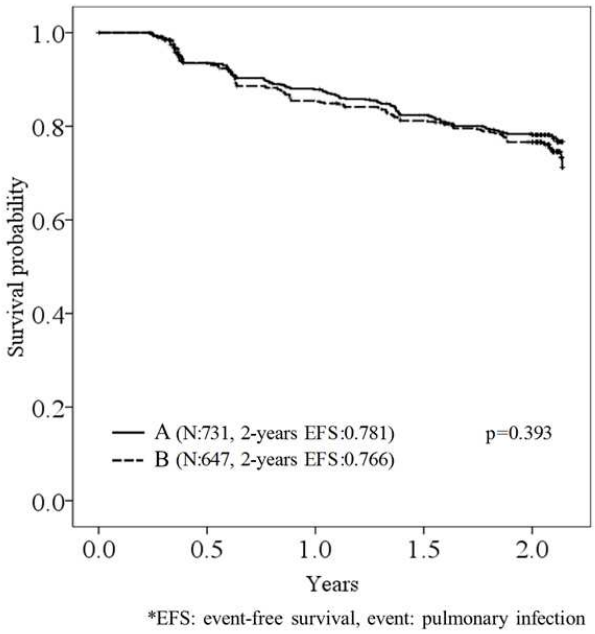
Figure D



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
All the participants: unvaccinated, A; vaccinated, B

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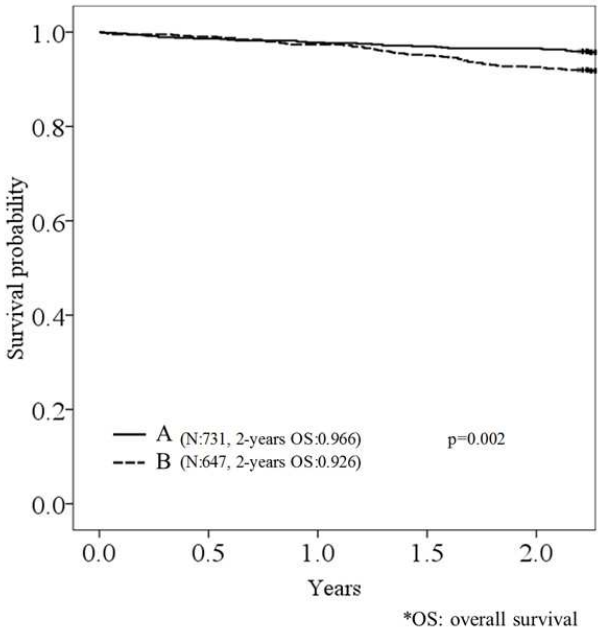
Figure E



Kaplan-Meier curves showing the proportion of patients free of death during the observation period
All the participants: unvaccinated, A; vaccinated, B

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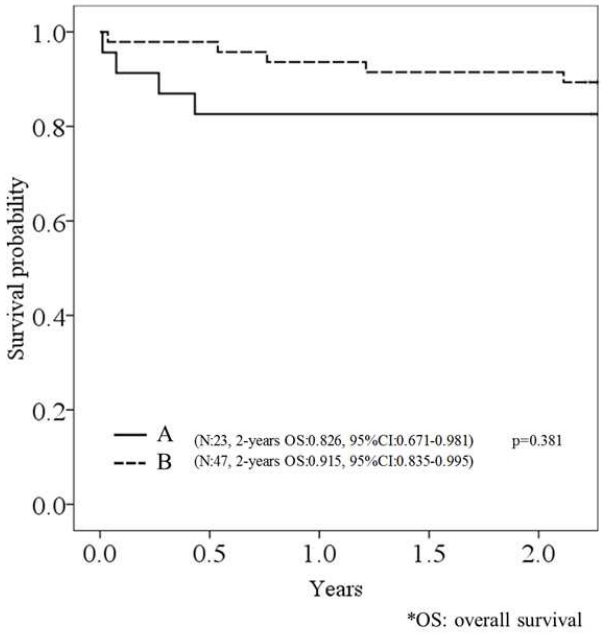
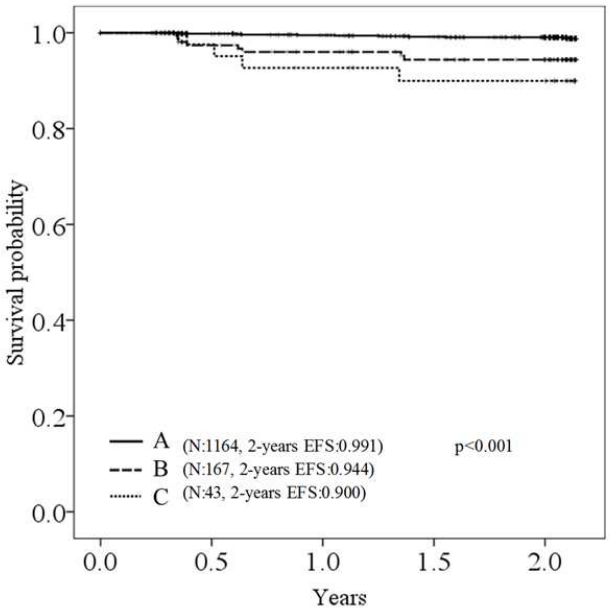
Figure F



Kaplan-Meier curves showing the proportion of patients free of death during the observation period Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

254x190mm (96 x 96 DPI)

Figure G



*EFS: event-free survival, event: pneumococcal pneumonia

Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period
Frequency of pulmonary infection during the pre-vaccine period: zero episodes, A; one episode, B; more than 1 episode, C

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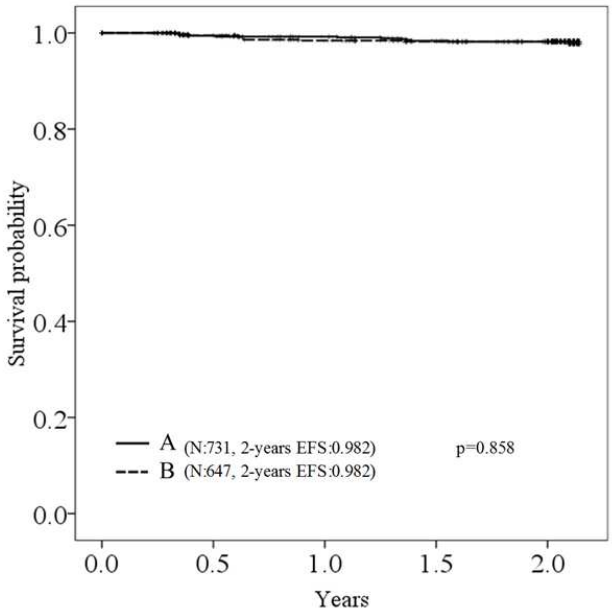
Figure H



Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period
All the participants: unvaccinated, A; vaccinated, B

254x190mm (96 x 96 DPI)

Table A: The effects of pulmonary infection during the pre-vaccine period and chronic respiratory failure on death of any cause-free survival after PPV23 vaccination

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	N	event*	Death of any cause-free survival at the end of the study*	95%CI	P value†
0	(−)	1094	46	0.956	0.951 – 0.975	0.001
0	(+)	70	9	0.886	0.793 – 0.949	
1	(−)	147	17	0.891	0.833 – 0.935	0.096
1	(+)	20	5	0.750	0.560 – 0.940	
>1	(−)	36	6	0.917	0.787 – 0.991	0.346
>1	(+)	7	2	0.857	0.379 – 1.049	

*Event represented the number of patient death during the observation period.

†Data was analyzed using the log-rank test.

Table B: The cause of death (total 85) among all the participants during the observation period

	Vaccinated (54)	Unvaccinated (31)
Pulmonary infection (pneumococcal)	11 (5)	8 (2)
Chronic respiratory failure	13	6
Chronic heart failure	5	2
Cardiovascular disease	1	0
Lung cancer	12	9
Cerebrovascular disease	5	0
Liver cirrhosis	0	1
Unknown	7	5

Table C: The underlying pulmonary conditions of patients who were diagnosed with pneumococcal pulmonary infection during the observation period

Pulmonary infection during the pre-vaccine period	Chronic respiratory failure	N (total = 22)*
0	-	10
	+	0
1	-	6
	+	2
>1	-	3
	+	1

*Data represents the number of patient in each group.

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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients: Prospective cohort study

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Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine caused by various underlying conditions of chronic pulmonary disease in elderly patients: Prospective cohort study

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ABSTRACT

Objective

To determine the ideal conditions for use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in elderly outpatients with chronic pulmonary diseases.

Design

Prospective cohort study

Participants

A total of 1,378 outpatients with chronic pulmonary diseases ≥60 years of age

Intervention

Participants were educated about PPV23, and those who responded affirmatively were vaccinated between August and November 2002. The participants who chose no intervention served as controls. The pre-vaccine period was defined as August 2001 to August 2002. Participants were followed for 2 years from December 2002 or until death.

Main outcome measures

Events of interest included the first episode of bacterial (including pneumococcal) pulmonary infection (primary endpoint) and death of any cause (secondary endpoint).

Results

Frequent episodes of pulmonary infection during the pre-vaccine period significantly decreased event-free survival during the 2-year observation period ($p < 0.001$). Chronic respiratory failure was associated with a decreased event-free survival only when the pulmonary infection episode did not occur in the pre-vaccine period ($p < 0.001$). No significant differences in event-free survival were observed between the vaccinated and unvaccinated group during analysis of the entire cohort. In the Cox proportional hazards

regression model, event-free survival decreased significantly when pulmonary infection occurred in the pre-vaccine period. In the subgroup analysis, the first episode of bacterial pulmonary infection (but not death of any cause) was reduced significantly by PPV23 only in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period ($p = 0.019$).

Conclusion

The efficacy of PPV23 against pulmonary infection and death of any cause might be unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs to be given to elderly patients with chronic pulmonary disease at an earlier time in which infectious complications in the lung have not yet occurred.

Summary

- Article focus (hypothesis):

The efficacy of PPV23 might be compromised by an episode of pulmonary infection in the pre-vaccine period or chronic respiratory failure in elderly patients with chronic pulmonary disease.

- Key messages:

1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the pre-vaccine period.
2. The episode of pulmonary infection could be prevented by PPV23 in elderly patients with noninfectious complications such as chronic respiratory failure.
3. Elderly patients with chronic pulmonary disease need to receive the PPV23 vaccination at an earlier time in which infectious complications in the lung have not yet

occurred.

- Strengths and limitations of this study:

1. Only participants who responded affirmatively received PPV23. They were not assigned randomly to a group.

2. The diagnosis of pneumococcal pulmonary disease was not made in the majority of patients who had pulmonary infection during the study period. The microbiological diagnosis in the lower respiratory tract, which is not normally sterile, is ambiguous.

INTRODUCTION

Streptococcus pneumoniae continues to be one of the main causative pathogens in community-acquired pneumonia and meningitis.[1-2] Due to the high mortality rate of *S. pneumoniae* infections, especially in elderly and very young patients, prophylactic use of 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for people at an increased risk of pneumococcal disease in developed countries.[3-7] The efficacy of PPV23, however, remains controversial. Despite the fact that the results of pre- and post-licensed trials in immunocompetent people were supportive of regulatory approval of vaccine use, clinical studies in elderly or young adults with comorbidities in developed countries produced little convincing evidence of effectiveness against a common manifestation of pneumococcal infections such as pneumonia.[8-12] A retrospective study conducted in 1999 suggested that PPV23 was associated with significant reductions in hospitalisation and mortality rates of elderly patients with chronic lung disease and contributed to medical care cost savings, although meta-analytical reviews published thereafter failed to show statistically significant

evidence of the protective effects of PPV23 against the development of pneumonia in elderly patients with chronic illnesses.[13-15]

We previously reported a 2-year cohort clinical study of elderly outpatients with chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial and pneumococcal pulmonary infection onset and outcome.[16] Analysis of the comparison between the vaccinated and unvaccinated group showed a decline in the incidence of bacterial pulmonary infection only in the vaccinated group. This result might be associated with PPV23 effectiveness, although detailed background information regarding underlying pulmonary conditions was not provided. Subgroup analysis needs to be carried out since chronic pulmonary disease includes various clinical and pathophysiological pictures. Underlying pulmonary diseases could cause chronic respiratory failure if repeatedly complicated by lung infections, and such heterogeneity may generate different outcomes after vaccination.[17] We decided to reanalyse the data to study the influence of clinical background during the pre-vaccine period on PPV23 efficacy in elderly patients with chronic pulmonary disease.

METHODS

Study population

All the outpatients ≥60 years of age (a total of 1,378 participants at the start of the study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory Diseases Centre were included in this study. These patients were informed of the prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic pulmonary diseases in this study included bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous

mycobacteria, and others (Table 1). Patients who presented with a fever (≥37.5 °C) were excluded from the study according to the Preventive Vaccination Law issued by the Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these patients became stable, they were invited to participate in the study. Home oxygen therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS) Guidelines for 97 participants with chronic respiratory failure upon study initiation (Table 1), but no patients were newly prescribed HOT during the observation period.

Study design

We did not adopt a randomised controlled study design since the PPV23 vaccination is considered a part of standard care in many developed countries. Additionally, some elderly participants with chronic pulmonary disease were in an immunocompromised status; therefore, a randomised controlled study of vaccine effectiveness may violate ethical principles and human rights. Written informed consent forms were obtained from all participants. To avoid selection bias, doctors and other medical staffs were not allowed to assign patients to the vaccine or non-vaccine group; instead, individual patients decided whether or not to be vaccinated. The same form, which included an explanation of the study, was provided to all the participants. A total of 647 patients were injected with PPV23 (Pneumovax, Merck, NJ, USA) intramuscularly into their non-dominant upper arm with between August and November 2002. The pre-vaccine period was defined as 1 year prior to PPV23 vaccination (August 2001 to July 2002).

Data collection

Participants were followed from December 2002 to the end of the study in November

2004 (for 2 years) or until death in the clinic approximately every 2 months as long as clinical status remained stable. A diagnosis of pulmonary infection was made by respiratory physicians according to the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults. In brief, pulmonary infection was suspected if more than 2 of the following criteria were present: temperature ≥ 37.0 °C, white blood cell count > 8,000/mm^3, and C-reactive protein > 0.7 mg/dl. A diagnosis of pneumonia was made when chest radiographs revealed alveolar opacities. If a cough with yellow sputum production was observed in the absence of the alveolar opacities on the chest radiograph, the patients were diagnosed with acute bronchitis or exacerbation of chronic bronchitis. It was very difficult to clearly distinguish pneumonia from acute bronchitis or an acute exacerbation of chronic bronchitis in some patients since there were considerable clinical overlaps between these illnesses including the symptoms, blood test results, causative pathogens, and antibiotic treatment. Hence, pulmonary infection was expressed as a dichotomous variable.

A diagnosis of pneumococcal pulmonary infection was made if *Streptococcus pneumoniae* was the dominant organism stained with Gram stain in the sputum smear or if the sputum culture was positive (> 10^7 colony forming units/ml). When *S. pneumoniae* was not identified, patients were diagnosed with a pulmonary infection caused by an identified pathogen or with a bacterial pulmonary infection if no possible causative pathogen was detected but if the clinical data were highly suggestive of bacterial infection in the lung. Empirical antibiotic therapy was started in all the patients promptly once clinical data sufficient to satisfy the definition of pulmonary infection were obtained. The initial treatment was replaced by second-line therapy of antibiotics

chosen according to the sensitivity results.

Event of interest

We hypothesised that repeated pulmonary infection and concomitant gradual loss of lung function might be related to a reduced PPV23 efficacy. Participants were grouped based on these factors: frequency of infectious (including pneumococcal) pulmonary infection episode within 1 year prior to the PPV23 vaccination (0 episodes, 1 episode, and >1 episode), and chronic respiratory failure represented by HOT usage. Events of interest included the first episode of bacterial or pneumococcal pulmonary infection (pneumonia, acute bronchitis, or exacerbation of chronic bronchitis) where antibiotic treatment was required (primary endpoint), and death of any cause (secondary endpoint). The case of death with missing values was not counted as an event of interest but was included in the mortality rate.

Statistical analysis

Differences in event-free survival were depicted with Kaplan-Meier curves, and the log-rank test was applied for analysis. The primary and secondary endpoints (the first episode of pulmonary infection and death of any cause, respectively) were analysed separately. Cross-tabulated data were compared by the Wilcoxon test or the Pearson's chi-square test. Relative risks for the events were estimated using the Cox proportional hazards regression model. The covariates used in the analysis were: (1) pulmonary infection during the pre-vaccine period, (2) chronic respiratory failure, and (3) PPV23 vaccination. For further analysis, gender and age were added as covariates and the data were analyzed. No any other variables were regarded as covariates in relation to

event-free survival. The PASW statistics 18 (SPSS Inc. IL, USA) and SAS software (SAS Institute Inc. NC, USA) were used for the statistical analysis.

RESULTS

Participant characteristics are shown in Table 1. Significant reductions in vaccination rate, age, and frequency of chronic respiratory failure were observed in the group without pulmonary infection during the pre-vaccine period compared with the other 2 groups with at least 1 episode of infectious lung complications. No significant gender difference was seen among groups.

The effects of underlying pulmonary conditions on event occurrences were analysed before PPV23 effectiveness were evaluated. Event-free survival in the Kaplan-Meier method dropped significantly as the frequency of pulmonary infection in the pre-vaccine period increased: the first episode of pulmonary infection, Figure 1; death of any cause, Supplemental Figure A. Chronic respiratory failure was associated with a significant decrease in event-free survival only in the absence of pulmonary infection in the pre-vaccine period: the first episode of pulmonary infection, Supplemental Figure B, Table 2; death of any cause, Supplemental Figure C, Supplemental Table A.

Participants were not randomly assigned to groups; vaccination was chosen or declined by each individual. As a result, the number of vaccinated patients was significantly higher than the number of unvaccinated patients when pulmonary infection occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness against the development of first episode of pulmonary infection during the observation period was seen between the vaccinated and unvaccinated group in the Kaplan-Meier method (Supplemental Figure D). The mortality rate was, however, significantly high in

the vaccinated group (Supplemental Figure E). This result may be misleading due to the vaccination imbalance among groups. In the Cox proportional hazards regression model applied for covariate adjustment, no hazardous effects of PPV23 on the incidence or timing of the first episode of pulmonary infection or death of any cause were observed. The hazard ratio for the first episode of pulmonary infection or death of any cause increased significantly due to some covariates such as pulmonary infection during the pre-vaccine period and chronic respiratory failure. Other covariates including gender, and age were not associated with the first episode of pulmonary infection but were associated with death of any cause (Table 3). The cause of death (n = 85) among all the participants during the observation period was shown in Supplemental Table B.

A subgroup analysis was performed to find the ideal condition for PPV23 use in elderly patients with chronic pulmonary disease. There are no significant differences in pulmonary infection-free survival between vaccinated and unvaccinated patients when grouped only by frequency of pulmonary infection in the pre-vaccine period (not shown). Pulmonary infection-free survival was somewhat improved when patients with chronic respiratory failure were vaccinated ($p = 0.078$). This effectiveness became significant when patients who had at least 1 episode of pulmonary infection in the pre-vaccine period were excluded (Figure 2) (Table 4). The mortality was not reduced by PPV23 in patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period (Supplemental Figure F). The cause of death (n = 9) among patients with chronic respiratory failure who had no episodes of pulmonary infection during the pre-vaccine period was as follows: chronic respiratory failure, 2; cerebrovascular disease, 2; and unknown, 1 in vaccinated patients and chronic respiratory failure, 2; lung cancer, 1; and unknown, 1 in unvaccinated patients. In this

group, PPV23 was shown to have an effect on the first episode of pulmonary infection but it did not reduce the number of deaths due to any cause.

There were only 29 pneumococcal pulmonary infection during the observation period (pneumococcal pulmonary infection, 22; death, 7; Supplemental Table C). The pneumococcal pneumonia-free survival decreased significantly in the presence of pulmonary infection during the pre-vaccine period ($p < 0.001$; Supplemental Figure G). No effects of chronic respiratory failure on pneumococcal pneumonia-free survival were observed ($p = 0.196$). PPV23 vaccination did not show significant protective effects against the development of pneumococcal pneumonia (Supplemental Figure H).

DISCUSSION

The effects of the PPV23 vaccination on elderly patients with chronic pulmonary disease varied in accordance with the frequency of lung infection episodes and the presence of chronic respiratory failure during the pre-vaccine period. Our findings suggest the following: PPV23 vaccination might work effectively unless previous lung infection episodes had occurred; and subgroup analysis of the underlying disease associated with pneumococcal complications might be useful for finding the possible ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the presence of pulmonary infection episodes prior to vaccination or chronic pulmonary failure in elderly patients with chronic pulmonary disease.

Comparison with other studies

Previous pulmonary infection was highly associated with poor clinical prognosis. This

finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly people with chronic pulmonary disease in the presence of infectious complications during the pre-vaccine period. In a multicentre double-blind controlled study conducted in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly non-immunocompromised individuals who had been treated for community-acquired pneumonia.[18] In that study, the survival rate calculated by the Kaplan-Meier method was still >80% in both vaccinated and unvaccinated populations after 2-year observation, while our results showed that the survival rate was <60% if episodes of pulmonary infection had occurred within 1 year prior to vaccination. These results are consistent with previous suggestions that chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that protective effects of PPV23 could not be obtained.[19-21] Conflicting results were shown in some other reports in which the beneficial effects of PPV23 in patients with COPD were indicated, although previous episodes of pneumonia prior to vaccination were not considered and participants were not limited to the elderly.[13, 22] Alfageme et al showed PPV23 effectiveness in patients <65 years of age with COPD in a randomised controlled study in 596 patients.[23] These results and our data indicate that PPV23 might be inefficacious on the elderly population with chronic pulmonary disease especially when complicated by lung infection prior to the vaccination. Despite the strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD), altered immune response, disruption of a physical barrier in the airways due to progressive chronic pulmonary disease, and repeated pulmonary infection could compromise the benefits.[1, 24] PPV23 vaccination should be given to patients with chronic pulmonary disease at an earlier stage in which infectious complications have not

yet occurred.

The probability of survival was significantly increased by PPV23 in the presence of chronic respiratory failure in patients without episodes of pulmonary infection during the pre-vaccine period. The pulmonary infection-free survival rate was 75.5% at the end of the observation period when PPV23 was given. Without PPV23, survival was reduced to 45.0%, almost the same level as that in the case where infectious lung complications had occurred during the pre-vaccine period. This result indicates that pulmonary infection due to chronic respiratory failure could be prevented by the PPV23 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be administered in COPD patients when airflow is severe and chronic respiratory failure is present, but these treatments were suggested to be risk factors for community-acquired pneumonia.[25-27] Additionally, bacterial colonisation of the distal airway may occur due to the altered pulmonary defense.[24] We suggest that patients receive the PPV23 vaccination soon after the diagnosis of chronic respiratory disease such as COPD, especially when maintenance treatments for impaired lung function are expected to be risk factors for pneumonia. In this study, the number of participants with chronic respiratory failure who were free of lung infections during the pre-vaccine period was only 70. Thus, a large scale study is warranted.

Strengths and limitations of the study

When informed consents were obtained prior to the study initiation, PPV23 vaccine recommendations were made and only participants who responded affirmatively received the vaccination. This method may be associated with these results: the vaccination rate increased significantly in high-risk patients who had at least 1 episode

of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory failure; and the mortality rate was higher in vaccinated patients, although the presence of adverse effects of PPV23 is unlikely because PPV23 had generally been considered safe based on clinical experience since 1977.[7] In the Cox proportional hazards model, PPV23 was not a risk factor for the events. All of the participants in this study were elderly patients with chronic pulmonary disease, and all of them could be categorised into groups for which PPV23 vaccination is recommended in the United States and some European countries.[3, 7, 14] In Japan, no vaccine recommendations against pneumococcal infection are issued by the Japanese Ministry of Health, Labour and Welfare.[11] Japanese participants need to accept some risks for the public benefit and not for their own if selected for the unvaccinated group. This condition is different from that in some developed countries where unvaccinated control subjects in clinical trials of the PPV23 vaccine could still be protected by previous vaccination and indirect immunity from other people, including children.[28-30] Pneumococcal infection was associated with increasing mortality rates, while the beneficial effects of PPV23 without any severe adverse events were suggested in some previous clinical trials.[1, 8, 15, 31-32] Therefore, we decided to conduct a nonrandomised clinical study to ensure that participants were treated with respect and dignity.

The doctors had access to the patients' vaccination record during the observation period. However, at the time of this study, PPV23 had already been approved by the Japanese Ministry of Health, Labour and Welfare, and there were no conflicts of interest with pharmaceutical companies. All the treatments were supported by the public health care system funded by the Japanese government; no specific grants were provided from any funding agencies. Diagnosis of pulmonary infection was made according to the

same diagnostic criteria. Therefore it is unlikely that treatment bias occurred during the observation period.

The diagnosis of pneumococcal disease was not made in the majority of patients who had pulmonary infections during the observation period. Identification of *S. pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However, compared to IPD defined as any condition in which *S. pneumonia* is identified in a normally sterile body site, microbiological diagnosis in the lower respiratory tract is ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for pneumococcal identification might be unreliable due to the technical difficulties in obtaining good-quality sputum and in distinguishing causative specimens from colonisation.[21] The positive results in urine antigen testing might be related to previous infection or colonisation.[33] It might be difficult to assess PPV23 effectiveness on pneumococcal pulmonary infection using these procedures. Blood cultures are recommended for patients hospitalised after a diagnosis of community-acquired pneumonia, although its cost-effectiveness has been questioned in several studies.[34] Less expensive, novel techniques for accurate diagnosis of pneumonia need to be developed.

Conclusions and policy implications

Our data demonstrated that the beneficial effects of the PPV23 vaccination may not be obtainable if an episode of pulmonary infection occurred during the pre-vaccine period in elderly patients with chronic pulmonary disease. We suggest that PPV23 needs to be given soon after chronic pulmonary disease is diagnosed. In developed countries, including Japan, elderly populations with chronic pulmonary disease are growing in

number. The Japanese Ministry of Health, Labour and Welfare should introduce the PPV23 vaccination for patients with chronic pulmonary disease and in routine vaccination of children along with pneumococcal conjugate vaccine that could provide indirect beneficial effects to the population in whom PPV23 efficacy may not be expected.

Table 1: Baseline characteristics of 1378 outpatients with chronic pulmonary disease

	Frequency of pulmonary infection during the pre-vaccine period			P Value†
	0 (n = 1164)	1 (n = 167)	>1 (n = 43)	
Age				
Mean ± SD	71.3 ± 7.0	73.3 ± 6.9	73.0 ± 7.0	< 0.001
Median	71	73	73	
Male	626 (53.8%)	98 (58.7%)	27 (62.8%)	0.272
Female	538 (46.2%)	69 (41.3%)	16 (37.2%)	
Chronic respiratory disease*				
Bronchial asthma	517	59	16	
Chronic pulmonary emphysema	197	40	14	
Old tuberculosis	157	33	10	
Chronic bronchitis	106	18	5	
Interstitial pneumonia	100	9	0	
Non-tuberculous mycobacteria	84	10	2	
Bronchioectasis	31	13	5	
Others	103	15	4	
PPV23-vaccinated	512 (44.0%)	109 (65.3%)	25 (58.1%)	< 0.001
PPV23-unvaccinated	652 (56.0%)	58 (34.7%)	18 (41.9%)	
Chronic respiratory failure				
+	70 (6.0%)	20 (12.0%)	7 (16.3%)	< 0.001
-	1094 (94.0%)	147 (88.0%)	36 (83.7%)	

*Some patients were diagnosed as having more than one chronic respiratory disease.

†Data was analyzed using the Wilcoxon test or the Pearson's test.

Table 2: The effects of pulmonary infection during the pre-vaccine period and chronic respiratory failure on pulmonary infection-free survival after PPV23 vaccination

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	N	event*	Pulmonary infection-free survival at the end of the study*	95%CI	P value†
0	(-)	1094	154	0.840	0.816 – 0.864	<0.001
0	(+)	70	19	0.653	0.525 – 0.781	
1	(-)	147	59	0.550	0.462 – 0.638	0.506
1	(+)	20	10	0.409	0.168 – 0.649	
>1	(-)	36	25	0.315	0.161 – 0.469	0.348
>1	(+)	7	6	0.143	0.000 – 0.402	

*Event represented the number of patients who were diagnosed with pulmonary infection during the observation period.

†Data was analyzed using the log-rank test.

Table 3: Association of the frequency of pulmonary infection during the pre-vaccine period, chronic respiratory failure, PPV23, gender and age with the first episode of pulmonary infection or death of any cause

	Hazard ratio	95% CI	P Value
Covariates for the risk of the first episode of pulmonary infection			
Pulmonary infection during the pre-vaccine period			
1 episode	3.251*	2.436 – 4.338	<0.001
>1 episode	6.480*	4.380 – 9.589	<0.001
Chronic respiratory failure	1.767	1.227 – 2.546	0.002
PPV23 vaccination	1.096	0.848 – 1.416	0.396
Gender	0.911	0.712 – 1.166	0.457
Age	0.994	0.976 – 1.013	0.553
Covariates for the risk of death of any cause			
Pulmonary infection during the pre-vaccine period			
1 episode	2.289*	1.380 – 3.797	0.001
>1 episode	3.134*	1.486 – 6.612	0.003
Chronic respiratory failure	2.152	1.234 – 3.752	0.007
PPV23 vaccination	0.795	0.499 – 1.264	0.332
Gender	0.340	0.199 – 0.580	<0.001
Age	1.040	1.008 – 1.072	0.014

*Hazard ratio was estimated in relative to the case of outpatients with no episode of pulmonary infection during the pre-vaccine period.

Table 4: The influence of pulmonary infection during the pre-vaccine period and chronic respiratory failure on the PPV23 vaccine efficacy

Frequency of pulmonary infection during the pre-vaccine period	Chronic respiratory failure	Vaccinated*	Unvaccinated*	P Value†
(-)	(-)	0.846 (465)	0.836 (629)	0.931
	(+)	0.755 (47)	0.450 (23)	0.019
1 episode	(-)	0.557 (92)	0.490 (55)	0.665
	(+)	0.431 (17)	0.333 (3)	0.876
>1 episode	(-)	0.317 (22)	0.214 (13)	0.200
	(+)	0.000 (3)	0.250 (4)	0.093

*Data represented the pulmonary infection-free survival (%) at the end of the study (2 years after PPV23 vaccination). Numbers in parenthesis indicate numbers of patients.

†Data was analyzed using the log-rank test.

Contributions: SI was responsible for interpretation of the data, and drafted the manuscript. YW was responsible for study design, collection and interpretation of the data. YW also revised the drafted manuscript. Dr. Tetsuji Kaneko (TK) and Dr. Satoshi Morita (SM) provided statistical support including analysis of the data and training in the use of statistical software. TK and SM also drafted the statistical analysis part in the manuscript and revised the drafted manuscript. TS, NM, Dr. Takeshi Kaneko and YI helped interpreting the findings and contributed to critical revision of the drafted manuscript, particularly regarding pulmonary infection issues. YN and Dr. Shunsaku Mizushima helped interpreting the data, provided very useful suggestion regarding immunization and public health policy, and revised the drafted manuscript. All authors approved the final version of the manuscript.

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Deleted: ¶

Competing interests: None declared.

Ethical approval: Full approval of Institutional Review Board in the Kanagawa Cardiovascular and Respiratory Diseases Centre was obtained prior to the study initiation.

Data sharing: No additional data available.

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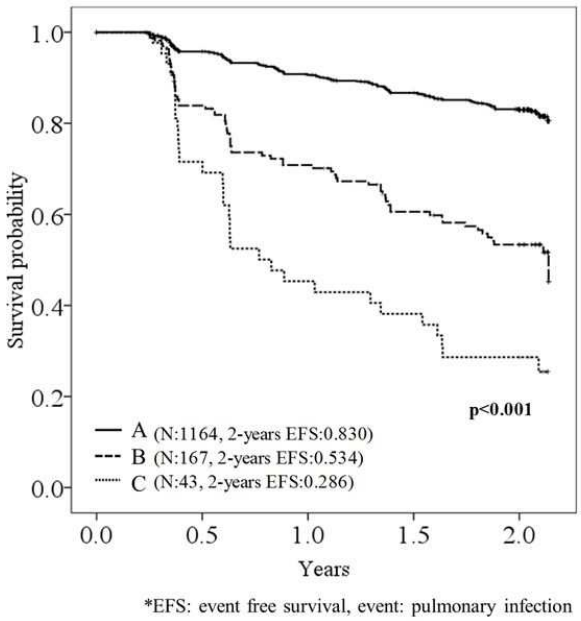
Figure 1



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Frequency of pulmonary infection during the pre-vaccine period: zero episodes, A; one episode, B; more than 1 episode, C

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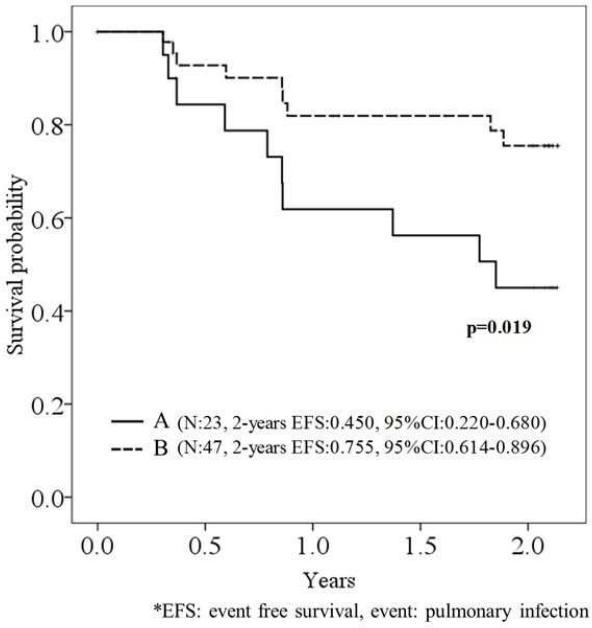
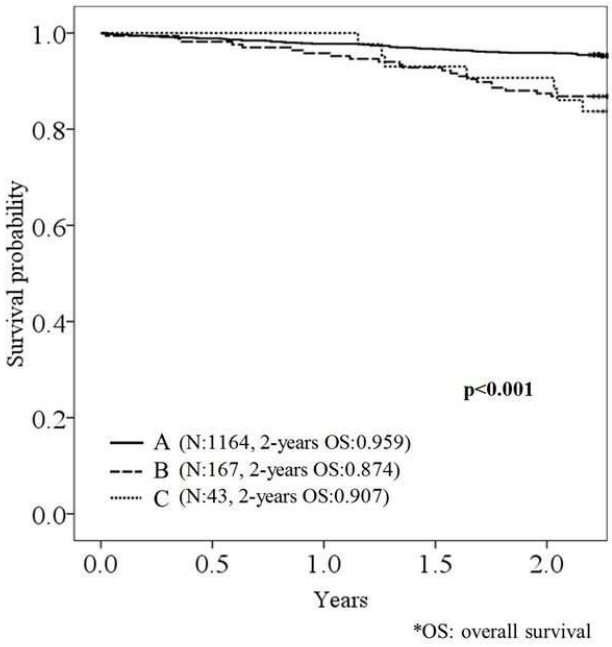
Figure 2



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

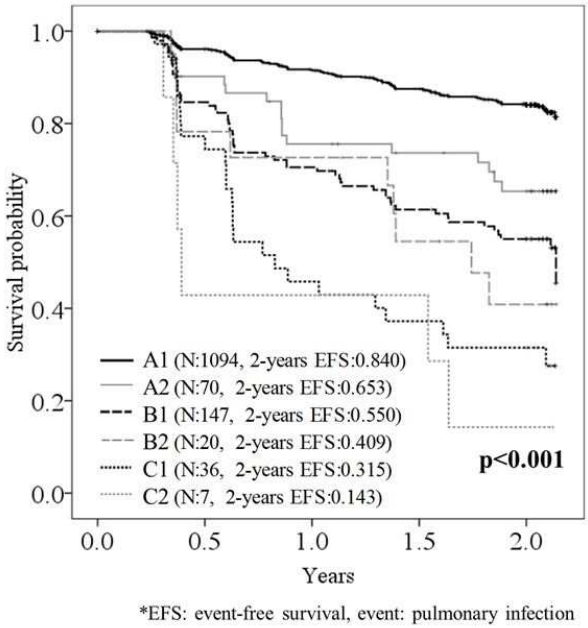
Figure A



Kaplan-Meier curves showing the proportion of patients free of death during the observation period
Frequency of pulmonary infection during the pre-vaccine period: 0 episodes, A; one episode, B; more than one episode, C

81x60mm (300 x 300 DPI)

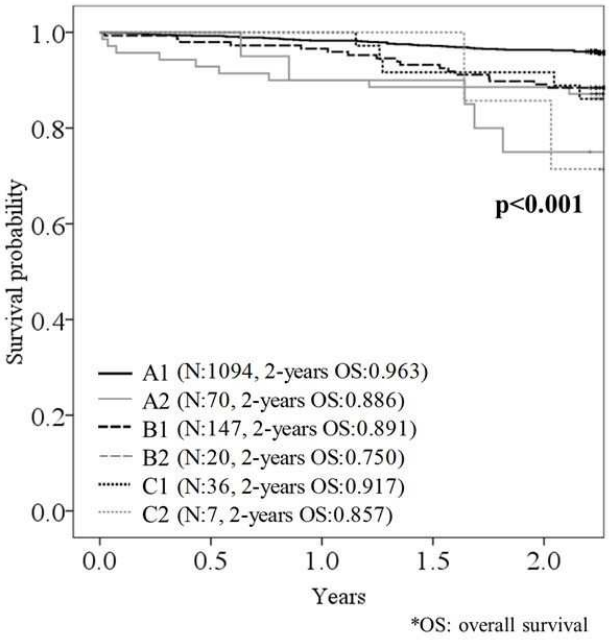
Figure B



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2
One episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, B1; with chronic respiratory failure, B2
More than 1 episode of pulmonary infection during the pre-vaccine period without chronic respiratory failure, C1; with chronic respiratory failure, C2

81x60mm (300 x 300 DPI)

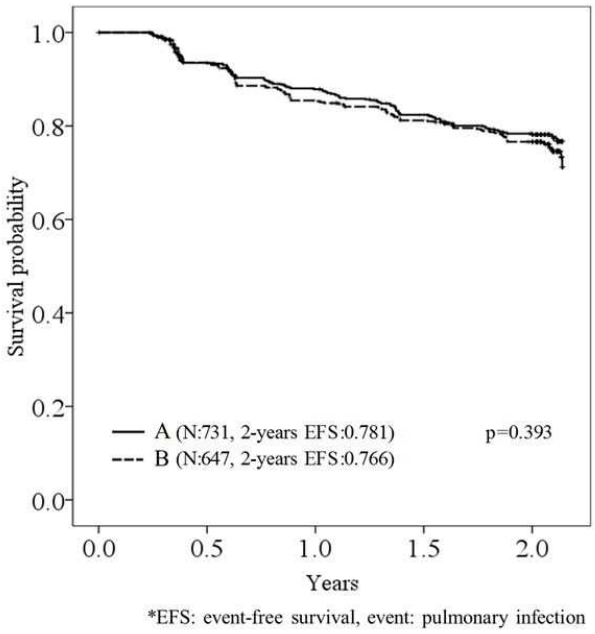
Figure C



Kaplan-Meier curves showing the proportion of patients free of death during the observation period
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2
One episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, B1; with chronic respiratory failure, B2
More than 1 episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, C1; with chronic respiratory failure, C2

81x60mm (300 x 300 DPI)

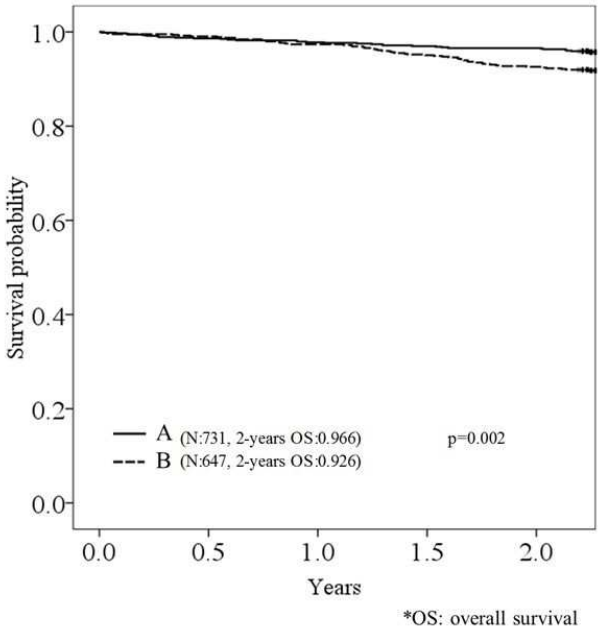
Figure D



Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
All the participants: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

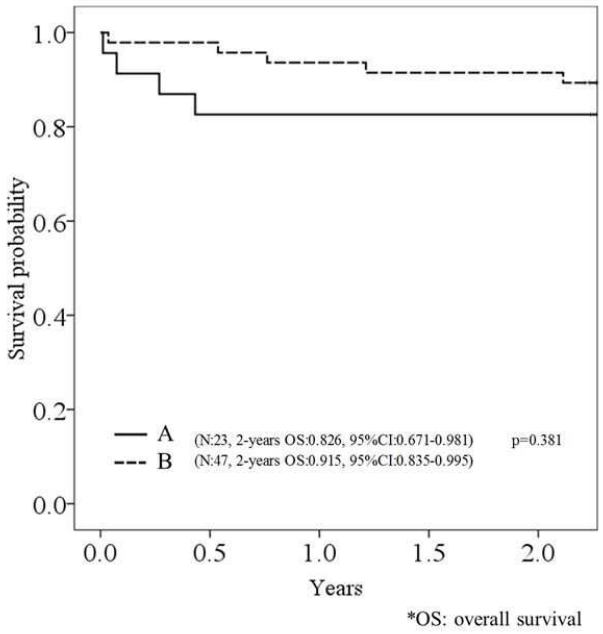
Figure E



Kaplan-Meier curves showing the proportion of patients free of death during the observation period
All the participants: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

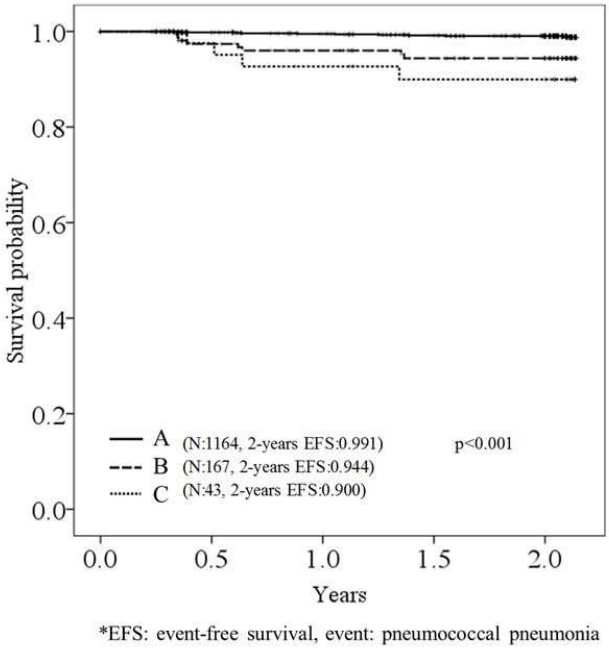
Figure F



Kaplan-Meier curves showing the proportion of patients free of death during the observation period Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

Figure G

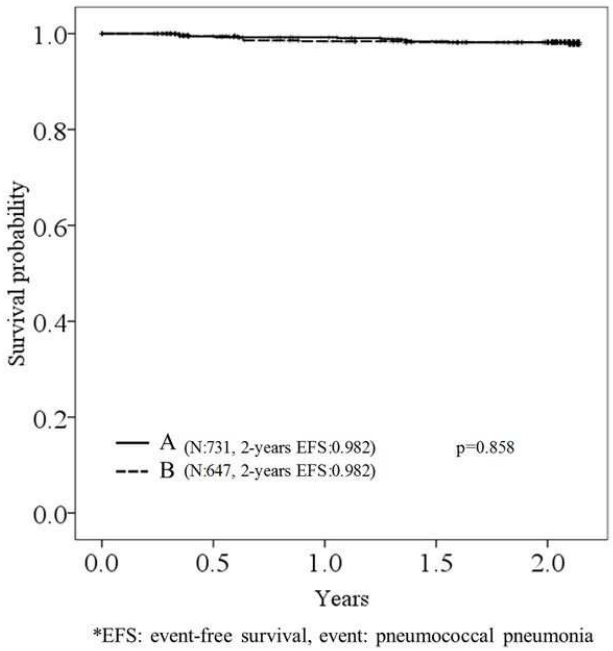


*EFS: event-free survival, event: pneumococcal pneumonia

Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period
Frequency of pulmonary infection during the pre-vaccine period: zero episodes, A; one episode, B; more than 1 episode, C

81x60mm (300 x 300 DPI)

Figure H



Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period
All the participants: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)