



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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Complete List of Authors:	Inoue, Satoshi; Yokohama City University, Department of Epidemiology and Public Health Watanuki, Yuji Kaneko, Tetsuji Sato, Takashi Miyazawa, Naoki Kaneko, Takeshi Ishigatsubo, Yoshiaki Morita, Satoshi Natsumeda, Yutaka Mizushima, Shunsaku
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6 **Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine**
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8 **caused by various underlying conditions of chronic pulmonary disease in elderly**
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10 **patients**

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12 Satoshi Inoue,^{1,5} Yuji Watanuki,² Tetsuji Kaneko,³ Takashi Sato,² Naoki Miyazawa,²
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14 Takeshi Kaneko,⁴ Yoshiaki Ishigatsubo,² Satoshi Morita,³ Yutaka Natsumeda,⁵ Shunsaku
15
16 Mizushima,¹

17
18
19
20
21
22 ¹Department of Epidemiology and Public Health, Yokohama City University Graduate
23
24 School of Medicine, 3-9 Fukuura, Kanazawa-ku Yokohama 236-0004 Japan

25
26
27 ²Department of Internal Medicine and Clinical Immunology, Yokohama City University
28
29 Graduate School of Medicine, Yokohama, Japan

30
31
32 ³Department of Biostatistics and Epidemiology, Yokohama City University Graduate
33
34 School of Medicine, Yokohama, Japan

35
36
37 ⁴Department of Pulmonary Medicine, Yokohama City University Graduate School of
38
39 Medicine, Yokohama, Japan

40
41
42 ⁵Department of Clinical Research, Yokohama City University Graduate School of
43
44 Medicine, Yokohama, Japan

45
46
47
48 Corresponding author:

49
50
51 Satoshi Inoue, MD, PhD

52
53
54 Tel: 81-45-787-2610

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56
57 Fax: 81-45-787-2609

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60 E-mail: ino999@yokohama-cu.ac.jp

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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

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

17 **Conclusion**

18
19 The efficacy of PPV23 against pulmonary infection and death of any cause might be
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21 unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs
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23 to be given to elderly patients with chronic pulmonary disease at an earlier time in
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25 which infectious complications in the lung have not yet occurred.
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32 **Summary**

33 ● Article focus (hypothesis):

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35 The efficacy of PPV23 might be compromised by an episode of pulmonary infection in
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37 the pre-vaccine period or chronic respiratory failure in elderly patients with chronic
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39 pulmonary disease.
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43 ● Key messages:

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45 1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the
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47 pre-vaccine period.
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51 2. The event rate could be reduced by PPV23 in patients with noninfectious
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53 complications such as chronic respiratory failure.
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57 3. Elderly patients with chronic pulmonary disease need to receive the PPV23
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59 vaccination at an earlier time in which infectious complications in the lung have not yet
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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]

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6 We previously reported a 2-year cohort clinical study of elderly outpatients with
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8 chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial
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10 and pneumococcal pulmonary infection onset and outcome.[14] Analysis of the
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12 comparison between the vaccinated and unvaccinated group showed a decline in the
13
14 incidence of bacterial pulmonary infection only in the vaccinated group. This result
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16 might be associated with PPV23 effectiveness, although detailed background
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18 information regarding underlying pulmonary conditions was not provided. Subgroup
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20 analysis needs to be carried out since chronic pulmonary disease includes various
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22 clinical and pathophysiological pictures. Underlying pulmonary diseases could cause
23
24 chronic respiratory failure if repeatedly complicated by lung infections, and such
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26 heterogeneity may generate different outcomes after vaccination.[15] We decided to
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28 reanalyse the data to study the influence of clinical background during the pre-vaccine
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30 period on PPV23 efficacy in elderly patients with chronic pulmonary disease.
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38 **METHODS**

39 **Study population**

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

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

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41 Participants were followed from December 2002 to the end of the study in November
42 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as
43 clinical status remained stable. A diagnosis of pulmonary infection was made by
44 respiratory physicians according to the Japanese Respiratory Society Guidelines for the
45 Management of Community-Acquired Pneumonia in Adults. In brief, patients were
46 diagnosed with an infectious lung complication when they presented with fever
47 (≥ 38 °C), cough, yellow sputum, or chest pain and blood testing revealed marked
48 inflammatory responses such as elevated levels of neutrophils and serum C-reactive
49 protein. Chest radiography was performed when an infective inflammatory process in
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6 the lung was suspected to distinguish pneumonia from acute bronchitis or infectious
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8 exacerbation of chronic bronchitis. In addition to a urinary pneumococcal antigen test,
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10 Gram staining and sputum culture were conducted when a diagnosis of bacterial
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12 pulmonary infection was made to determine the causative microorganisms and the
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14 pattern of antibiotic susceptibility. Empirical antibiotic therapy was started promptly
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16 after diagnosis of infection in the lung was made. The initial treatment was replaced by
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18 second-line therapy of antibiotics chosen according to the sensitivity results.
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24 **Event of interest**

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26 We hypothesised that repeated pulmonary infection and concomitant gradual loss of
27
28 lung function might be related to a reduced PPV23 efficacy. Participants were grouped
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30 based on these factors: frequency of infectious (including pneumococcal) pulmonary
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32 infection episode within 1 year prior to the PPV23 vaccination (0 episodes, 1 episode,
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34 and >1 episode), and chronic respiratory failure represented by HOT usage. Events of
35
36 interest included the first episode of bacterial or pneumococcal pulmonary infection
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38 (pneumonia, acute bronchitis, or exacerbation of chronic bronchitis) where antibiotic
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40 treatment was required, and death of any cause. The case of death with missing values
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42 was not counted as an event of interest but was included in the mortality rate.
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50 **Statistical analysis**

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52 Differences in event rates were depicted with Kaplan-Meier curves, and the log-rank
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54 test was applied for analysis. Cross-tabulated data were compared by the Wilcoxon test
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56 or the Pearson's chi-square test. Relative risks for the events were estimated using the
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58 Cox proportional hazards regression model. The PASW statistics 18 (SPSS Inc. IL,
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6 USA) and SAS software (SAS Institute Inc. NC, USA) were used for the statistical
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8 analysis.
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10 11 12 13 **RESULTS**

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15 A total of 1,378 patients ≥ 60 years old with chronic pulmonary disease were enrolled in
16
17 this study between August and November 2002. The pre-vaccine period was defined as
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19 1 year prior to PPV23 vaccination (August 2001 to August 2002). Patient characteristics
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21 are shown in Table 1. In the group without pulmonary infection during the pre-vaccine
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23 period, significant reductions in vaccination rate, age, and frequency of chronic
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25 respiratory failure were observed compared with the other 2 groups with at least 1
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27 episode of infectious lung complications. No significant gender difference was seen
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29 among groups.
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34 The effects of underlying pulmonary conditions on event occurrences were analysed
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36 before PPV23 effectiveness were evaluated. The survival rate in the Kaplan-Meier
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38 method dropped significantly as the frequency of pulmonary infection in the
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40 pre-vaccine period increased (Figure 1). Chronic respiratory failure was associated with
41
42 a significant event rate increase only in the absence of pulmonary infection in the
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44 pre-vaccine period (Table 2). A higher mortality rate was seen in patients with
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46 pulmonary infection during the pre-vaccine period and in chronic pulmonary failure (p
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48 < 0.001).
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53 Participants were not randomly assigned to groups; vaccination was chosen or
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55 declined by each individual. As a result, the number of vaccinated patients was
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57 significantly higher than the number of unvaccinated patients when pulmonary infection
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59 occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness
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6 was seen between the vaccinated and unvaccinated group in the Kaplan-Meier method
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8 (log rank test, $p = 0.391$). The mortality rate was, however, significantly high in the
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10 vaccinated group (log-rank test, $p = 0.008$). This result may be misleading due to the
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12 vaccination imbalance among groups. The Cox proportional hazards regression model
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14 applied for covariate adjustment showed that the episodes of pulmonary infection and
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16 chronic respiratory failure in the pre-vaccine period were associated with an increased
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18 risk of pulmonary infection and death after PPV23 vaccination (Table 3). No significant
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20 effects of PPV23 on mortality rate were observed (Table 3). These results suggested the
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22 following: PPV23 efficacy might be compromised by some factors such as pulmonary
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24 infection in the pre-vaccine period or chronic respiratory failure; and imbalance of
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26 PPV23 distribution among the groups may be associated with an increased mortality
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28 rate in the vaccinated group.
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34 A subgroup analysis was performed to find the ideal condition for PPV23 use in
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36 elderly patients with chronic pulmonary disease. There are no significant differences
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38 between vaccinated and unvaccinated patients when grouped only by frequency of
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40 pulmonary infection in the pre-vaccine period (not shown). The event rate was
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42 somewhat reduced when patients with chronic respiratory failure were vaccinated ($p =$
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44 0.071). This effectiveness became significant when patients who had an episode of
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46 pulmonary infection in the pre-vaccine period were excluded (Figure 2). Of note, the
47
48 final event-free survival rate was 0.755, which was close to the levels observed in
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50 patients who had not had an episode of pulmonary infection and chronic respiratory
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52 failure during the pre-vaccine period (Table 4). These results suggest that PPV23 might
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54 provide beneficial effects in elderly patients with chronic respiratory failure if episodes
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56 of pulmonary infection during the pre-vaccine period did not occur.
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6 There were only 29 pneumococcal events during the observation period
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8 (pneumococcal pulmonary infection, 22; death, 7). The probability of pneumococcal
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10 events increased significantly in the presence of pulmonary infection during the
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12 pre-vaccine period (log-rank test, $p < 0.001$). No effects of chronic respiratory failure on
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14 survival rate were observed. PPV23 vaccination did not show significant protective
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16 effects against the development of pneumococcal events even after subgroup analysis
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18 (data not shown).
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24 **DISCUSSION**

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

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

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

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45 When informed consents were obtained prior to the study initiation, PPV23 vaccine
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47 recommendations were made and only participants who responded affirmatively
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49 received the vaccination. This method may be associated with these results: the
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51 vaccination rate increased significantly in high-risk patients who had at least 1 episode
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53 of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory
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55 failure; and the mortality rate was higher in vaccinated patients, although the presence
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57 of adverse effects of PPV23 is unlikely because PPV23 had generally been considered
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6 safe based on clinical experience since 1977.[7] In the Cox proportional hazards model,
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8 PPV23 was not a risk factor for the events. All of the participants in this study were
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10 elderly patients with chronic pulmonary disease, and all of them could be categorised
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12 into groups for which PPV23 vaccination is recommended in the United States and
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14 some European countries.[3, 7, 12] In Japan, no vaccine recommendations against
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16 pneumococcal infection are issued by the Japanese Ministry of Health, Labor and
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18 Welfare.[26] Japanese participants need to accept some risks for the public benefit and
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20 not for their own if selected for the unvaccinated group. This condition is different from
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22 that in some developed countries where unvaccinated control subjects in clinical trials
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24 of the PPV23 vaccine could still be protected by previous vaccination and indirect
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26 immunity from other people, including children.[27-29] Pneumococcal infection was
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28 associated with increasing mortality rates, while the beneficial effects of PPV23 without
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30 any severe adverse events were suggested in some previous clinical trials.[1, 8, 13,
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32 30-31] Therefore, we decided to conduct a nonrandomised clinical study to ensure that
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34 participants were treated with respect and dignity.
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41 The diagnosis of pneumococcal disease was not made in the majority of patients
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43 who had pulmonary infections during the observation period. Identification of *S.*
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45 *pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However,
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47 compared to IPD defined as any condition in which *S. pneumonia* is identified in a
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49 normally sterile body site, microbiological diagnosis in the lower respiratory tract is
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51 ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for
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53 pneumococcal identification might be unreliable due to the technical difficulties in
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55 obtaining good-quality sputum and in distinguishing causative specimens from
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57 colonisation.[19, 32] The positive results in urine antigen testing might be related to
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6 previous infection or colonisation. It might be difficult to assess PPV23 effectiveness on
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8 pneumococcal pulmonary infection using these procedures. Blood cultures are
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10 recommended for patients hospitalised after a diagnosis of community-acquired
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12 pneumonia, although its cost-effectiveness has been questioned in several studies.[33]
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15 Less expensive, novel techniques for accurate diagnosis of pneumonia need to be
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17 developed.
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22 **Conclusions and policy implications**

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

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6 **Contributions:** SI analysed the data, and drafted and revised the paper. YW designed
7
8 the whole study, and collected the data from the clinical records of the participants. TK
9
10 wrote the statistical analysis plan, and analysed the data. TS, NM, TK and YI interpreted
11
12 the findings, and revised the draft paper. SM, YN and SM supervised data analysis and
13
14 assessment.
15

16
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18
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21

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23

24 **Ethical approval:** Full approval of Institutional Review Board in the Kanagawa
25
26 Cardiovascular and Respiratory Diseases Centre was obtained prior to the study
27
28 initiation.
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31 **Data sharing:** No additional data available.
32

33 **Acknowledgement**

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

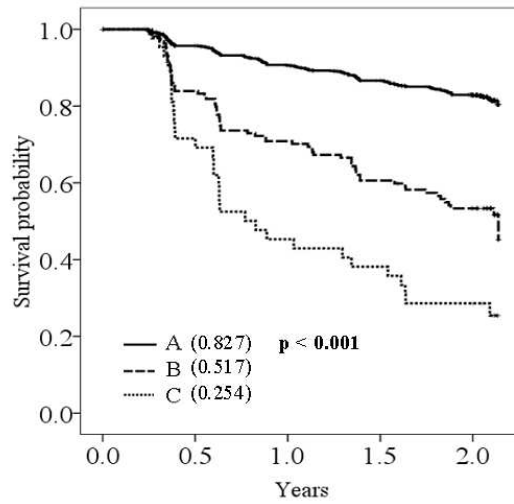
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	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.

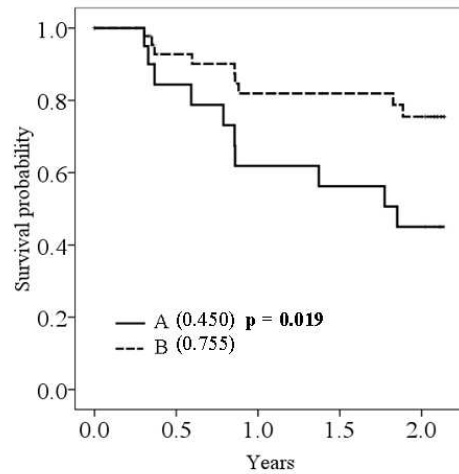
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Kaplan-Meier survival curves of patients with/without episodes of pulmonary infection during the pre-vaccine period: A, 0 episodes; B, 1 episode; C, > 1 episode
Numbers in parenthesis indicate the survival rate at the end of the study.

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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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000105.R1
Article Type:	Research
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Subject Heading:	Infectious diseases
Keywords:	Infection control < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE

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4 **Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine**
5 **caused by various underlying conditions of chronic pulmonary disease in elderly**
6 **patients**
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10 Satoshi Inoue,^{1,5} Yuji Watanuki,² Tetsuji Kaneko,³ Takashi Sato,² Naoki Miyazawa,²
11 Takeshi Kaneko,⁴ Yoshiaki Ishigatsubo,² Satoshi Morita,³ Yutaka Natsumeda,⁵ Shunsaku
12 Mizushima,¹
13
14
15

16
17
18 ¹Department of Epidemiology and Public Health, Yokohama City University Graduate
19 School of Medicine, 3-9 Fukuura, Kanazawa-ku Yokohama 236-0004 Japan
20
21

22 ²Department of Internal Medicine and Clinical Immunology, Yokohama City University
23 Graduate School of Medicine, Yokohama, Japan
24
25

26 ³Department of Biostatistics and Epidemiology, Yokohama City University Graduate
27 School of Medicine, Yokohama, Japan
28
29

30 ⁴Department of Pulmonary Medicine, Yokohama City University Graduate School of
31 Medicine, Yokohama, Japan
32
33

34 ⁵Department of Clinical Research, Yokohama City University Graduate School of
35 Medicine, Yokohama, Japan
36
37
38
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40 Corresponding author:

41
42 Satoshi Inoue, MD, PhD

43
44 Tel: 81-45-787-2610

45
46 Fax: 81-45-787-2609

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48 E-mail: ino999@yokohama-cu.ac.jp
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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.

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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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4 regression model, event-free survival decreased significantly when pulmonary infection
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6 occurred in the pre-vaccine period. In the subgroup analysis, the first episode of
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8 bacterial pulmonary infection (but not death of any cause) was reduced significantly by
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10 PPV23 only in patients with chronic respiratory failure who had no episodes of
11
12 pulmonary infection during the pre-vaccine period (p = 0.019).

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14 Conclusion

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16 The efficacy of PPV23 against pulmonary infection and death of any cause might be
17
18 unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs
19
20 to be given to elderly patients with chronic pulmonary disease at an earlier time in
21
22 which infectious complications in the lung have not yet occurred.

26 Summary

27 ● Article focus (hypothesis):

28
29 The efficacy of PPV23 might be compromised by an episode of pulmonary infection in
30
31 the pre-vaccine period or chronic respiratory failure in elderly patients with chronic
32
33 pulmonary disease.

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36 ● Key messages:

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38 1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the
39
40 pre-vaccine period.

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

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46 3. Elderly patients with chronic pulmonary disease need to receive the PPV23
47
48 vaccination at an earlier time in which infectious complications in the lung have not yet
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50 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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4 We previously reported a 2-year cohort clinical study of elderly outpatients with
5 chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial
6 and pneumococcal pulmonary infection onset and outcome.^[16] Analysis of the
7 comparison between the vaccinated and unvaccinated group showed a decline in the
8 incidence of bacterial pulmonary infection only in the vaccinated group. This result
9 might be associated with PPV23 effectiveness, although detailed background
10 information regarding underlying pulmonary conditions was not provided. Subgroup
11 analysis needs to be carried out since chronic pulmonary disease includes various
12 clinical and pathophysiological pictures. Underlying pulmonary diseases could cause
13 chronic respiratory failure if repeatedly complicated by lung infections, and such
14 heterogeneity may generate different outcomes after vaccination.^[17] We decided to
15 reanalyse the data to study the influence of clinical background during the pre-vaccine
16 period on PPV23 efficacy in elderly patients with chronic pulmonary disease.
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31 METHODS

32 Study population

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34 All the outpatients ≥ 60 years of age (a total of 1,378 participants at the start of the
35 study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory
36 Diseases Centre were included in this study. These patients were informed of the
37 prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic
38 pulmonary diseases in this study included bronchial asthma, chronic pulmonary
39 emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous
40 mycobacteria, and others (Table 1). Patients who presented with a fever (≥ 37.5 °C) were
41 excluded from the study according to the Preventive Vaccination Law issued by the
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4 Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these
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6 patients became stable, they were invited to participate in the study. Home oxygen
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8 therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS)
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10 Guidelines for 97 participants with chronic respiratory failure upon study initiation
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12 (Table 1), but no patients were newly prescribed HOT during the observation period.
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16 Study design

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

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46 Participants were followed from December 2002 to the end of the study in November
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48 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as
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50 clinical status remained stable. A diagnosis of pulmonary infection was made by
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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 $> 8,000/\text{mm}^3$, 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.

Deleted: 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.

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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Deleted: 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.

Deleted: Empirical antibiotic therapy was started promptly after diagnosis of infection in the lung was made.

Deleted: The doctors had access to the patients' vaccination record during the follow-up 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.¶

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

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

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

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40 When informed consents were obtained prior to the study initiation, PPV23 vaccine
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42 recommendations were made and only participants who responded affirmatively
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44 received the vaccination. This method may be associated with these results: the
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46 vaccination rate increased significantly in high-risk patients who had at least 1 episode
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48 of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory
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50 failure; and the mortality rate was higher in vaccinated patients, although the presence
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4 of adverse effects of PPV23 is unlikely because PPV23 had generally been considered
5 safe based on clinical experience since 1977.[7] In the Cox proportional hazards model,
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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.

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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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4 The diagnosis of pneumococcal disease was not made in the majority of patients
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6 who had pulmonary infections during the observation period. Identification of *S.*
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8 *pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However,
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10 compared to IPD defined as any condition in which *S. pneumonia* is identified in a
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12 normally sterile body site, microbiological diagnosis in the lower respiratory tract is
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14 ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for
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16 pneumococcal identification might be unreliable due to the technical difficulties in
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18 obtaining good-quality sputum and in distinguishing causative specimens from
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20 colonisation.[21] The positive results in urine antigen testing might be related to
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22 previous infection or colonisation.[33] It might be difficult to assess PPV23
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24 effectiveness on pneumococcal pulmonary infection using these procedures. Blood
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26 cultures are recommended for patients hospitalised after a diagnosis of
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28 community-acquired pneumonia, although its cost-effectiveness has been questioned in
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30 several studies.[34] Less expensive, novel techniques for accurate diagnosis of
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32 pneumonia need to be developed.
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34 35 36 **Conclusions and policy implications**

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

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	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

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*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.

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4 **Contributions:** SI analysed the data, and drafted and revised the paper. YW designed
5 the whole study, and collected the data from the clinical records of the participants. TK
6 wrote the statistical analysis plan, and analysed the data. TS, NM, TK and YI interpreted
7 the findings, and revised the draft paper. SM, YN and SM supervised data analysis and
8 assessment.
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15 public, commercial or not-for-profit sectors.
16

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18 **Competing interests:** None declared.
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21 **Ethical approval:** Full approval of Institutional Review Board in the Kanagawa
22 Cardiovascular and Respiratory Diseases Centre was obtained prior to the study
23 initiation.
24

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26 **Data sharing:** No additional data available.
27

28 **Acknowledgement**

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30 The material (clinical data) that had been used for ref. 14 is modified and printed with
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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.



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

Satoshi Inoue,^{1,5} Yuji Watanuki,² Tetsuji Kaneko,³ Takashi Sato,² Naoki Miyazawa,² Takeshi Kaneko,⁴ Yoshiaki Ishigatsubo,² Satoshi Morita,³ Yutaka Natsumeda,⁵ Shunsaku Mizushima,¹

¹Department of Epidemiology and Public Health, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku Yokohama 236-0004 Japan

²Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

³Department of Biostatistics and Epidemiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

⁴Department of Pulmonary Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan

⁵Department of Clinical Research, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Corresponding author:

Satoshi Inoue, MD, PhD

Tel: 81-45-787-2610

Fax: 81-45-787-2609

E-mail: ino999@yokohama-cu.ac.jp

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6 Key word: PPV23, chronic pulmonary disease, elderly patient, respiratory infection
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For peer review only

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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6 regression model, event-free survival decreased significantly when pulmonary infection
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8 occurred in the pre-vaccine period. In the subgroup analysis, the first episode of
9
10 bacterial pulmonary infection (but not death of any cause) was reduced significantly by
11
12 PPV23 only in patients with chronic respiratory failure who had no episodes of
13
14 pulmonary infection during the pre-vaccine period ($p = 0.019$).

17 **Conclusion**

18
19 The efficacy of PPV23 against pulmonary infection and death of any cause might be
20
21 unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs
22
23 to be given to elderly patients with chronic pulmonary disease at an earlier time in
24
25 which infectious complications in the lung have not yet occurred.
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32 **Summary**

33 ● Article focus (hypothesis):

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35 The efficacy of PPV23 might be compromised by an episode of pulmonary infection in
36
37 the pre-vaccine period or chronic respiratory failure in elderly patients with chronic
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39 pulmonary disease.
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43 ● Key messages:

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45 1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the
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47 pre-vaccine period.
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51 2. The episode of pulmonary infection could be prevented by PPV23 in elderly patients
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53 with noninfectious complications such as chronic respiratory failure.
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57 3. Elderly patients with chronic pulmonary disease need to receive the PPV23
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59 vaccination at an earlier time in which infectious complications in the lung have not yet
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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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6 We previously reported a 2-year cohort clinical study of elderly outpatients with
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8 chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial
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10 and pneumococcal pulmonary infection onset and outcome.[16] Analysis of the
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12 comparison between the vaccinated and unvaccinated group showed a decline in the
13
14 incidence of bacterial pulmonary infection only in the vaccinated group. This result
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16 might be associated with PPV23 effectiveness, although detailed background
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18 information regarding underlying pulmonary conditions was not provided. Subgroup
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20 analysis needs to be carried out since chronic pulmonary disease includes various
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22 clinical and pathophysiological pictures. Underlying pulmonary diseases could cause
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24 chronic respiratory failure if repeatedly complicated by lung infections, and such
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26 heterogeneity may generate different outcomes after vaccination.[17] We decided to
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28 reanalyse the data to study the influence of clinical background during the pre-vaccine
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30 period on PPV23 efficacy in elderly patients with chronic pulmonary disease.
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39 **METHODS**

40 **Study population**

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42 All the outpatients ≥ 60 years of age (a total of 1,378 participants at the start of the
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44 study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory
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46 Diseases Centre were included in this study. These patients were informed of the
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48 prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic
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50 pulmonary diseases in this study included bronchial asthma, chronic pulmonary
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52 emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous
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54 mycobacteria, and others (Table 1). Patients who presented with a fever (≥ 37.5 °C) were
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56 excluded from the study according to the Preventive Vaccination Law issued by the
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6 Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these
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8 patients became stable, they were invited to participate in the study. Home oxygen
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10 therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS)
11
12 Guidelines for 97 participants with chronic respiratory failure upon study initiation
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14 (Table 1), but no patients were newly prescribed HOT during the observation period.
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17 18 19 20 **Study design**

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

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55 Participants were followed from December 2002 to the end of the study in November
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57 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as
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59 clinical status remained stable. A diagnosis of pulmonary infection was made by
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6 respiratory physicians according to the Japanese Respiratory Society Guidelines for the
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8 Management of Community-Acquired Pneumonia in Adults. In brief, pulmonary
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10 infection was suspected if more than 2 of the following criteria were present:
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12 temperature ≥ 37.0 °C, white blood cell count $> 8,000/\text{mm}^3$, and C-reactive protein $>$
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14 0.7 mg/dl. A diagnosis of pneumonia was made when chest radiographs revealed
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16 alveolar opacities. If a cough with yellow sputum production was observed in the
17
18 absence of the alveolar opacities on the chest radiograph, the patients were diagnosed
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20 with acute bronchitis or exacerbation of chronic bronchitis. It was very difficult to
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22 clearly distinguish pneumonia from acute bronchitis or an acute exacerbation of chronic
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24 bronchitis in some patients since there were considerable clinical overlaps between
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26 these illnesses including the symptoms, blood test results, causative pathogens, and
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28 antibiotic treatment. Hence, pulmonary infection was expressed as a dichotomous
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30 variable.
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36 A diagnosis of pneumococcal pulmonary infection was made if *Streptococcus*
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38 *pneumoniae* was the dominant organism stained with Gram stain in the sputum smear or
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40 if the sputum culture was positive ($> 10^7$ colony forming units/ml). When *S.*
41
42 *pneumoniae* was not identified, patients were diagnosed with a pulmonary infection
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44 caused by an identified pathogen or with a bacterial pulmonary infection if no possible
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46 causative pathogen was detected but if the clinical data were highly suggestive of
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48 bacterial infection in the lung. Empirical antibiotic therapy was started in all the patients
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50 promptly once clinical data sufficient to satisfy the definition of pulmonary infection
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52 were obtained. The initial treatment was replaced by second-line therapy of antibiotics
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54 chosen according to the sensitivity results.
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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.

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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5 applied for covariate adjustment, no hazardous effects of PPV23 on the incidence or
6 timing of the first episode of pulmonary infection or death of any cause were observed.
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8 The hazard ratio for the first episode of pulmonary infection or death of any cause
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10 increased significantly due to some covariates such as pulmonary infection during the
11 pre-vaccine period and chronic respiratory failure. Other covariates including gender,
12 and age were not associated with the first episode of pulmonary infection but were
13 associated with death of any cause (Table 3). The cause of death (n = 85) among all the
14 participants during the observation period was shown in Supplemental Table B.
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25 A subgroup analysis was performed to find the ideal condition for PPV23 use in
26 elderly patients with chronic pulmonary disease. There are no significant differences in
27 pulmonary infection-free survival between vaccinated and unvaccinated patients when
28 grouped only by frequency of pulmonary infection in the pre-vaccine period (not
29 shown). Pulmonary infection-free survival was somewhat improved when patients with
30 chronic respiratory failure were vaccinated ($p = 0.078$). This effectiveness became
31 significant when patients who had at least 1 episode of pulmonary infection in the
32 pre-vaccine period were excluded (Figure 2) (Table 4). The mortality was not reduced
33 by PPV23 in patients with chronic respiratory failure who had no episodes of
34 pulmonary infection during the pre-vaccine period (Supplemental Figure F). The cause
35 of death (n = 9) among patients with chronic respiratory failure who had no episodes of
36 pulmonary infection during the pre-vaccine period was as follows: chronic respiratory
37 failure, 2; cerebrovascular disease, 2; and unknown, 1 in vaccinated patients and chronic
38 respiratory failure, 2; lung cancer, 1; and unknown, 1 in unvaccinated patients. In this
39 group, PPV23 was shown to have an effect on the first episode of pulmonary infection
40 but it did not reduce the number of deaths due to any cause.
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6 There were only 29 pneumococcal pulmonary infection during the observation
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8 period (pneumococcal pulmonary infection, 22; death, 7; Supplemental Table C). The
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10 pneumococcal pneumonia-free survival decreased significantly in the presence of
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12 pulmonary infection during the pre-vaccine period ($p < 0.001$; Supplemental Figure G).
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14 No effects of chronic respiratory failure on pneumococcal pneumonia-free survival were
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16 observed ($p = 0.196$). PPV23 vaccination did not show significant protective effects
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18 against the development of pneumococcal pneumonia (Supplemental Figure H).
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24 **DISCUSSION**

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26 The effects of the PPV23 vaccination on elderly patients with chronic pulmonary
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28 disease varied in accordance with the frequency of lung infection episodes and the
29
30 presence of chronic respiratory failure during the pre-vaccine period. Our findings
31
32 suggest the following: PPV23 vaccination might work effectively unless previous lung
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34 infection episodes had occurred; and subgroup analysis of the underlying disease
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36 associated with pneumococcal complications might be useful for finding the possible
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38 ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise
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40 PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the
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42 presence of pulmonary infection episodes prior to vaccination or chronic pulmonary
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44 failure in elderly patients with chronic pulmonary disease.
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53 **Comparison with other studies**

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55 Previous pulmonary infection was highly associated with poor clinical prognosis. This
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57 finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly
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59 people with chronic pulmonary disease in the presence of infectious complications
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6 during the pre-vaccine period. In a multicentre double-blind controlled study conducted
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8 in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly
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10 non-immunocompromised individuals who had been treated for community-acquired
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12 pneumonia.[18] In that study, the survival rate calculated by the Kaplan-Meier method
13
14 was still >80% in both vaccinated and unvaccinated populations after 2-year
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16 observation, while our results showed that the survival rate was <60% if episodes of
17
18 pulmonary infection had occurred within 1 year prior to vaccination. These results are
19
20 consistent with previous suggestions that chronic pulmonary disease such as chronic
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22 obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that
23
24 protective effects of PPV23 could not be obtained.[19-21] Conflicting results were
25
26 shown in some other reports in which the beneficial effects of PPV23 in patients with
27
28 COPD were indicated, although previous episodes of pneumonia prior to vaccination
29
30 were not considered and participants were not limited to the elderly.[13, 22] Alfageme
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32 et al showed PPV23 effectiveness in patients <65 years of age with COPD in a
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34 randomised controlled study in 596 patients.[23] These results and our data indicate that
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36 PPV23 might be inefficacious on the elderly population with chronic pulmonary disease
37
38 especially when complicated by lung infection prior to the vaccination. Despite the
39
40 strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD),
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42 altered immune response, disruption of a physical barrier in the airways due to
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44 progressive chronic pulmonary disease, and repeated pulmonary infection could
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46 compromise the benefits.[1, 24] PPV23 vaccination should be given to patients with
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48 chronic pulmonary disease at an earlier stage in which infectious complications have not
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50 yet occurred.
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The probability of survival was significantly increased by PPV23 in the presence of

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6 chronic respiratory failure in patients without episodes of pulmonary infection during
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8 the pre-vaccine period. The pulmonary infection-free survival rate was 75.5% at the end
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10 of the observation period when PPV23 was given. Without PPV23, survival was
11
12 reduced to 45.0%, almost the same level as that in the case where infectious lung
13
14 complications had occurred during the pre-vaccine period. This result indicates that
15
16 pulmonary infection due to chronic respiratory failure could be prevented by the PPV23
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18 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be
19
20 administered in COPD patients when airflow is severe and chronic respiratory failure is
21
22 present, but these treatments were suggested to be risk factors for community-acquired
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24 pneumonia.[25-27] Additionally, bacterial colonisation of the distal airway may occur
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26 due to the altered pulmonary defense.[24] We suggest that patients receive the PPV23
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28 vaccination soon after the diagnosis of chronic respiratory disease such as COPD,
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30 especially when maintenance treatments for impaired lung function are expected to be
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32 risk factors for pneumonia. In this study, the number of participants with chronic
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34 respiratory failure who were free of lung infections during the pre-vaccine period was
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36 only 70. Thus, a large scale study is warranted.
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46 **Strengths and limitations of the study**

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48 When informed consents were obtained prior to the study initiation, PPV23 vaccine
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50 recommendations were made and only participants who responded affirmatively
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52 received the vaccination. This method may be associated with these results: the
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54 vaccination rate increased significantly in high-risk patients who had at least 1 episode
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56 of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory
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58 failure; and the mortality rate was higher in vaccinated patients, although the presence
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6 of adverse effects of PPV23 is unlikely because PPV23 had generally been considered
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8 safe based on clinical experience since 1977.[7] In the Cox proportional hazards model,
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10 PPV23 was not a risk factor for the events. All of the participants in this study were
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12 elderly patients with chronic pulmonary disease, and all of them could be categorised
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14 into groups for which PPV23 vaccination is recommended in the United States and
15
16 some European countries.[3, 7, 14] In Japan, no vaccine recommendations against
17
18 pneumococcal infection are issued by the Japanese Ministry of Health, Labour and
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20 Welfare.[11] Japanese participants need to accept some risks for the public benefit and
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22 not for their own if selected for the unvaccinated group. This condition is different from
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24 that in some developed countries where unvaccinated control subjects in clinical trials
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26 of the PPV23 vaccine could still be protected by previous vaccination and indirect
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28 immunity from other people, including children.[28-30] Pneumococcal infection was
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30 associated with increasing mortality rates, while the beneficial effects of PPV23 without
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32 any severe adverse events were suggested in some previous clinical trials.[1, 8, 15,
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34 31-32] Therefore, we decided to conduct a nonrandomised clinical study to ensure that
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36 participants were treated with respect and dignity.
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44 The doctors had access to the patients' vaccination record during the observation
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46 period. However, at the time of this study, PPV23 had already been approved by the
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48 Japanese Ministry of Health, Labour and Welfare, and there were no conflicts of interest
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50 with pharmaceutical companies. All the treatments were supported by the public health
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52 care system funded by the Japanese government; no specific grants were provided from
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54 any funding agencies. Diagnosis of pulmonary infection was made according to the
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56 same diagnostic criteria. Therefore it is unlikely that treatment bias occurred during the
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58 observation period.
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6 The diagnosis of pneumococcal disease was not made in the majority of patients
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8 who had pulmonary infections during the observation period. Identification of *S.*
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10 *pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However,
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12 compared to IPD defined as any condition in which *S. pneumonia* is identified in a
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14 normally sterile body site, microbiological diagnosis in the lower respiratory tract is
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16 ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for
17
18 pneumococcal identification might be unreliable due to the technical difficulties in
19
20 obtaining good-quality sputum and in distinguishing causative specimens from
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22 colonisation.[21] The positive results in urine antigen testing might be related to
23
24 previous infection or colonisation.[33] It might be difficult to assess PPV23
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26 effectiveness on pneumococcal pulmonary infection using these procedures. Blood
27
28 cultures are recommended for patients hospitalised after a diagnosis of
29
30 community-acquired pneumonia, although its cost-effectiveness has been questioned in
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32 several studies.[34] Less expensive, novel techniques for accurate diagnosis of
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34 pneumonia need to be developed.
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43 **Conclusions and policy implications**

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

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.

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6 **Contributions:** SI was responsible for interpretation of the data, and drafted, revised the
7 manuscript. YW was responsible for study design, collection and interpretation of the
8 data. TK and SM provided statistical support including analysis of the data and training
9 in the use of statistical software. TK and SM also drafted the statistical analysis part in
10 the manuscript. TS, NM, TK and YI helped interpreting the findings and contributed to
11 critical revision of the drafted manuscript, particularly regarding pulmonary infection
12 issues. YN and SM helped interpreting the data, provided very useful suggestion
13 regarding immunization and public health policy, and revised the drafted manuscript.
14 All authors approved the final version of the manuscript.
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28 public, commercial or not-for-profit sectors.
29

30
31 **Competing interests:** None declared.
32

33
34 **Ethical approval:** Full approval of Institutional Review Board in the Kanagawa
35 Cardiovascular and Respiratory Diseases Centre was obtained prior to the study
36 initiation.
37
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41 **Data sharing:** No additional data available.
42

43 **Acknowledgement**

44
45 The material (clinical data) that had been used for ref. 14 is modified and printed with
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

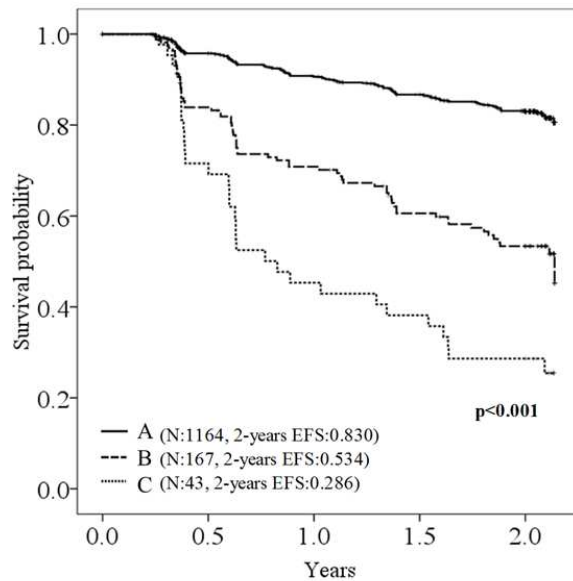
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-5
Introduction			
Background/rationale	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



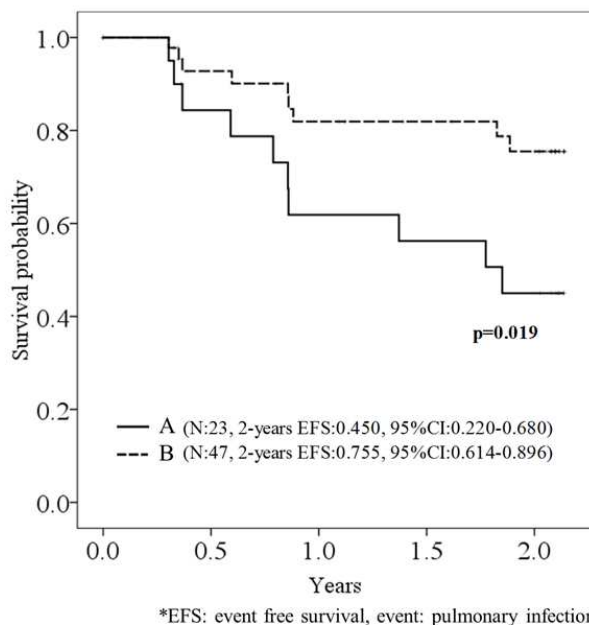
*EFS: event free survival, event: pulmonary infection

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

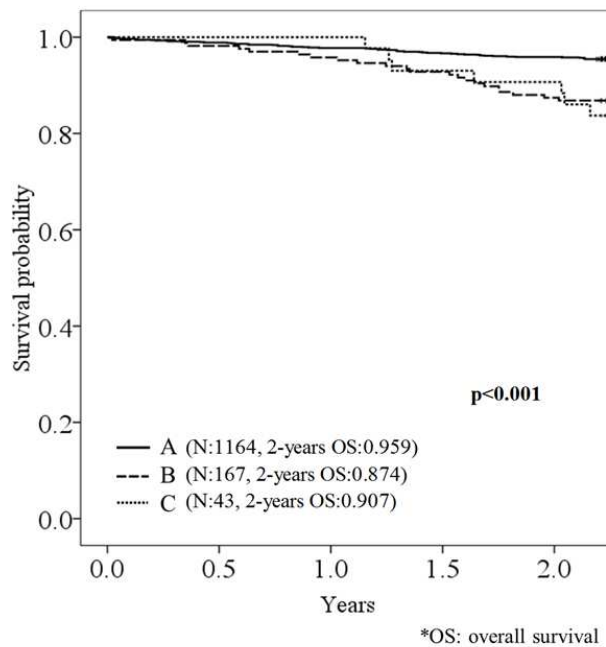


Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
 Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

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Figure A

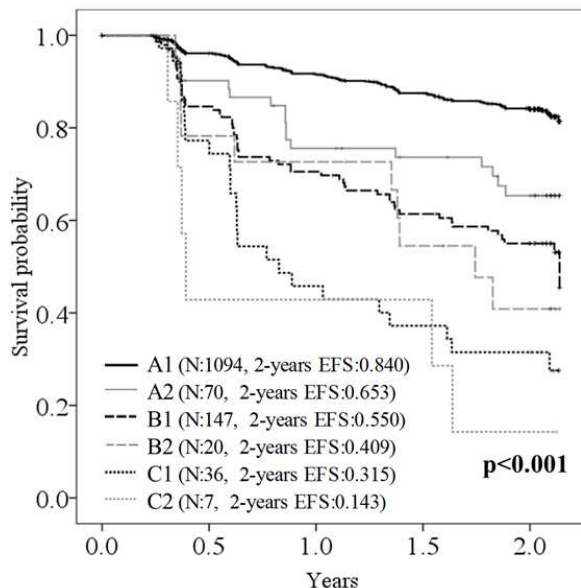


Kaplan-Meier curves showing the proportion of patients free of death during the observation period
Frequency of pulmonary infection during the pre-vaccine period: 0 episodes, A; one episode, B;
more than one episode, C

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Figure B



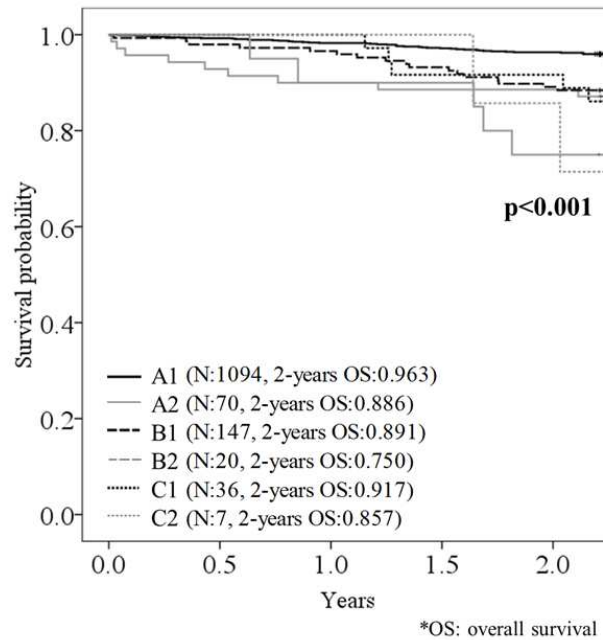
*EFS: event-free survival, event: pulmonary infection

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)

only

Figure C



Kaplan-Meier curves showing the proportion of patients free of death during the observation period

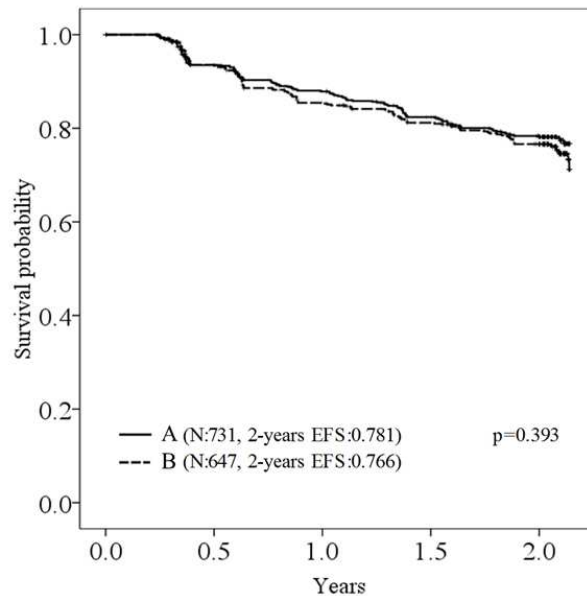
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2

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

254x190mm (96 x 96 DPI)

Figure D



*EFS: event-free survival, event: pulmonary infection

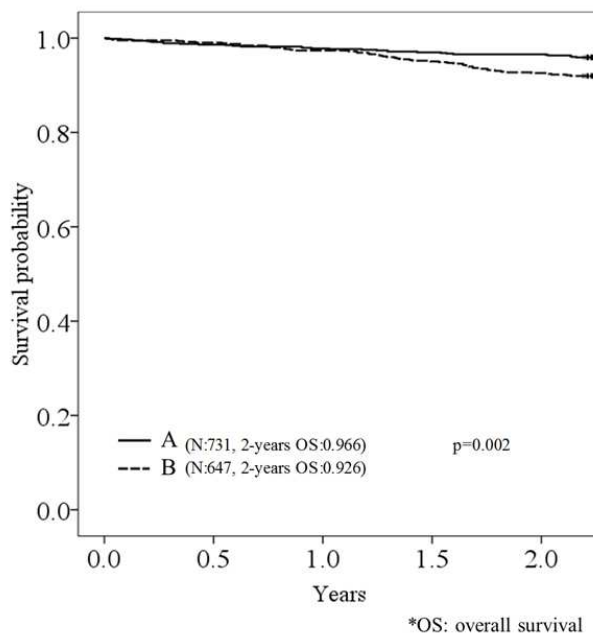
Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period

All the participants: unvaccinated, A; vaccinated, B

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Figure E



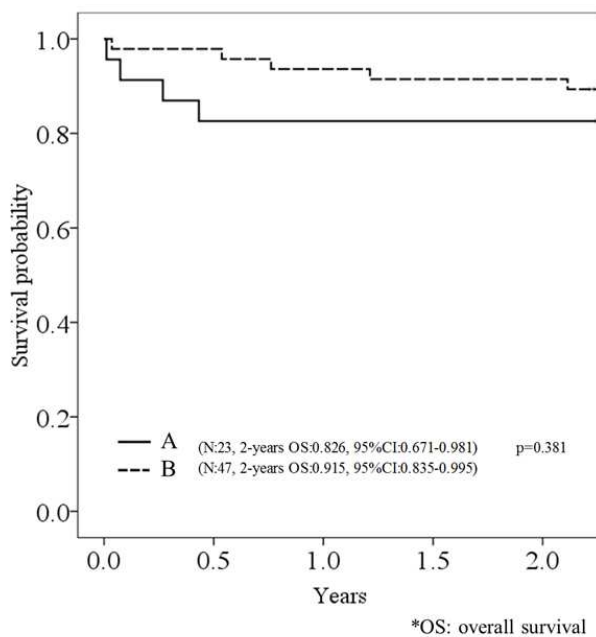
Kaplan-Meier curves showing the proportion of patients free of death during the observation period
All the participants: unvaccinated, A; vaccinated, B

254x190mm (96 x 96 DPI)

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Figure F

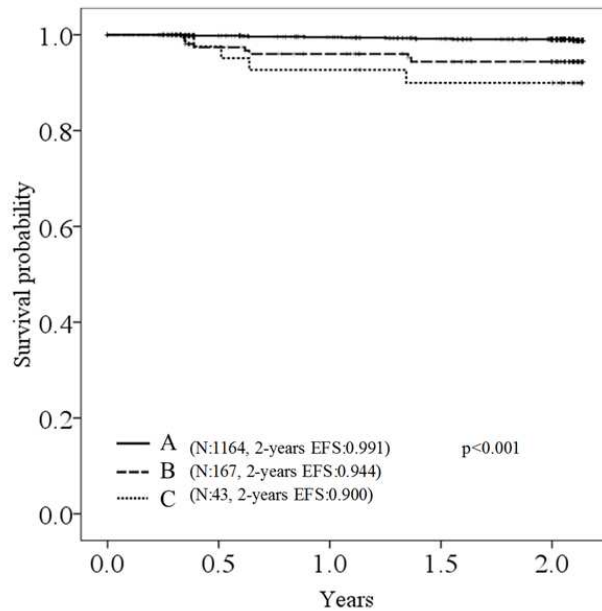


Kaplan-Meier curves showing the proportion of patients free of death during the observation period
 Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-
 vaccine period: unvaccinated, A; vaccinated, B

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Figure G



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

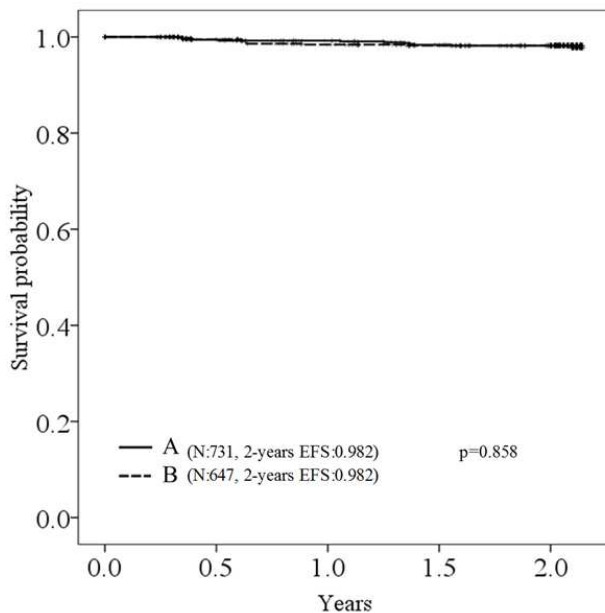
Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period

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



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

Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period

All the participants: unvaccinated, A; vaccinated, B

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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.



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000105.R3
Article Type:	Research
Date Submitted by the Author:	05-May-2011
Complete List of Authors:	Inoue, Satoshi; Yokohama City University, Department of Epidemiology and Public Health Watanuki, Yuji Kaneko, Tetsuji Sato, Takashi Miyazawa, Naoki Kaneko, Takeshi Ishigatsubo, Yoshiaki Morita, Satoshi Natsumeda, Yutaka Mizushima, Shunsaku
Subject Heading:	Infectious diseases
Keywords:	Infection control < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE

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Manuscripts

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4 **Heterogeneity of the efficacy of the 23-valent pneumococcal polysaccharide vaccine**
5 **caused by various underlying conditions of chronic pulmonary disease in elderly**
6 **patients: Prospective cohort study**
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10 Satoshi Inoue,^{1,5} Yuji Watanuki,² Tetsuji Kaneko,³ Takashi Sato,² Naoki Miyazawa,²
11 Takeshi Kaneko,⁴ Yoshiaki Ishigatsubo,² Satoshi Morita,³ Yutaka Natsumeda,⁵ Shunsaku
12 Mizushima,¹
13
14
15

16
17
18 ¹Department of Epidemiology and Public Health, Yokohama City University Graduate
19 School of Medicine, 3-9 Fukuura, Kanazawa-ku Yokohama 236-0004 Japan
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21

22 ²Department of Internal Medicine and Clinical Immunology, Yokohama City University
23 Graduate School of Medicine, Yokohama, Japan
24
25

26 ³Department of Biostatistics and Epidemiology, Yokohama City University Graduate
27 School of Medicine, Yokohama, Japan
28
29

30 ⁴Department of Pulmonary Medicine, Yokohama City University Graduate School of
31 Medicine, Yokohama, Japan
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34 ⁵Department of Clinical Research, Yokohama City University Graduate School of
35 Medicine, Yokohama, Japan
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40 Corresponding author:

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42 Satoshi Inoue, MD, PhD

43
44 Tel: 81-45-787-2610

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46 Fax: 81-45-787-2609

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48 E-mail: ino999@yokohama-cu.ac.jp
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Key word: PPV23, chronic pulmonary disease, elderly patient, respiratory infection

Word count: 3262

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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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4 regression model, event-free survival decreased significantly when pulmonary infection
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6 occurred in the pre-vaccine period. In the subgroup analysis, the first episode of
7
8 bacterial pulmonary infection (but not death of any cause) was reduced significantly by
9
10 PPV23 only in patients with chronic respiratory failure who had no episodes of
11
12 pulmonary infection during the pre-vaccine period ($p = 0.019$).

14 **Conclusion**

15
16 The efficacy of PPV23 against pulmonary infection and death of any cause might be
17
18 unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs
19
20 to be given to elderly patients with chronic pulmonary disease at an earlier time in
21
22 which infectious complications in the lung have not yet occurred.
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26 **Summary**

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29 • Article focus (hypothesis):

30
31 The efficacy of PPV23 might be compromised by an episode of pulmonary infection in
32
33 the pre-vaccine period or chronic respiratory failure in elderly patients with chronic
34
35 pulmonary disease.
36

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38 • Key messages:

- 39
40 1. The PPV23 efficacy might be unachievable if pulmonary infection occurs during the
41
42 pre-vaccine period.
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44 2. The episode of pulmonary infection could be prevented by PPV23 in elderly patients
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46 with noninfectious complications such as chronic respiratory failure.
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48 3. Elderly patients with chronic pulmonary disease need to receive the PPV23
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50 vaccination at an earlier time in which infectious complications in the lung have not yet
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4 occurred.

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6 • Strengths and limitations of this study:

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

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

22
23 *Streptococcus pneumoniae* continues to be one of the main causative pathogens in
24 community-acquired pneumonia and meningitis.[1-2] Due to the high mortality rate of *S.*
25 *pneumoniae* infections, especially in elderly and very young patients, prophylactic use
26 of 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for people
27 at an increased risk of pneumococcal disease in developed countries.[3-7] The efficacy
28 of PPV23, however, remains controversial. Despite the fact that the results of pre- and
29 post-licensed trials in immunocompetent people were supportive of regulatory approval
30 of vaccine use, clinical studies in elderly or young adults with comorbidities in
31 developed countries produced little convincing evidence of effectiveness against a
32 common manifestation of pneumococcal infections such as pneumonia.[8-12] A
33 retrospective study conducted in 1999 suggested that PPV23 was associated with
34 significant reductions in hospitalisation and mortality rates of elderly patients with
35 chronic lung disease and contributed to medical care cost savings, although
36 meta-analytical reviews published thereafter failed to show statistically significant
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4 evidence of the protective effects of PPV23 against the development of pneumonia in
5 elderly patients with chronic illnesses.[13-15]
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8 We previously reported a 2-year cohort clinical study of elderly outpatients with
9 chronic pulmonary disease to investigate the prophylactic effects of PPV23 on bacterial
10 and pneumococcal pulmonary infection onset and outcome.[16] Analysis of the
11 comparison between the vaccinated and unvaccinated group showed a decline in the
12 incidence of bacterial pulmonary infection only in the vaccinated group. This result
13 might be associated with PPV23 effectiveness, although detailed background
14 information regarding underlying pulmonary conditions was not provided. Subgroup
15 analysis needs to be carried out since chronic pulmonary disease includes various
16 clinical and pathophysiological pictures. Underlying pulmonary diseases could cause
17 chronic respiratory failure if repeatedly complicated by lung infections, and such
18 heterogeneity may generate different outcomes after vaccination.[17] We decided to
19 reanalyse the data to study the influence of clinical background during the pre-vaccine
20 period on PPV23 efficacy in elderly patients with chronic pulmonary disease.
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36 **METHODS**

37 **Study population**

38 All the outpatients ≥ 60 years of age (a total of 1,378 participants at the start of the
39 study) with chronic pulmonary disease in the Kanagawa Cardiovascular and Respiratory
40 Diseases Centre were included in this study. These patients were informed of the
41 prophylactic effects of PPV23 on infectious pulmonary exacerbations. Chronic
42 pulmonary diseases in this study included bronchial asthma, chronic pulmonary
43 emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, nontuberculous
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4 mycobacteria, and others (Table 1). Patients who presented with a fever (≥ 37.5 °C) were
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6 excluded from the study according to the Preventive Vaccination Law issued by the
7
8 Japanese Ministry of Health, Labour and Welfare. Once the clinical status of these
9
10 patients became stable, they were invited to participate in the study. Home oxygen
11
12 therapy (HOT) had been prescribed according to the Japanese Respiratory Society (JRS)
13
14 Guidelines for 97 participants with chronic respiratory failure upon study initiation
15
16 (Table 1), but no patients were newly prescribed HOT during the observation period.
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20 **Study design**

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22 We did not adopt a randomised controlled study design since the PPV23 vaccination is
23
24 considered a part of standard care in many developed countries. Additionally, some
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26 elderly participants with chronic pulmonary disease were in an immunocompromised
27
28 status; therefore, a randomised controlled study of vaccine effectiveness may violate
29
30 ethical principles and human rights. Written informed consent forms were obtained from
31
32 all participants. To avoid selection bias, doctors and other medical staffs were not
33
34 allowed to assign patients to the vaccine or non-vaccine group; instead, individual
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36 patients decided whether or not to be vaccinated. The same form, which included an
37
38 explanation of the study, was provided to all the participants. A total of 647 patients
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40 were injected with PPV23 (Pneumovax, Merck, NJ, USA) intramuscularly into their
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42 non-dominant upper arm with between August and November 2002. The pre-vaccine
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44 period was defined as 1 year prior to PPV23 vaccination (August 2001 to July 2002).
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49 **Data collection**

50 Participants were followed from December 2002 to the end of the study in November
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4 2004 (for 2 years) or until death in the clinic approximately every 2 months as long as
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6 clinical status remained stable. A diagnosis of pulmonary infection was made by
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8 respiratory physicians according to the Japanese Respiratory Society Guidelines for the
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10 Management of Community-Acquired Pneumonia in Adults. In brief, pulmonary
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12 infection was suspected if more than 2 of the following criteria were present:
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14 temperature ≥ 37.0 °C, white blood cell count $> 8,000/\text{mm}^3$, and C-reactive protein $>$
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16 0.7 mg/dl. A diagnosis of pneumonia was made when chest radiographs revealed
17
18 alveolar opacities. If a cough with yellow sputum production was observed in the
19
20 absence of the alveolar opacities on the chest radiograph, the patients were diagnosed
21
22 with acute bronchitis or exacerbation of chronic bronchitis. It was very difficult to
23
24 clearly distinguish pneumonia from acute bronchitis or an acute exacerbation of chronic
25
26 bronchitis in some patients since there were considerable clinical overlaps between
27
28 these illnesses including the symptoms, blood test results, causative pathogens, and
29
30 antibiotic treatment. Hence, pulmonary infection was expressed as a dichotomous
31
32 variable.

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34 A diagnosis of pneumococcal pulmonary infection was made if *Streptococcus*
35
36 *pneumoniae* was the dominant organism stained with Gram stain in the sputum smear or
37
38 if the sputum culture was positive ($> 10^7$ colony forming units/ml). When *S.*
39
40 *pneumoniae* was not identified, patients were diagnosed with a pulmonary infection
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42 caused by an identified pathogen or with a bacterial pulmonary infection if no possible
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44 causative pathogen was detected but if the clinical data were highly suggestive of
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46 bacterial infection in the lung. Empirical antibiotic therapy was started in all the patients
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48 promptly once clinical data sufficient to satisfy the definition of pulmonary infection
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50 were obtained. The initial treatment was replaced by second-line therapy of antibiotics
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4 chosen according to the sensitivity results.
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8 **Event of interest**

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

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

11 Participant characteristics are shown in Table 1. Significant reductions in vaccination
12 rate, age, and frequency of chronic respiratory failure were observed in the group
13 without pulmonary infection during the pre-vaccine period compared with the other 2
14 groups with at least 1 episode of infectious lung complications. No significant gender
15 difference was seen among groups.
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22 The effects of underlying pulmonary conditions on event occurrences were analysed
23 before PPV23 effectiveness were evaluated. Event-free survival in the Kaplan-Meier
24 method dropped significantly as the frequency of pulmonary infection in the
25 pre-vaccine period increased: the first episode of pulmonary infection, Figure 1; death
26 of any cause, Supplemental Figure A. Chronic respiratory failure was associated with a
27 significant decrease in event-free survival only in the absence of pulmonary infection in
28 the pre-vaccine period: the first episode of pulmonary infection, Supplemental Figure B,
29 Table 2; death of any cause, Supplemental Figure C, Supplemental Table A.
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38 Participants were not randomly assigned to groups; vaccination was chosen or
39 declined by each individual. As a result, the number of vaccinated patients was
40 significantly higher than the number of unvaccinated patients when pulmonary infection
41 occurred during the pre-vaccine period (Table 1). No significant PPV23 effectiveness
42 against the development of first episode of pulmonary infection during the observation
43 period was seen between the vaccinated and unvaccinated group in the Kaplan-Meier
44 method (Supplemental Figure D). The mortality rate was, however, significantly high in
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4 the vaccinated group (Supplemental Figure E). This result may be misleading due to the
5 vaccination imbalance among groups. In the Cox proportional hazards regression model
6 applied for covariate adjustment, no hazardous effects of PPV23 on the incidence or
7 timing of the first episode of pulmonary infection or death of any cause were observed.
8
9 The hazard ratio for the first episode of pulmonary infection or death of any cause
10 increased significantly due to some covariates such as pulmonary infection during the
11 pre-vaccine period and chronic respiratory failure. Other covariates including gender,
12 and age were not associated with the first episode of pulmonary infection but were
13 associated with death of any cause (Table 3). The cause of death (n = 85) among all the
14 participants during the observation period was shown in Supplemental Table B.
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24 A subgroup analysis was performed to find the ideal condition for PPV23 use in
25 elderly patients with chronic pulmonary disease. There are no significant differences in
26 pulmonary infection-free survival between vaccinated and unvaccinated patients when
27 grouped only by frequency of pulmonary infection in the pre-vaccine period (not
28 shown). Pulmonary infection-free survival was somewhat improved when patients with
29 chronic respiratory failure were vaccinated (p = 0.078). This effectiveness became
30 significant when patients who had at least 1 episode of pulmonary infection in the
31 pre-vaccine period were excluded (Figure 2) (Table 4). The mortality was not reduced
32 by PPV23 in patients with chronic respiratory failure who had no episodes of
33 pulmonary infection during the pre-vaccine period (Supplemental Figure F). The cause
34 of death (n = 9) among patients with chronic respiratory failure who had no episodes of
35 pulmonary infection during the pre-vaccine period was as follows: chronic respiratory
36 failure, 2; cerebrovascular disease, 2; and unknown, 1 in vaccinated patients and chronic
37 respiratory failure, 2; lung cancer, 1; and unknown, 1 in unvaccinated patients. In this
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4 group, PPV23 was shown to have an effect on the first episode of pulmonary infection
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6 but it did not reduce the number of deaths due to any cause.
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9 There were only 29 pneumococcal pulmonary infection during the observation
10 period (pneumococcal pulmonary infection, 22; death, 7; Supplemental Table C). The
11 pneumococcal pneumonia-free survival decreased significantly in the presence of
12 pulmonary infection during the pre-vaccine period ($p < 0.001$; Supplemental Figure G).
13
14 No effects of chronic respiratory failure on pneumococcal pneumonia-free survival were
15 observed ($p = 0.196$). PPV23 vaccination did not show significant protective effects
16 against the development of pneumococcal pneumonia (Supplemental Figure H).
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24 **DISCUSSION**

25
26 The effects of the PPV23 vaccination on elderly patients with chronic pulmonary
27 disease varied in accordance with the frequency of lung infection episodes and the
28 presence of chronic respiratory failure during the pre-vaccine period. Our findings
29 suggest the following: PPV23 vaccination might work effectively unless previous lung
30 infection episodes had occurred; and subgroup analysis of the underlying disease
31 associated with pneumococcal complications might be useful for finding the possible
32 ideal conditions for PPV23 use. To our knowledge, this is the first report to characterise
33 PPV23 effectiveness due to the heterogeneity of underlying lung conditions such as the
34 presence of pulmonary infection episodes prior to vaccination or chronic pulmonary
35 failure in elderly patients with chronic pulmonary disease.
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48 **Comparison with other studies**

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50 Previous pulmonary infection was highly associated with poor clinical prognosis. This
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4 finding suggests that beneficial PPV23 effectiveness might be unachievable for elderly
5 people with chronic pulmonary disease in the presence of infectious complications
6 during the pre-vaccine period. In a multicentre double-blind controlled study conducted
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8 in Sweden, PPV23 was not efficacious against overall pneumonia in middle or elderly
9
10 non-immunocompromised individuals who had been treated for community-acquired
11
12 pneumonia.[18] In that study, the survival rate calculated by the Kaplan-Meier method
13
14 was still >80% in both vaccinated and unvaccinated populations after 2-year
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16 observation, while our results showed that the survival rate was <60% if episodes of
17
18 pulmonary infection had occurred within 1 year prior to vaccination. These results are
19
20 consistent with previous suggestions that chronic pulmonary disease such as chronic
21
22 obstructive pulmonary disease (COPD) is a risk factor for repeated pneumonia and that
23
24 protective effects of PPV23 could not be obtained.[19-21] Conflicting results were
25
26 shown in some other reports in which the beneficial effects of PPV23 in patients with
27
28 COPD were indicated, although previous episodes of pneumonia prior to vaccination
29
30 were not considered and participants were not limited to the elderly.[13, 22] Alfageme
31
32 et al showed PPV23 effectiveness in patients <65 years of age with COPD in a
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34 randomised controlled study in 596 patients.[23] These results and our data indicate that
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36 PPV23 might be inefficacious on the elderly population with chronic pulmonary disease
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38 especially when complicated by lung infection prior to the vaccination. Despite the
39
40 strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD),
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42 altered immune response, disruption of a physical barrier in the airways due to
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44 progressive chronic pulmonary disease, and repeated pulmonary infection could
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46 compromise the benefits.[1, 24] PPV23 vaccination should be given to patients with
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48 chronic pulmonary disease at an earlier stage in which infectious complications have not
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4 yet occurred.
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6 The probability of survival was significantly increased by PPV23 in the presence of
7 chronic respiratory failure in patients without episodes of pulmonary infection during
8 the pre-vaccine period. The pulmonary infection-free survival rate was 75.5% at the end
9 of the observation period when PPV23 was given. Without PPV23, survival was
10 reduced to 45.0%, almost the same level as that in the case where infectious lung
11 complications had occurred during the pre-vaccine period. This result indicates that
12 pulmonary infection due to chronic respiratory failure could be prevented by the PPV23
13 vaccination. Oxygen therapy and inhalation therapy containing corticosteroids may be
14 administered in COPD patients when airflow is severe and chronic respiratory failure is
15 present, but these treatments were suggested to be risk factors for community-acquired
16 pneumonia.[25-27] Additionally, bacterial colonisation of the distal airway may occur
17 due to the altered pulmonary defense.[24] We suggest that patients receive the PPV23
18 vaccination soon after the diagnosis of chronic respiratory disease such as COPD,
19 especially when maintenance treatments for impaired lung function are expected to be
20 risk factors for pneumonia. In this study, the number of participants with chronic
21 respiratory failure who were free of lung infections during the pre-vaccine period was
22 only 70. Thus, a large scale study is warranted.
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42 **Strengths and limitations of the study**

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44 When informed consents were obtained prior to the study initiation, PPV23 vaccine
45 recommendations were made and only participants who responded affirmatively
46 received the vaccination. This method may be associated with these results: the
47 vaccination rate increased significantly in high-risk patients who had at least 1 episode
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4 of bacterial pulmonary infection during the pre-vaccine period or chronic respiratory
5 failure; and the mortality rate was higher in vaccinated patients, although the presence
6 of adverse effects of PPV23 is unlikely because PPV23 had generally been considered
7 safe based on clinical experience since 1977.[7] In the Cox proportional hazards model,
8 PPV23 was not a risk factor for the events. All of the participants in this study were
9 elderly patients with chronic pulmonary disease, and all of them could be categorised
10 into groups for which PPV23 vaccination is recommended in the United States and
11 some European countries.[3, 7, 14] In Japan, no vaccine recommendations against
12 pneumococcal infection are issued by the Japanese Ministry of Health, Labour and
13 Welfare.[11] Japanese participants need to accept some risks for the public benefit and
14 not for their own if selected for the unvaccinated group. This condition is different from
15 that in some developed countries where unvaccinated control subjects in clinical trials
16 of the PPV23 vaccine could still be protected by previous vaccination and indirect
17 immunity from other people, including children.[28-30] Pneumococcal infection was
18 associated with increasing mortality rates, while the beneficial effects of PPV23 without
19 any severe adverse events were suggested in some previous clinical trials.[1, 8, 15,
20 31-32] Therefore, we decided to conduct a nonrandomised clinical study to ensure that
21 participants were treated with respect and dignity.

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41 The doctors had access to the patients' vaccination record during the observation
42 period. However, at the time of this study, PPV23 had already been approved by the
43 Japanese Ministry of Health, Labour and Welfare, and there were no conflicts of interest
44 with pharmaceutical companies. All the treatments were supported by the public health
45 care system funded by the Japanese government; no specific grants were provided from
46 any funding agencies. Diagnosis of pulmonary infection was made according to the
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4 same diagnostic criteria. Therefore it is unlikely that treatment bias occurred during the
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6 observation period.
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9 The diagnosis of pneumococcal disease was not made in the majority of patients
10 who had pulmonary infections during the observation period. Identification of *S.*
11 *pneumoniae* using a sputum Gram stain is required for definitive diagnosis. However,
12 compared to IPD defined as any condition in which *S. pneumonia* is identified in a
13 normally sterile body site, microbiological diagnosis in the lower respiratory tract is
14 ambiguous.[1, 5] It was noted by many authors that respiratory secretion samples for
15 pneumococcal identification might be unreliable due to the technical difficulties in
16 obtaining good-quality sputum and in distinguishing causative specimens from
17 colonisation.[21] The positive results in urine antigen testing might be related to
18 previous infection or colonisation.[33] It might be difficult to assess PPV23
19 effectiveness on pneumococcal pulmonary infection using these procedures. Blood
20 cultures are recommended for patients hospitalised after a diagnosis of
21 community-acquired pneumonia, although its cost-effectiveness has been questioned in
22 several studies.[34] Less expensive, novel techniques for accurate diagnosis of
23 pneumonia need to be developed.
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40 **Conclusions and policy implications**

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

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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.

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

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30 **Competing interests:** None declared.

31
32 **Ethical approval:** Full approval of Institutional Review Board in the Kanagawa
33 Cardiovascular and Respiratory Diseases Centre was obtained prior to the study
34 initiation.
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38 **Data sharing:** No additional data available.

39 40 **Acknowledgement**

41
42 The material (clinical data) that had been used for ref. 14 is modified and printed with
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47 48 **Copyright license statement**

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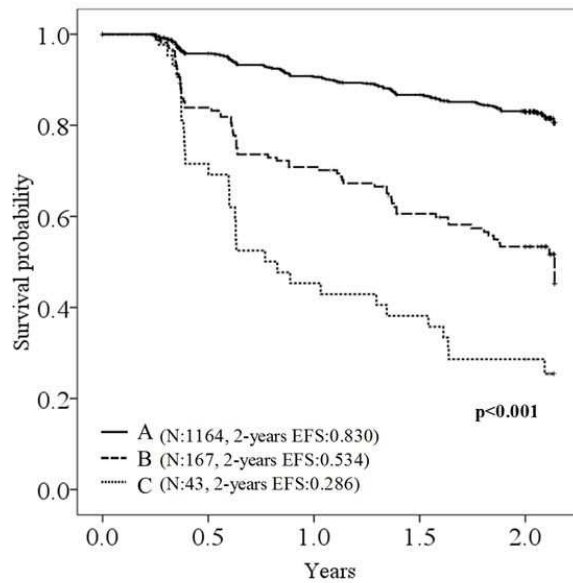
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Figure 1



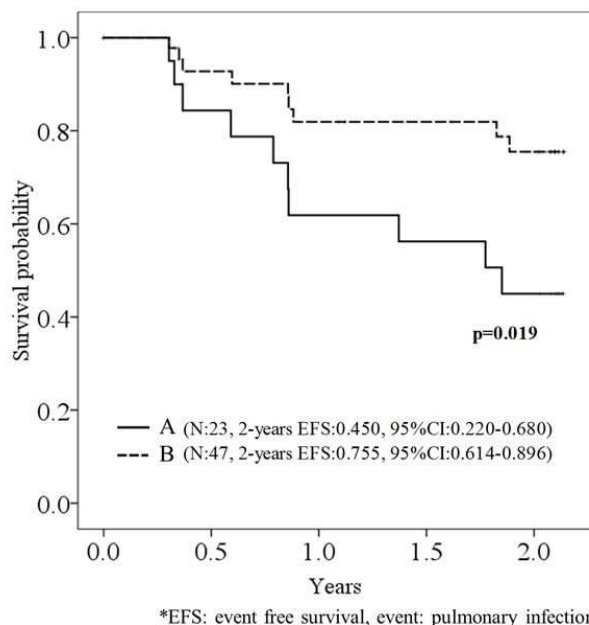
*EFS: event free survival, event: pulmonary infection

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

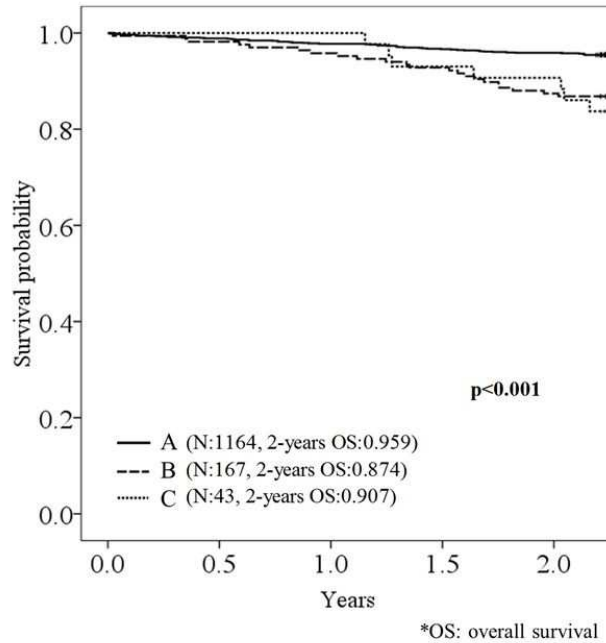


Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period
 Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-vaccine period: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

only

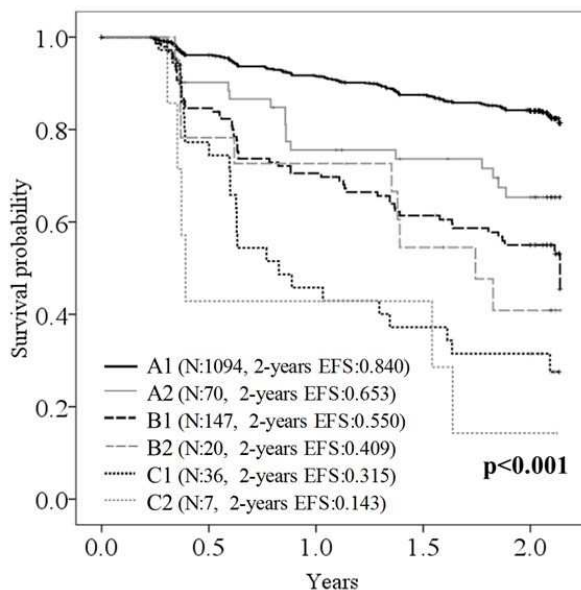
Figure A



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



*EFS: event-free survival, event: pulmonary infection

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

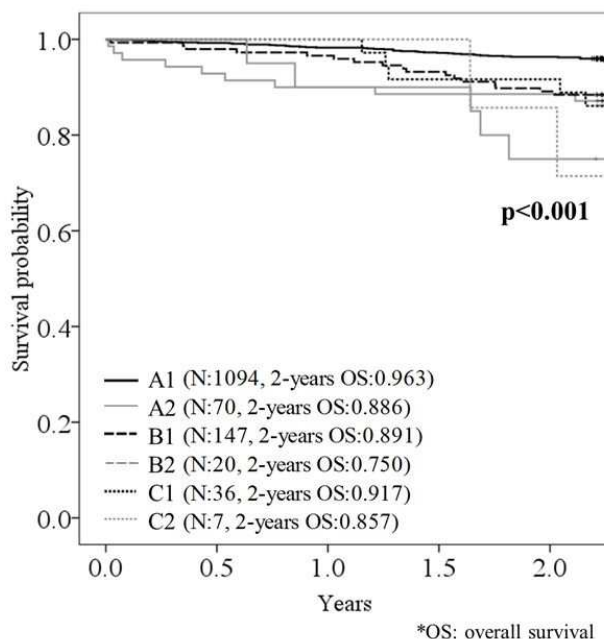
One episode of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, B1; with chronic respiratory failure, B2

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)

only

Figure C



Kaplan-Meier curves showing the proportion of patients free of death during the observation period

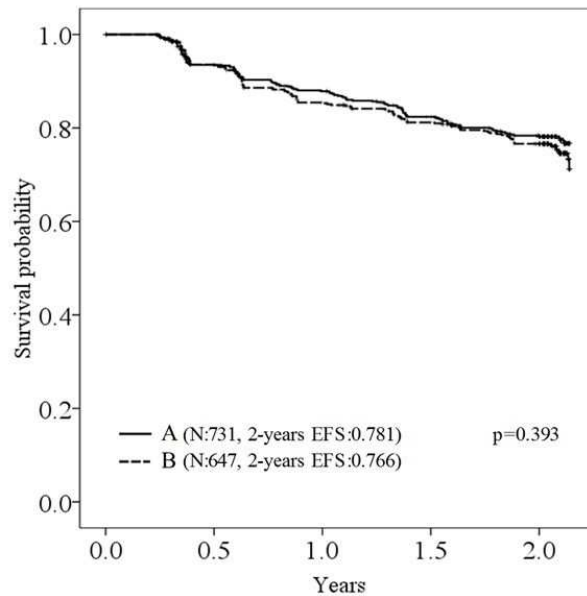
Zero episodes of pulmonary infection during the pre-vaccine period: without chronic respiratory failure, A1; with chronic respiratory failure, A2

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



*EFS: event-free survival, event: pulmonary infection

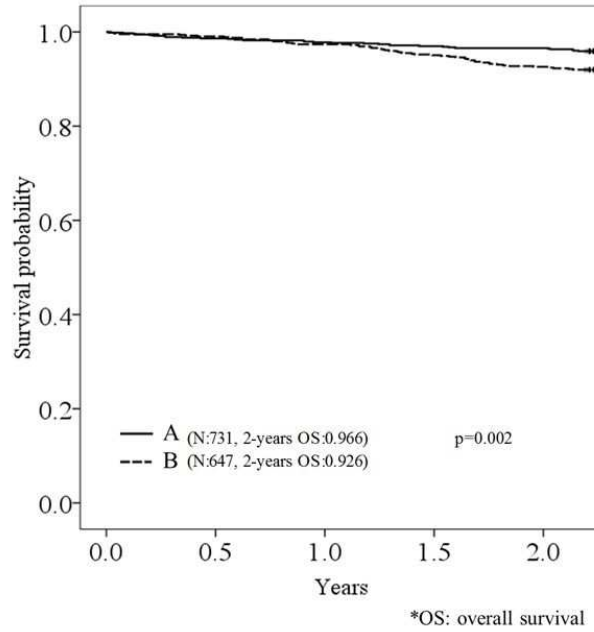
Kaplan-Meier curves showing the proportion of patients free of the first episode of pulmonary infection during the observation period

All the participants: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

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Figure E



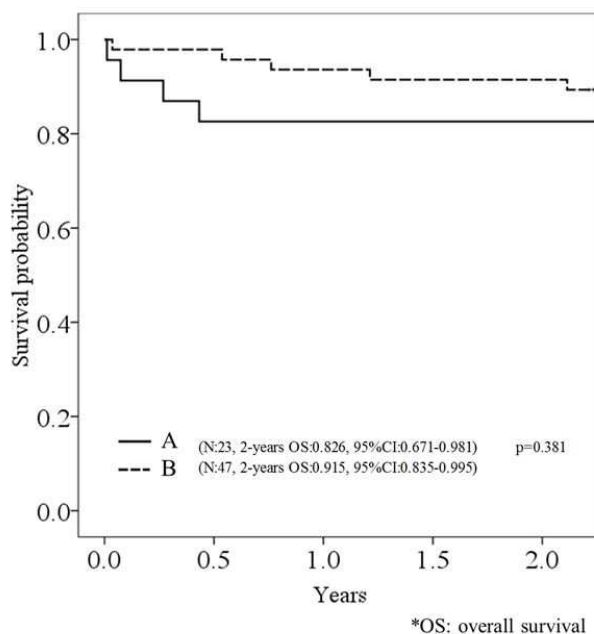
Kaplan-Meier curves showing the proportion of patients free of death during the observation period
All the participants: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

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Figure F

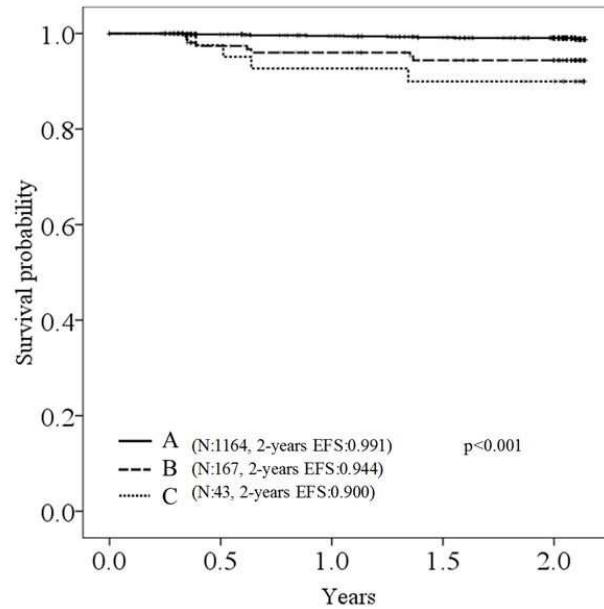


Kaplan-Meier curves showing the proportion of patients free of death during the observation period
 Patients with chronic respiratory failure who had 0 episodes of pulmonary infection during the pre-
 vaccine period: unvaccinated, A; vaccinated, B

81x60mm (300 x 300 DPI)

Peer Review Only

Figure G



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

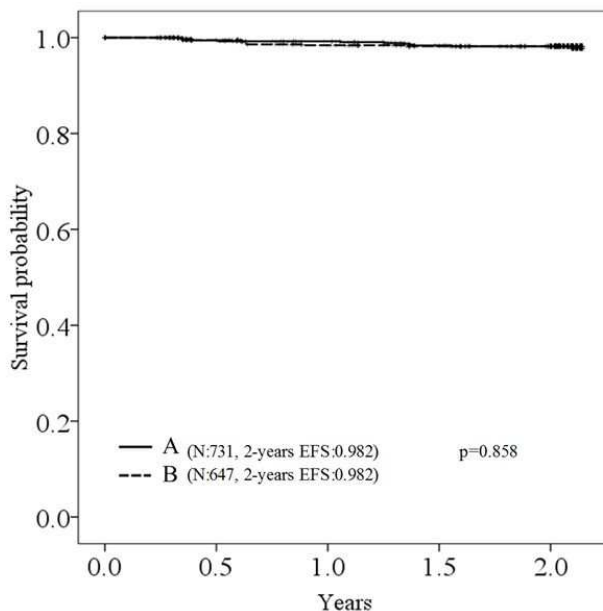
Kaplan-Meier curves showing the proportion of patients free of pneumococcal pulmonary infection during the observation period

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)

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Figure H



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

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)

For peer review only