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RESEARCH PAPER

Preventive effects of pneumococcal and influenza vaccines on community-acquired pneumonia in older individuals in Japan: a case-control study

Kanzo Suzuki[a,b], Kyoko Kondo[c], Masakazu Washio[d], Kei Nakashima[e], Sakae Kan[f], Seiichiro Imai[g,h], Kunihiko Yoshimura[i], Chiharu Ota[j], Satoko Ohfuji[k,l], Wakaba Fukushima[k,l], and Yoshio Hirota[k,m,n] and the Study Group for Pneumonia in the Elderly Individuals[#]

[a]Department of Community-based Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [b]School of Nursing, Nagoya City University, Nagoya, Japan; [c]Osaka City University Hospital administration division, Osaka, Japan; [d]Department of Community Health and Clinical Epidemiology, St. Mary's College, Kurume, Japan; [e]Department of Pulmonary Medicine, Kameda Medical Center, Chiba, Japan; [f]Kaisei Hospital, Nagoya, Japan; [g]Department of Respiratory Medicine, Kyoto University Hospital, Kyoto, Japan; [h]Preemptive Medicine and Lifestyle-related Disease Research Center, Kyoto University Hospital, Kyoto, Japan; [i]Department of Pulmonology, Mitsui Memorial Hospital, Tokyo, Japan; [j]Department of Pulmonology, Asahi Rosai Hospital, Owariasahi, Japan; [k]Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan; [l]Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, Osaka, Japan; [m]Clinical Epidemiology Research Center, Medical Co. LTA, Fukuoka, Japan; [n]College of Healthcare Management, Miyama, Japan

ABSTRACT

At present, there are few reports that have clarified the effectiveness of 23-valent pneumococcal polysaccharide vaccine (PPSV23) against all-cause pneumonia or pneumococcal pneumonia in community-acquired pneumonia (CAP) in older individuals in Japan. We conducted a hospital-based matched case-control study to investigate separately the preventive effects of PPSV23 and trivalent influenza vaccine (TIV) on all-cause CAP and pneumococcal CAP in older individuals in Japan. Cases were individuals aged 65 years or older who were newly diagnosed with CAP from October 2010 to September 2014. Two control patients with a different disease (one respiratory medicine and one non-respiratory medicine) matched for sex, age, date of outpatient visit, and medical institution were selected for each case. Odds ratios (ORs) and 95% confidence intervals (CIs) of PPSV23 and TIV for the occurrence of all-cause CAP and pneumococcal CAP were calculated using conditional and unconditional logistic regression models. The analysis included 161 cases and 308 controls from the 4-year period. The adjusted OR for the occurrence of all-cause CAP was 0.76 (95%CI = 0.44–1.32) with PPSV23 vaccination and 0.79 (95%CI = 0.50–1.25) with TIV vaccination compared with unvaccinated individuals. When the outcome index was restricted to pneumococcal CAP, the adjusted OR significantly decreased to 0.23 (95%CI = 0.08–0.66) with PPSV23 vaccination, but not with TIV vaccination (adjusted OR = 0.65, 95%CI = 0.31–1.36). PPSV23 vaccination is likely effective in reducing incidence of pneumococcal CAP in older individuals, although its preventive effect for all-cause CAP has not been achieved.

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Introduction

Pneumonia is the third leading cause of death in Japan, and the mortality rate by age group for this condition is high in older individuals, especially in the group aged 80 years or older.[1] In Japan, the population is aging at an unprecedented rate compared to other countries and is rapidly becoming a super-aged society. Thus, preventing pneumonia in older individuals has become an urgent issue to address.

Previously, several overseas studies investigated the preventive effects of both pneumococcal and influenza vaccines on pneumonia in older individuals. A cohort study from the United States spanning three influenza seasons demonstrated that pneumococcal vaccination alone, influenza vaccination alone, and both vaccinations together significantly decreased hospitalization and deaths caused by pneumonia or influenza.[2] A large-scale observational study from Sweden showed a significant decrease in hospitalization and deaths during hospitalization caused by pneumonia in individuals who were vaccinated with one or both vaccines compared to those who were unvaccinated.[3] A report by Christenson et al. found that hospitalization due to pneumonia or influenza and deaths during hospitalization due to pneumonia significantly decreased in the dual-vaccinated group compared to the unvaccinated group.[4] Vaccination with both vaccines in older individuals with chronic diseases in Hong Kong resulted in the prevention of not only pneumonia and deaths but also cerebral and myocardial infarctions.[5] Subsequent retrospective cohort studies showed that dual vaccination decreased hospitalization, death, and hospitalization fees,[6] or reduced the duration of hospitalization.[7]

In Japan, there are very few studies that have investigated separately the preventive effects of pneumococcal and influenza vaccines on all-cause community-acquired pneumonia (CAP) or pneumococcal CAP in older individuals. In a study

CONTACT Kanzo Suzuki kanso48@med.nagoya-cu.ac.jp Department of Community-based Medical Education, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

[#]Other members of the Pneumonia in Elderly People Study Group are listed in Note.

that investigated the preventive effect of 23-valent pneumococcal polysaccharide vaccine (PPSV23) against pneumococcal pneumonia in older individuals, study subjects were limited to nursing home residents.[8] Another study showed the effectiveness of PPSV23 against all-cause CAP in the group aged 70 years or older.[9] However, the authors could not assess separately the preventive effects of PPSV23 and trivalent influenza vaccine (TIV) on all-cause CAP in the study, because study subjects were all vaccinated with TIV. In the previous article, we mainly assessed and discussed the selection of controls with regard to the effectiveness of PPSV23 and TIV for all-cause pneumonia among the elderly in our hospital-based matched case-control study from October 2009 to September 2014.[10] In the current study, we focused on evaluation of the preventive effects of PPSV23 and TIV on all-cause CAP and pneumococcal CAP in older individuals from October 2010 to September 2014, excluding the first year of the same study period, because a pandemic of influenza A (H1N1) occurred during the study period.

Currently, in Japan, vaccinations of both pneumococcal vaccines (PPSV23 or 13-valent pneumococcal conjugate vaccine [PCV13]) and influenza vaccine for preventing pneumonia in older individuals are recommended,[11] similar to recommendations in the United States and most of the Western countries. However, at the time of the study, no national immunization program for use of PPSV23 or PCV13 in adults aged 65 years or older has not been launched. After PPSV23 became available in 1988, a small portion of patients with chronic respiratory disease or cardiac disease have been vaccinated at the advice of their attending physicians. In addition, adults aged 65 years or older and patients with chronic respiratory disease or cardiac disease have been partially subsidized for PPSV23 vaccination by their municipality since 2001.[12] This was implemented for all adults aged 65 years or older and individuals aged 60–64 years with underlying disease under the national immunization program in October 2014.[13] PCV13 became available in adults aged 65 years or older since June 2014, although it is still not designated as the national immunization program at present. Therefore, pneumococcal vaccine evaluated in this study was solely PPSV23 because PCV13 has seldom been used in older individuals during the study period. With regard to TIV, the adults aged 65 years or older have been subsidized by their municipality since 2001 under the national immunization program. The rates of PPSV23 and TIV vaccination in adults aged 65 years or older were around 25% and 50% at the time of the study in 2013, respectively.[14,15]

Results

A total of 469 individuals (161 cases and 308 controls) without missing data for the examined variables were analyzed. Among the 161 cases with pneumonia, two controls were enrolled for 147 cases and one control was enrolled for 14 cases. The characteristics of cases and controls are shown in Table 1. The proportion of PPSV23 vaccination was 28% in cases and 30% in controls, and the proportion of TIV vaccination was 47% in cases and 53% in controls. The percentage of patients with body mass index (BMI) of <18.5 was significantly greater in cases compared to controls (22% vs. 12%).

Table 1. Comparison of characteristics between cases and controls (N = 469).

Characteristics*	Cases (n = 161)	Controls (n = 308)	P
Age (years)			
Mean (range)	75.5 (65–92)	75.3 (65–98)	0.690†
Sex			
Male	111 (69)	212 (69)	0.980‡
Female	50 (31)	96 (31)	
Vaccination			
Pneumococcal vaccine			
Unvaccinated	116 (72)	215 (70)	0.613‡
Vaccinated	45 (28)	93 (30)	
Influenza vaccine			
Unvaccinated	85 (53)	145 (47)	0.240‡
Vaccinated	76 (47)	163 (53)	
Body mass index (kg/m^2)			
<18.5	36 (22)	38 (12)	
18.5–24.9	100 (62)	201 (65)	0.009‡
≥25.0	25 (16)	69 (22)	
Underlying disease			
Respiratory disease	76 (47)	131 (43)	0.333‡
Hypertension	69 (43)	171 (56)	0.009‡
Dyslipidemia	27 (17)	60 (19)	0.473‡
Heart disease	22 (14)	61 (20)	0.098‡
Cerebral hemorrhage, cerebral	13 (8)	21 (7)	0.618‡
infarction, stroke			
Diabetes mellitus	23 (14)	84 (27)	0.002‡
Renal disease	3 (2)	11 (4)	0.399§
Activities of daily living			
Self-supported	144 (89)	286 (93)	0.203‡
Non-self-supported	17 (11)	22 (7)	
Living with children aged ≤6 years			
No	149 (93)	295 (96)	0.139‡
Yes	12 (7)	13 (4)	
Pneumococcal pneumonia	41 (25)		

*All data except age are expressed as n (%), †Wilcoxon rank-sum test, ‡Chi-square test, §Fisher's exact test.

The frequencies of hypertension (43% vs. 56%, p = 0.009) and diabetes mellitus (14% vs. 27%, p = 0.002) were significantly greater in controls than in cases. Forty-one of 161 cases (25%) had pneumococcal pneumonia. As for microbiological test results concerning the diagnosis of pneumococcal pneumonia, *Streptococcus pneumoniae* was isolated by sputum culture in 21% (24/112) of cases and by blood culture in 5% (2/39). In addition, *S. pneumoniae* was detected by sputum Gram staining in 22% (22/93), and was detected by the urinary antigen test in 23% (33/145).

The crude and adjusted odds ratios (ORs) for all-cause CAP by each variable are shown in Table 2. The adjusted OR with vaccination decreased for both PPSV23 (adjusted OR = 0.76, 95% confidence interval [CI]) = 0.44–1.32) and TIV (adjusted OR = 0.79, 95%CI = 0.50–1.25), but did not reach statistical significance. Although the crude OR was significantly increased in subjects with BMI of <18.5, the significance was lost after adjustment. Significant associations with CAP were not shown with other variables.

In winter months, in which 104 cases and 197 controls were analyzed, the adjusted OR with PPSV23 vaccination for all-cause CAP decreased, but did not reach statistical significance (adjusted OR = 0.60, 95%CI = 0.29–1.23). TIV vaccination was not associated with all-cause CAP (adjusted OR = 1.05, 95%CI = 0.59–1.86). In summer months, in which 57 cases and 111 controls were collected, PPSV23 vaccination was not associated with all-cause CAP (adjusted OR = 0.95, 95%CI = 0.35–2.62) and the adjusted OR with TIV

Table 2. Odds ratio for all-cause community-acquired pneumonia (2010/11 season to 2013/14 season, N = 469).

	Crude			Adjusted		
	OR	95% CI	P	OR*	95% CI	P
Vaccination						
Pneumococcal vaccine						
Unvaccinated	1			1		
Vaccinated	0.87	0.54–1.43	0.590	0.76	0.44–1.32	0.335
Influenza vaccine						
Unvaccinated	1			1		
Vaccinated	0.76	0.50–1.16	0.197	0.79	0.50–1.25	0.314
Body mass index (BMI, kg/m^2)						
<18.5	1.95	1.12–3.37	0.017	1.55	0.85–2.82	0.152
18.5–24.9	1			1		
≥25.0	0.71	0.42–1.19	0.191	0.86	0.49–1.50	0.594
Underlying respiratory disease						
No	1			1		
Yes	1.16	0.80–1.69	0.426	1.05	0.70–1.58	0.804
Activities of daily living (ADL)						
Self-supported	1			1		
Non-self-supported	1.48	0.74–2.96	0.273	1.34	0.62–2.93	0.458
Living with children aged ≤6 years						
No	1			1		
Yes	1.90	0.85–4.26	0.118	1.74	0.73–4.14	0.215

*Variables included in the model: vaccination (pneumococcal vaccine, influenza vaccine), BMI, underlying respiratory disease, hypertension, diabetes mellitus, ADL, and living with children aged 6 years or younger.

vaccination for all-cause CAP decreased, but did not reach statistical significance (adjusted OR = 0.49, 95% CI = 0.21–1.16).

The comparative data on characteristics when cases were limited to those with pneumococcal CAP are exhibited in Table 3. PPSV23 (12% in cases vs. 30% in controls) and TIV (39% vs. 53%, respectively) vaccination proportion were both greater in controls. Additionally, hypertension was more commonly observed in controls.

The crude and adjusted ORs for pneumococcal CAP by each variable are shown in Table 4. PPSV23 vaccination significantly reduced the crude OR to 0.32 (95%CI = 0.12–0.84) and the OR further decreased after adjustment, which was statistically significant (adjusted OR = 0.23, 95%CI = 0.08–0.66). TIV vaccination seemed to result in a decrease of the crude OR at 0.57 (95% CI = 0.29–1.11), but did not reach significance after adjustment (adjusted OR = 0.65, 95%CI = 0.31–1.36).

Discussion

In this study of elderly individuals aged 65 years or older, we found that PPSV23 was effective against pneumococcal CAP but not against all-cause CAP. The results of our study are not so different from those of similar studies conducted in other countries.[16] To our knowledge, this is considered the first study to show separately the preventive effects of PPSV23 and TIV on all-cause CAP and pneumococcal CAP in older individuals in Japan. Further, this is the first study to show the significant preventive effect of PPSV23 on pneumococcal CAP, although few studies had investigated the preventive effect of PPSV23 on pneumococcal CAP in older individuals in Japan.[17]

There are few overseas studies that have elucidated the preventive effects of pneumococcal vaccine on pneumococcal pneumonia in older individuals.[18–20] A large-scale cohort study conducted in Spain showed that PPSV23 effectively prevented overall pneumococcal CAP [hazard ratio (HR) = 0.55, 95% CI = 0.34–0.88] and decreased the rate of overall CAP

Table 3. Comparison of characteristics between cases (limited to pneumococcal pneumonia) and controls (N = 349).

Characteristics*	Cases (pneumococcal pneumonia) (n = 41)	Controls (n = 308)	P
Age (years)			
Mean (range)	75.5 (66–92)	75.3 (65–98)	0.976†
Sex			
Male	29 (71)	212 (69)	0.805‡
Female	12 (29)	96 (31)	
Vaccination			
Pneumococcal vaccine			
Unvaccinated	36 (88)	215 (70)	0.016‡
Vaccinated	5 (12)	93 (30)	
Influenza vaccine			
Unvaccinated	25 (61)	145 (47)	0.094‡
Vaccinated	16 (39)	163 (53)	
Body mass index (kg/m^2)			
<18.5	5 (12)	38 (12)	
18.5–24.9	29 (71)	201 (65)	0.727‡
≥25.0	7 (17)	69 (22)	
Underlying disease			
Respiratory disease	18 (44)	131 (43)	0.868‡
Hypertension	16 (39)	171 (56)	0.047‡
Dyslipidemia	4 (10)	60 (19)	0.131‡
Heart disease	4 (10)	61 (20)	0.121‡
Cerebral hemorrhage, cerebral infarction, stroke	3 (7)	21 (7)	0.752‡
Diabetes mellitus	7 (17)	84 (27)	0.162‡
Renal disease	0 (0)	11 (4)	0.375§
Activities of daily living			
Self-supported	38 (93)	286 (93)	1.000‡
Non-self-supported	3 (7)	22 (7)	
Living with children aged ≤6 years			
No	37 (90)	295 (96)	0.125‡
Yes	4 (10)	13 (4)	

*All data except age are expressed as n (%), †Wilcoxon rank-sum test, ‡Chi-square test, §Fisher's exact test.

Table 4. Odds ratio for pneumococcal community-acquired pneumonia (2010/11 season to 2013/14 season, N = 349).

	Unconditional model					
	Crude			Adjusted		
	OR*	95% CI	P	OR*	95% CI	P
Vaccination						
Pneumococcal vaccine						
Unvaccinated	1			1		
Vaccinated	0.32	0.12–0.84	0.021	0.23	0.08–0.66	0.006
Influenza vaccine						
Unvaccinated	1			1		
Vaccinated	0.57	0.29–1.11	0.098	0.65	0.31–1.36	0.248
Body mass index (BMI, kg/m^2)						
<18.5	0.91	0.33–2.51	0.858	0.94	0.30–2.94	0.921
18.5–24.9	1			1		
≥25.0	0.70	0.30–1.68	0.428	1.11	0.42–2.91	0.836
Underlying respiratory disease						
No	1			1		
Yes	1.06	0.55–2.04	0.868	0.95	0.47–1.93	0.883
Activities of daily living (ADL)						
Self-supported	1			1		
Non-self-supported	1.03	0.29–3.59	0.967	1.02	0.22–4.72	0.984
Living with children aged ≤6 years						
No	1			1		
Yes	2.45	0.76–7.92	0.133	2.70	0.74–9.85	0.134

*Variables included in the model: vaccination (pneumococcal vaccine, influenza vaccine), BMI, underlying respiratory disease, hypertension, diabetes mellitus, ADL, living with children aged 6 years or younger, and matching variables (sex, age).

(HR = 0.79, 95%CI = 0.64–0.98) in older individuals aged 65 years or older.[18] PPSV23 vaccination against all pneumococcal pneumonia was significantly effective for people aged 65 years or older in a matched case-control study (adjusted OR:0.47, 95%CI = 0.32–0.67).[19] A recent large-scale cohort study conducted in Spain showed that PPSV23 exhibited preventive effects on overall pneumococcal CAP (HR = 0.49, 95% CI = 0.29–0.84) and all-cause CAP (HR = 0.75, 95% CI = 0.58–0.98) in older individuals aged 60 years or older within 5 years of vaccination.[20] Additionally, a study that included nursing home residents in Japan demonstrated that PPSV23 prevents pneumococcal pneumonia and consequently reduces mortality rate due to the disease.[8] Moreover, in all-cause CAP in older individuals aged 65 years or older vaccinated with TIV, the effectiveness of PPSV23 was observed within the first year of the study period in the group aged 75 years or older.[9] A multicenter prospective study that used a test-negative design demonstrated that effectiveness of PPSV23 was 33.5% (95%CI = 5.6–53.1) against PPSV23-type pneumococcal pneumonia, and 27.4% (95%CI = 3.2–45.6) against all pneumococcal pneumonia in older individuals aged 65 years or older with community-onset pneumonia (COP).[17] Stratified analyses showed that effectiveness of PPSV23 was 13.4% (95%CI = – 23.0–39.0) in individuals with CAP while 42.9% (95%CI = 3.1–66.4) in those with healthcare-associated pneumonia, when analyzing those with all pneumococcal pneumonia.

Pneumococcal infections in adults have declined as an indirect effect of the widespread use of pneumococcal conjugate vaccines in children.[21–23] Feikin et al. examined serotype replacement after receiving the 7-valent pneumococcal conjugate vaccine (PCV7) and suggested that serotype replacement would not be expected within 2 years after the introduction of PCV13.[24] In Japan, PCV7 was introduced as a part of the national immunization program in children aged 5 years or younger in April 2013 and was subsequently replaced with PCV13 in November 2013. One Japanese study which was carried out during our study period demonstrated that the serotype coverage rate of PPSV23 was 67% in 142 pneumococcal strains isolated from sputum samples of adult patients with COP.[25] The serotype coverage rate of PPSV23 was 84.3% in pneumococcal strains isolated from adult pneumonia patients with invasive pneumococcal disease from April 2010 to March 2013 in Japan.[21] During the current study period, serotype replacement did not particularly advance, indicating that PPSV23 was still effective against pneumococcal pneumonia.

Aspiration pneumonia has been reported to represent a considerable number of CAP or hospital-acquired pneumonia infections among older patients.[26] Recent data have suggested that aspiration pneumonia caused by silent aspiration is an important mechanism for the pathogenesis of pneumonia in older people.[26] We excluded aspiration pneumonia caused by inhalation during eating or vomiting because this type of aspiration pneumonia was considered to be due to physical factors unrelated to the effectiveness of vaccines.

In subanalysis, the significant effect of TIV for the occurrence of CAP was not found in both winter months and summer months. It is reported that CAP associated with influenza virus infection was much more common in winter months than in summer months in Japan.[27,28] The effectiveness of the influenza vaccine could be measured during a period in which the vaccine provides protection when the virus is prevalent.[29–32] Further studies may be needed to answer if influenza vaccine could prevent pneumonia associated with influenza virus infection in winter months in older individuals living in the community.

There are several limitations in our current study. First, we were not able to collect data on study participants' vaccination behavior, that is, whether vaccination had been decided by the study participants themselves or at the advice of their attending physicians. Since PPSV23 was not yet included in the national immunization program during the study period, it was possible that the vaccination behavior had differed based on the individual clinical departments responsible for participants, or on their underlying diseases.[10] Therefore, we included underlying diseases in the multivariate analysis model in consideration of the background factors which affect physicians' recommendation of vaccination. Nevertheless, it is hard to exclude the possibility that PPSV23 effectiveness in the present study might have been overestimated by selection bias of controls. Second, the enrollment date differed between cases and controls. In our protocol, we enrolled controls as soon as possible after enrolling each case. We believe that the bias due to the enrollment date of the controls was minimal because they were enrolled on average 10 days after the corresponding case. Third, although we obtained information regarding vaccination status from each patient's questionnaire, we were unable to confirm the validity of this information. Fourth, our cases and controls were not free from selection bias, because the present study was a hospital-based case-control study. In this context, patients who died of pneumonia outside hospitals were not included in cases of this study, while healthy elderly individuals who did not need to visit hospitals were not included as controls in our study. Fifth, we could not investigate the effect of the timing of PPSV23 vaccination with regards to the time pneumonia developed,[16] or the effect of vaccination on the severity of pneumonia, which are considered to be important factors for evaluating the effectiveness of PPSV23 against pneumonia in the elderly. As it has been reported that the serum-specific antibody level decreases 3–5 years after PPSV23 vaccination,[33,34] further studies with shorter time since vaccination (i.e., within 3 years) are needed to investigate PPSV23 effectiveness in patients with pneumonia. Although the effectiveness of PPSV23 against severe pneumonia such as bacteremic pneumococcal pneumonia has been evaluated in other countries,[18–20] we evaluated the effectiveness of PPSV23 on mild CAP in our study. Further studies are needed to investigate the preventive effect of PPSV23 with classification by the severity of pneumonia in older individuals in Japan.[35] Finally, the major limitation of this study is the small sample size. Nonetheless, it should be noted that a significant association between PPSV23 vaccination and pneumococcal CAP has been observed.

In conclusion, PPSV23 vaccination is likely effective in reducing incidence of pneumococcal CAP in older individuals, although its preventive effect for all-cause CAP has

not been achieved. Further studies are needed to investigate PPSV23 effectiveness in patients with pneumococcal CAP after the introduction of the national immunization program in older individuals in Japan.

Materials and methods

Study design

Between October 1, 2010 and September 30, 2014, we conducted a hospital-based matched case-control study at 24 hospitals in Chiba, Tokyo, Shizuoka, Aichi, Gifu, Kyoto, and Fukuoka prefectures. The study outcome was focused on CAP, and cases were therefore restricted to older persons who lived at home when they developed pneumonia. All study participants received an explanation of the study and gave consent prior to participation. The study protocol was approved by the Ethics Review Board of Osaka City University Graduate School of Medicine and by each of the participating institutions and was carried out in accordance with the principles of the Declaration of Helsinki.

Definition of cases and controls

Cases were defined as individuals aged 65 years or older who were newly diagnosed with CAP by a physician at a participating institution. The diagnosis of pneumonia was made based on clinical symptoms (fever, cough, sputum), increased leukocyte count or C-reactive protein (CRP) level, and appearance of an infiltrative shadow on either chest X-ray or chest computed tomography. Pneumococcal pneumonia was diagnosed through sputum culture (semi-quantitative culture method), blood culture, sputum Gram staining (positive) or through pneumococcal urinary antigen test (positive).

Controls were non-pneumonia patients who were matched for sex, age (5-year age groups), date of outpatient visit (i.e., within 2 months of confirming each case), and medical institution. When possible, two controls (one respiratory medicine and one non-respiratory medicine) were selected for each case.

Exclusion criteria were as follows: nursing home residents, patients with aspiration pneumonia (i.e., pneumonia caused by inhalation during eating or vomiting), patients with malignant tumors, patients currently undergoing treatment with oral steroids or immunosuppressants, and patients with a history of splenectomy.

Data collection

The attending physician of cases and controls recorded the following clinical information on the questionnaire: a) Sex, age, and presence/absence of underlying respiratory disease (pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, or pulmonary tuberculosis sequelae); b) Pneumonia-related information (for cases only) including date of diagnosis, clinical symptoms (fever, cough, sputum) or laboratory data related to pneumonia diagnosis (leukocyte count, or CRP level), and results from diagnostic tests (rapid diagnostic influenza test, pneumococcal urinary antigen test, sputum Gram staining, or sputum/blood culture).

Study subjects were also asked to fill out a self-administered questionnaire containing the following information: age, height/body weight, living with children aged 6 years or younger, activities of daily living (ADL; bedridden, semi-bedridden, semi-self-supported, or self-supported), presence/absence of underlying disease (hypertension, dyslipidemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, or renal disease), presence/absence of respiratory disease (pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, or pulmonary tuberculosis sequelae), and vaccination status (PPSV23 in the past 5 years, and/or TIV in the past 6 months).

Statistical analysis

It has been reported that the serum specific antibody level decreases 3–5 years after PPSV23 vaccination.[33,34] Consequently, we defined patients who had received the vaccine within the past 5 years as "vaccinated".[36] All underlying diseases were classified into "present vs. absent", and ADL was classified into "non-self-supported (bedridden, semi-bedridden, or semi-self-supported) vs. self-supported" for analyses. BMI was calculated as weight in kilograms (kg) divided by the square of height in meters (m^2), and BMI was categorized into 3 levels (<18.5, 18.5–24.9, and ≥25.0). The 6 months from November to April were defined as winter months and the other 6 months from May to October were defined as summer months.[28]

Comparison of characteristics between cases and controls was performed using the Wilcoxon rank-sum test, Chi-square test, or Fisher's exact test, as appropriate.

The ORs and 95% CIs of PPSV23 and TIV vaccinations for all-cause CAP were calculated using a conditional logistic regression model. As variables that showed a P-value of less than 0.05 or that seemed to be medically related to the disease were considered potential confounders for adjustment,[37] PPSV23 vaccination, TIV vaccination, BMI, underlying respiratory disease, hypertension, diabetes mellitus, ADL, and living with children aged 6 years or younger were included in the multivariate analysis model. The ORs and 95% CIs of PPSV23 and TIV vaccinations for pneumococcal CAP were calculated using an unconditional logistic regression model because of the small number of outcome indices. Variables used here were the same as those used in the multivariate analysis model calculated for all-cause pneumonia, in addition to matching variables (sex and age).

All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

ABBREVIATIONS

ADL	activities of daily living
BMI	body mass index
CAP	community-acquired pneumonia
CI	confidence interval

COP	community-onset pneumonia
CRP	C-reactive protein
HR	hazard ratio
OR	odds ratio
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
TIV	trivalent influenza vaccine

Disclosure of potential conflicts of interest

The authors have no competing interests to declare.

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Note

The other members of the Pneumonia in Elderly People Study Group are listed as follows with their affiliations: Satoru Adachi (Kasadera Hospital); Akiko Maeda (Department of Public Health, Osaka City University Graduate School of Medicine); Noriko Kojimahara (Tokyo Women's Medical University); Ikuji Usami, Munehiro Kato, Toshinobu Yamamoto (Asahi Rosai Hospital); Kazuhide Yamamoto (Kazu Clinic); Yoichi Nakanishi, Takanari Kitazono (Graduate School of Medical Sciences, Kyushu University); Nobumitsu Fujisawa, Takafumi Matsumoto, Hideki Tashiro (St. Mary's Hospital); Masahiko Taketomi (Doukai Clinic); Tomoaki Iwanaga, Hiroko Nogami (Fukuoka National Hospital); Koichi Takano (Nishifukuoka Hospital); Ken Tonegawa (Nagoya City Koseiin Geriatric Hospital); Yoshimitsu Hayashi (Kasugai Municipal Hospital); Ikuo Ikeda (Ikeda Clinic); Shigeki Sugiyama (Sugiyama Clinic); Masahiro Aoshima (Kameda Medical Center); Yoshitaka Nakamori, Yasushi Seida, Yoshiko Kichikawa (Mishuku Hospital); Atsushi Nakamura (Graduate School of Medical Sciences, Nagoya City University); Yasuhito Iwashima (Iwashima Clinic); Yasuhiro Kojima (Kojima Clinic); Yasuo Yamada (Yama Clinic); Hidekazu Kawamura (Kawamura Clinic); Toshiaki Niwa (Hamada Asai Clinic); Atsuro Kawai (Kawai Clinic); Yuuji Ito, Emi Aoyama (Daiyukai Hospital); Noriko Kusada, Chizuko Sumida (Inazawa Municipal Hospital); Naoyuki Miyashita (Department of Internal Medicine, Kawasaki Medical School).

ORCID

Kei Nakashima http://orcid.org/0000-0001-6080-1801

References

1. Health, labour and welfare statistics association. Annual statistical report of national health conditions. Journal of health and welfare statistics. 2014;61:49–82 [in Japanese].
2. Nichol KL. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine. 1999;17:S91–3. doi:10.1016/S0264-410X(99)00114-0.
3. Hedlund J, Christenson B, Lundbergh P, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines elderly in elderly people: a 1-year follow-up. Vaccine. 2003;21:3906–11. doi:10.1016/S0264-410X(03)00296-2.
4. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J. 2004;23:363–68. doi:10.1183/09031936.04.00063504.
5. Hung IFN, Leung AYM, Chu DWS, Leung D, Cheung T, Chan CK, Lam CLK, Liu S-H, Chu C-M, Ho P-L, et al. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: A prospective cohort study. CID. 2010;51:1007–16. doi:10.1086/656587.
6. Chang YC, Chou YJ, Liu JY, Yeh TF, Huang N. Additive benefits of pneumococcal and influenza vaccines among elderly persons aged 75 years or older in Taiwan — A representative population-based comparative study. J Infect. 2012;65:231–38. doi:10.1016/j.jinf.2012.04.014.
7. Li C, Gubbins PO, Chen GJ. Prior pneumococcal and influenza vaccinations and in-hospital outcomes for community-acquired pneumonia in elderly veterans. J Hosp Med. 2015;10:287–93. doi:10.1002/jhm.2328.
8. Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, D'Alessandro-Gabazza C, Nakayama S, Nishikubo K, Noguchi T, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomized and placebo controlled trial. BMJ. 2010;340:c1004. doi:10.1136/bmj.c1004.
9. Kawakami K, Ohkusa Y, Kuroki R, Tanaka T, Koyama K, Harada Y, Iwanaga K, Ymaryo T, Oishi K. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine. 2010;28:7063–69. doi:10.1016/j.vaccine.2010.08.010.
10. Kondo K, Suzuki K, Washio M, Ohfuji S, Fukushima W, Maeda A, Hirota Y. Effectiveness of 23-valent pneumococcal polysaccharide vaccine and seasonal influenza vaccine for pneumonia among the elderly –selection of controls in a case-control study. Vaccine. 2017;35:4806–10. doi:10.1016/j.vaccine.2017.07.005.
11. The Japanese respiratory society. The JRS guidelines 2017 for the management of pneumonia in adults. Tokyo:NPC; 2017. p.155–158 [in Japanese].
12. Hoshi SL, Kondo M, Okubo I. Pricing and uptake rate of public funded pneumococcal vaccination for the elderly in Japan. Nihon Koshu Eisei Zasshi. 2010;57(7):505–13. [in Japanese].
13. Pneumococcal infection (elderly person). Ministry of health, labour and welfare. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/haienkyukin/index_1.html [accessed 18 November 2018].
14. Naito T, Matsuda N, Tanei M, Watanabe Y, Watanabe A. Relationship between public subsidies and vaccination rates with the 23-valent pneumococcal vaccine in elderly persons, including the influence of the free vaccination campaign after the Great East Japan Earthquake. J Infect Chemother. 2014;20:450–53. doi:10.1016/j.jiac.2014.03.004.
15. The number of the periodical vaccination enforcers. Ministry of health, labour and welfare. https://www.mhlw.go.jp/topics/bcg/other/5.html [accessed 24 October 2018].
16. Tin Tin Htar M, Stuurman AL, Ferreira G, Alicino C, Bollaerts K, Paganino C, Reinert RR, Schmitt H-J, Trucchi C, Vestraeten T, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PLoS One. 2017;12(5):e0177985. doi:10.1371/journal.pone.0177985.
17. Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, Ishida M, Hamaguchi S, Aoshima M, Ariyoshi K, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17:313–21. doi:10.1016/S1473-3099(17)30049-X.
18. Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, Llor C. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly: the EVAN-65 study. CID. 2006;43:860–68. doi:10.1086/507340.
19. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, de Diego C, Valdivieso A, Hospital I, Gomez-Bertomeu F, Raga X. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. Vaccine. 2009;27:1504–10. doi:10.1016/j.vaccine.2009.01.013.

20. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, Gomez-Bertomeu F, Figuerola-Massana E, Raga-Luria X, Hospital-Guardiola I. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥60 years: 3 years of follow-up in the CAPAMIS study. CID. 2014;58:909–17. doi:10.1093/cid/ciu002.
21. Ubukata K, Chiba N, Hanada S, Morozumi M, Wajima T, Shouji M, Iwata S. Serotype changes and drug resistance in invasive pneumococcal diseases in adults after vaccinations in children, Japan, 2010-2013. Emerg Infect Dis. 2015;21:1956–65. doi:10.3201/eid2111.142029.
22. Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, Reingold A, Thomas A, Schaffner W, Craig AS, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201:32–41. doi:10.1086/648593.
23. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, Petit S, Zansky SM, Harrison LH, Reingold A, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015;15:301–09. doi:10.1016/S1473-3099(14)71081-3.
24. Feikin DR, Kagucia EW, Loo JD, Link-Gelles R, Puhan MA, Cherian T, Levine OS, Whitney CG, O'Brien KL, Moore MR. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013;10:e1001517. doi:10.1371/journal.pmed.1001517.
25. Morimoto K, Suzuki M, Ishifuji T, Yaegashi M, Asoh N, Hamashige N, Abe M, Aoshima M, Ariyoshi K. The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PLoS One. 2015;10:e0122247. doi:10.1371/journal.pone.0122247.
26. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. Japanese Study Group on Aspiration Pulmonary Disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56(3):577–79. doi:10.1111/j.1532-5415.2008.01597.x.
27. Ishiguro T, Takayanagi N, Yamaguchi S, Yamakawa H, Nakamoto K, Takaku Y, Miyahara Y, Kagiyama N, Kurashima K, Yanagisawa T, et al. Etiology and factors contributing to the severity and mortality of community-acquired pneumonia. Intern Med. 2013;52:317–24. doi:10.2169/internalmedicine.52.8830.
28. Washio M, Kondo K, Fujisawa N, Harada E, Tashiro H, Mizokami T, Nogami H, Iwanaga T, Nakanishi Y, Suzuki K, et al. Hypoalbuminemia, influenza vaccination and other factors related to the development of pneumonia acquired outside hospitals in southern Japan: A case–control study. Geriatr Gerontol Int. 2016;16:223–29. doi:10.1111/ggi.12456.
29. Govaert ThME, Thijs CTMCN, Masurel N, Sprenger MJW, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccine in elderly individuals: a randomized double-blind placebo-controlled trial. JAMA. 1994;272:1661–65. doi:10.1001/jama.1994.03520210045030.
30. Hirota Y, Fukushima W, Fujieda M, Ohfuji S, Maeda A. Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: a Japanese perspective. Vaccine. 2008;26:6455–58. doi:10.1016/j.vaccine.2008.06.041.
31. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine. 2013;31:2165–68. doi:10.1016/j.vaccine.2013.02.053.
32. Sullivan SG, Tay EL, Kelly H. Variable definitions of the influenza season and their impact on vaccine effectiveness estimates. Vaccine. 2013;31:4280–83. doi:10.1016/j.vaccine.2013.06.103.
33. Mufson MA, Krause HE, Schiffman G. Long-term persistence of antibody following immunization with pneumococcal polysaccharide vaccine. Proc Soc Exp Biol Med. 1983;173:270–75. doi:10.3181/00379727-173-41643.
34. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 1997;46(RR–8):1–24.
35. Sumitani M, Tochino Y, Kamimori T, Fujiwara H, Fujikawa T. Additive inoculation of influenza vaccine and 23-valent pneumococcal polysaccharide vaccine to prevent lower respiratory tract infections in chronic respiratory disease patients. Intern Med. 2008;47:1189–97. doi:10.2169/internalmedicine.47.0799.
36. Kondo K, Suzuki K, Washio M, Ohfuji S, Fukushima W, Maeda A, Hirota Y. Association between monovalent influenza A (H1N1) pdm09 vaccine and pneumonia among the elderly in the 2009–2010 season in Japan: a case-control study. Hum Vaccin Immunother. 2015;11:1088–93. doi:10.1080/21645515.2015.1016668.
37. Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y. Effectiveness of acellular pertussis vaccine in a routine immunization program: A multicenter, case-control study in Japan. Vaccine. 2015;33:1027–32. doi:10.1016/j.vaccine.2015.01.008.