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Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in older individuals after the introduction of childhood 13-valent pneumococcal conjugate vaccine: A multicenter hospital-based case-control study in Japan

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ABSTRACT

Background: In the era of childhood pneumococcal conjugate vaccine (PCV) immunization, especially 13-valent pneumococcal conjugate vaccine (PCV13) immunization, serotype replacement of *Streptococcus pneumoniae* and herd immunity in adults have been reported worldwide. Therefore, continuous evaluation of the effectiveness of the pneumococcal vaccine in adults is crucial because vaccine effectiveness may change owing to these factors. The purpose of this study was to evaluate the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) against all-cause pneumonia and pneumococcal pneumonia in older individuals with community-acquired pneumonia (CAP) after the introduction of childhood PCV13 in Japan, a topic that has remained largely unexplored.

Methods: We evaluated pneumococcal vaccine effectiveness in this multicenter, matched case-control study conducted in hospitals and clinics. Cases included patients (aged $\geq$ 65 years) newly diagnosed with CAP between October 2016 and September 2019. A maximum of five non-pneumonia control patients matched for sex, school grade, date of outpatient visit, and medical institution were selected for each case. Conditional logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of pneumococcal vaccines for the occurrence of all-cause CAP and pneumococcal CAP.

Results: The analysis included 740 individuals (142 patients and 598 controls). The median age of participants was 75 years (men: 54%). The adjusted OR for pneumococcal vaccination against all-cause CAP was 1.31 (95% CI: 0.84–2.06), while that for PPSV23 vaccination in the previous 5 years was 1.33 (95% CI: 0.85–2.09). The adjusted OR for PPSV23 vaccination in the previous 5 years against pneumococcal CAP was 0.93 (95% CI: 0.35–2.50).

Conclusions: This study was unable to demonstrate the effectiveness of PPSV23 against all-cause and pneumococcal pneumonia after the introduction of childhood PCV13 in Japan. Nonetheless, additional studies are needed to validate these results.

Abbreviations: ADL, Activities of daily living; BMI, body mass index; CAP, Community-acquired pneumonia; CI, confidence intervals; IPD, Invasive pneumococcal disease; OR, Odds ratio; PCV, Pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; VE, Vaccine effectiveness.

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1. Introduction

Community-acquired pneumonia (CAP) in the elderly is a leading cause of hospitalization, morbidity, and mortality globally [1]. Important preventive measures, such as vaccination, can substantially reduce the burden of pneumococcal diseases in vaccinated individuals, especially among older individuals [2,3]. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was administered worldwide to prevent pneumococcal disease. A *meta*-analysis assessing the efficacy of PPSV 23 published in 2013 showed a protective vaccine efficacy of 74% for invasive pneumococcal disease (IPD) and an effectiveness of 54% for noninvasive pneumococcal pneumonia [2]. Recently, upon the release of international guidelines, pneumococcal conjugate vaccines (PCVs) have been integrated into childhood immunization regimens globally to prevent IPD in vaccinated children [4–6]. In particular, the 13-valent pneumococcal conjugate vaccine (PCV13) has replaced the 7-valent pneumococcal conjugate vaccine (PCV7) as the standard PCV administered to children.

In Japan, several studies have evaluated the efficacy and effectiveness of PPSV23 toward CAP including all-cause pneumonia and pneumococcal pneumonia in elderly population since before PCV13 was introduced [7–10]. Fig. 1 shows the history of pneumococcal vaccine in Japan and reports on the efficacy and effectiveness of PPSV23 for pneumonia. Two randomized control trials (RCTs) were reported from 2005 to 2009 before the introduction of PCV7 for children [7,8]. The study conducted by Kawakami et al., conducted from October 2005 to November 2007 in older subjects aged ≥ 65 years who had already received the influenza vaccine, reported significant efficacy against all-cause pneumonia in a population over 75 years old (41.5%) and with difficulty walking (62.7%) [7]. The study by Maruyama et al. from March 2006 to March 2009 showed a 44.8% reduction in all-cause pneumonia and a 63.8% reduction in pneumococcal pneumonia among nursing home residents [8]. As for studies conducted after the introduction of PCV 7 (before the introduction of childhood PCV13), a test-negative case-control study conducted by Suzuki M et al., which used a multi-center registry of CAP from September 2011 to August 2014, showed a 27.4% effectiveness of PPSV23 against all pneumococcal pneumonia [9]. During the same period (October 2010 to September 2014), our group conducted a multicenter prospective case-control study in Japan, and we reported the significant effectiveness of PPSV23 for community-acquired pneumococcal pneumonia (adjusted odds ratio [OR]: 0.23, corresponding vaccine effectiveness [VE]: 77%) though we could not confirm the effectiveness of PPSV 23 for all-cause pneumonia [10].

In the era of childhood PCV immunization, especially PCV13, serotype replacement of pneumococcal disease and herd immunity in adults has been reported worldwide [11–14]. Continuous evaluation of pneumococcal vaccine effectiveness in adults is important because VE may change as a result of these factors. Evidence of the efficacy and effectiveness of pneumococcal vaccines in older individuals after the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in children is still limited. In Fig. 1, we show the transition of PCV7, PCV13, and PPSV23 in Japan. After PCV7 was licensed in Japan in February 2010, the estimated rates of PCV7 vaccination in children aged < 5 years increased from < 10% to 80–90% by 2012 and to > 95% by 2013 [15]. PCV7 was integrated into the national immunization program of Japan in April 2013 but was replaced by PCV13 in November 2013. The vaccination rate among children aged < 5 years remained at > 95% in the PCV13 era [16]. As a result of the introduction of pediatric PCV13 in Japan, the survey of pneumococcal pneumonia serotypes based on the same registry from September 2011 to August 2014 used by Suzuki M's study and the next period from May 2016 to April 2017 showed that the non-vaccine serotypes (non-PPSV23 and non-PCV13 serotypes) increased from 28 % to 49% [12]. In addition, from October 2014, individuals aged ≥ 65 years as well as those aged 60–64 years with underlying diseases were included in the national immunization program for vaccination with PPSV23. In this program, PPSV23 was annually administered to individuals aged ≥ 65 years who would become 65, 70, 75, 80, 85, 90, and

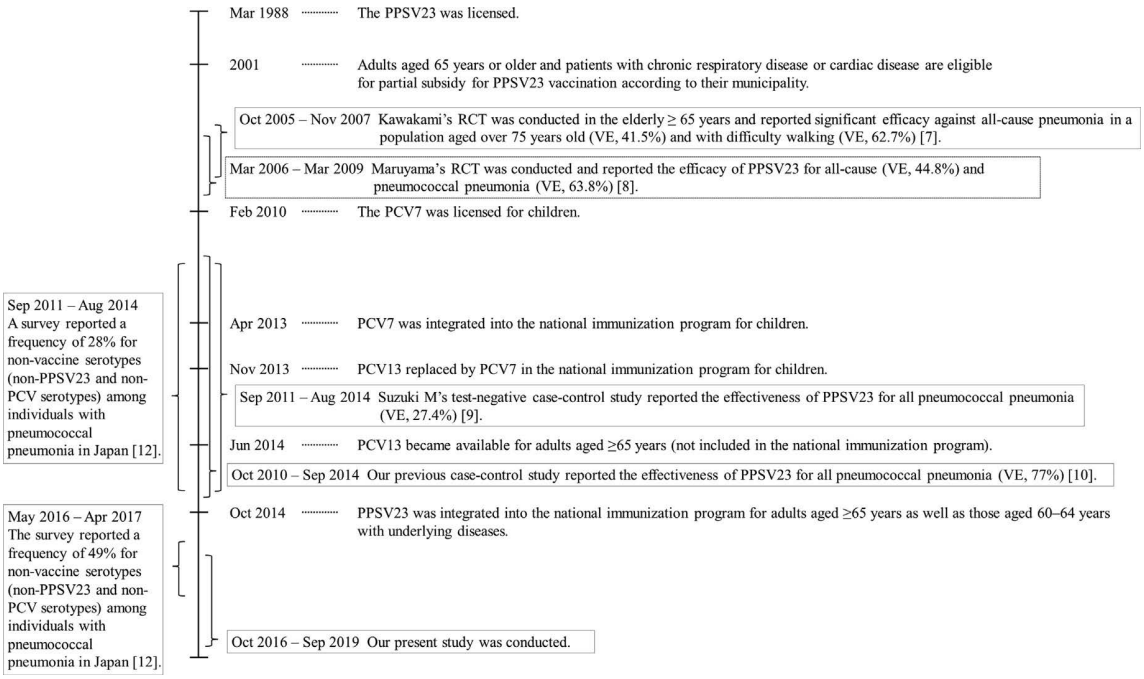

Fig. 1. History of pneumococcal vaccine in Japan and reports on the efficacy and effectiveness of PPSV23 for pneumonia. CAP, community-acquired pneumonia; OR, odds ratio; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RCT, randomized control trial; VE, vaccine efficacy/effectiveness.

95 years old from April 2nd to April 1st of the following year in 5-year increments. The PPSV23 vaccination rate in adults aged ≥ 65 years increased from 20% in 2013 to 50% in 2016 [17]. In June 2014, PCV13 vaccination became available for adults aged ≥ 65 years; however, it has not been included in the national immunization program. Under these circumstances, in this multicenter case-control study, we evaluated the protective ability of the pneumococcal vaccine against all-cause CAP and pneumococcal CAP from October 2016 to September 2019—after vaccination with PPSV23 was included in the national immunization program for adults aged ≥ 65 years—after the introduction of childhood PCV13 in Japan.

2. Material and methods

2.1. Study design

Between October 1, 2016 and December 31, 2019, we conducted a hospital-based matched case-control study at 41 health care facilities, which included 30 hospitals and 11 clinics in the Hokkaido, Tohoku, Hokuriku, Kanto, Tokai, Kinki, Shikoku, and Kyushu regions to cover all of Japan. Cases included in this study were restricted to older adults living at home who developed pneumonia, and the outcomes focused on CAP. Since cases in this study were patients with CAP diagnosed in the outpatient (including emergency) department in clinics or hospitals, we selected controls from outpatients of the same clinics or hospital. Japan does not have a family doctor system like the United Kingdom, and patients have free access to hospitals. Clinics generally treat patients with mild underlying diseases, while hospitals often treat patients with moderate to severe underlying diseases, but the situation varies by region. For example, doctors at hospitals in the countryside may also treat patients with mild underlying diseases and serve like family doctors. Some patients may regularly visit both the clinic (for mild disease) and the hospital (for moderate to severe disease). Vaccinations are administered at a clinic or hospital in the community where the patient lives. At the time of this study, a national immunization program of PPSV23 for elderly aged ≥ 65 years was recently started, and vaccinations were administered to eligible individuals at the clinic or hospital in the residential area. All study participants provided informed consent orally prior to participation after receiving an explanation of the study. The study protocol was approved by the Ethics Review Boards of Nagoya City University School of Nursing, Osaka City University Graduate School of Medicine, and Kameda Medical Center, and each of the participating institutions. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

2.2. Definition of cases and controls

Cases included individuals newly diagnosed with CAP aged ≥ 65 years at the outpatient department (including the emergency department) between October 1, 2016 and September 30, 2019. Although we do not clearly define the duration of the illnesses, patients were registered on the same day of diagnosis of pneumonia in the outpatient or emergency department. The pneumonia diagnosis was made by a physician at a participating institution based on clinical symptoms (fever, cough, sputum), an elevated leukocyte count or C-reactive protein level, and the appearance of an infiltration on either chest X-ray or chest computed tomography. Judgment of the radiological change caused by pneumonia on chest imaging was at the attending physician's discretion in this study. However, if past images are available, physicians usually diagnose pneumonia when new shadows are observed. Specific pneumococcal pneumonia diagnosis was confirmed by sputum culture (semiquantitative culture method) and Gram staining (Gram positive cocci in pairs), blood culture, or a positive pneumococcal urinary antigen test.

Controls were outpatients without pneumonia who visited the same clinics and hospitals as the cases and were matched for facility, sex, birth year (fiscal year), and the date (i.e., within 3 months of confirming each case). Routine pneumococcal vaccination in Japan is annually administered to individuals aged ≥ 65 years who would become 65, 70, 75, 80, 85, 90, and 95 years old from April 2nd to April 1st of the following year in 5-year increments; thus, we matched patients for birth year by fiscal year. We aimed to select up to five controls for each case where possible. In our previous case-control study, we discussed the importance of selecting controls when evaluating the effectiveness of a vaccine that is not routinely administered, taking into account background factors that may affect the physician's probability of recommending the vaccine (e.g., by selecting two controls for one case of pneumonia, one respiratory medicine control, and one non-respiratory medicine control) [18]. However, the current study was designed to evaluate the effectiveness of pneumococcal vaccine after the introduction of the national immunization program with PPSV23 in Japan, and thus, we considered that physician recommendations for pneumococcal vaccination would not differ significantly among the medical departments enrolling controls. Therefore, we defined "controls" as outpatients at the same medical institution and did not clearly stipulate the department that would select the controls in order to enroll controls (maximum 5) from a wide variety of clinical departments.

The exclusion criteria for cases and controls included: residing at a nursing home, having aspiration pneumonia (i.e., pneumonia caused by inhalation during eating or vomiting), having any malignant tumors, currently taking oral steroids or immunosuppressants, or having a history of splenectomy. Patients with malignancy were excluded because they may be immunosuppressed. In addition, nursing home residents were also excluded because, according to the latest guidelines at the time this study was initiated in 2016, they were classified in the category of healthcare-associated pneumonia (HCAP), which was considered to have characteristics similar to those of nosocomial pneumonia, including a different pneumonia pathogen and prognosis from those of patients with usual CAP [19].

Cases and controls were enrolled prospectively. After enrollment of the cases, corresponding matched controls from outpatient departments were enrolled within 3 months. In order to reduce the bias of number of cases between facilities, the maximum number of cases that each facility could enroll in a year was limited to up to 5 matched sets (5 cases and 25 controls).

2.3. Data collection

For both cases and controls, the attending physician collected the following clinical information via a questionnaire: a) sex, age, birth date, department (internal medicine department of the hospital, non-internal medicine departments of the hospital, or clinics), presence or absence of underlying respiratory disease (chronic bronchitis, pulmonary emphysema, interstitial pneumonia, asthma, pulmonary tuberculosis sequelae, or other respiratory disease), and vaccination status (date of the administration of PPSV23, PCV13, and quadrivalent influenza vaccine) via self-declaration; b) pneumonia-related information (for cases only), including date of diagnosis, clinical symptoms, or laboratory data in relation to the diagnosis of pneumonia (leukocyte count or level of C-reactive protein) and results from diagnostic tests (rapid diagnostic influenza test, pneumococcal urinary antigen test, or sputum culture).

In addition, the study participants or their next of kin were asked to complete a self-administered questionnaire that included the following information: age, height, body weight, co-residence with children aged ≤ 6 years, activities of daily living (ADL; bedridden, semi-bedridden, semi-self-supported, or self-supported), presence or absence of underlying diseases (hypertension, dyslipidemia, heart disease, stroke, diabetes mellitus, or renal disease), presence or absence of respiratory diseases (chronic bronchitis, pulmonary emphysema, interstitial pneumonia, asthma, pulmonary tuberculosis sequelae, or other respiratory disease), and vaccination status (PPSV23 in the past 5 years or influenza vaccination in the past 6 months).

2.4. Statistical analysis

Since this was an observational study, we performed an approximate sample size calculation to provide a guide for the numbers of participant enrolled. A previous randomized control trial showed an efficacy of approximately 40% of PPSV23 for all-cause CAP [8]. Based on this result, assuming an OR of 0.6 for "vaccinated" relative to "unvaccinated" for all-cause CAP, the proportion of "vaccinated" individuals in the control group to be 30% based on the results of our previous case-control study [10], $\alpha = 0.05$, $\beta = 0.8$, and a case: control ratio of 1:5, the number of subjects needed to detect a statistically significant effect was estimated at 200 cases and 1,000 controls, for a total of 1,200 participants.

All underlying diseases were classified as either present or absent, and ADL was classified as "not independent" (bedridden, semi-bedridden, or semi-self-supported) or "independent" for the analysis. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in meters (m^2) and was categorized into three levels (<18.5, 18.5–24.9, and ≥ 25.0).

Wilcoxon rank-sum test, chi-square test, or Fisher's exact test was used as appropriate for data comparison between cases and controls. A conditional logistic regression model was used to calculate the crude and adjusted ORs and 95% confidence intervals (CIs) for PPSV23 and influenza vaccinations for all-cause CAP. Potential confounders for adjustment included variables showing a p-value of < 0.20 or previously researched and established risk factors for pneumonia, including respiratory disease and diabetes mellitus [20]. The validity of including variables with a p-value of < 0.20 in the multivariate analyses has been described in previous studies [21–23].

First, we analyzed the effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) for all-cause CAP. Second, we analyzed the effectiveness of PPSV23 vaccination alone administered in the previous 5 years for all-cause CAP because the serum-specific antibody level decreases 3–5 years after PPSV23 vaccination [24]. Finally, we analyzed the effectiveness of PPSV23 vaccination alone administered in the previous 5 years for pneumococcal CAP.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

3. Results

A flowchart illustrating the enrollment of the study population for conditional logistic regression analysis is shown in Fig. 2. Although we could not reach our pre-calculated sample size of 1,200 participants, 834 (159 Cases and 675 controls) participants were finally enrolled. Out of the original sample of 834 participants, 37 controls were excluded because they did not meet the eligibility criteria; as a result, a total of 797 participants (159 cases and 638 controls) were considered eligible. The following is a breakdown of the data for the enrolled 797 participants (159 cases and 638 controls). Regarding the departments of enrolled participants, of the 159 cases, 115 were enrolled at the internal medicine department of the hospital, 3 were enrolled at unknown departments of the hospital, and 41 were enrolled at clinics. Among the controls, 349 were enrolled at the internal medicine department of the hospital, 60 were enrolled at non-internal medicine departments of the hospital (including 2 at the department of general surgery, 28 at the department of orthopedics, 5 at the department of dermatology, 12 at the department of ophthalmology, 6 at the department of otolaryngology, 5 at the department of urology, 1 at the department of gynecology, and 1 at an unknown department), 34 were enrolled at unknown departments of the hospital, and 195 were enrolled at clinics. After the exclusion of 46 participants due to missing values for the examined variables and 11 cases without controls, a total of 740 individuals (142 cases and 598 controls) were included in the analysis of the effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) for all-cause pneumonia. Of the 142 cases with pneumonia, 10 were matched with one control each, 7 with two controls, 11 with three controls, 18 with four controls, and 96 with five controls. Out of the 740 individuals included in the first analysis, 694 (138 cases and 556 controls) were included in the analysis of the effectiveness of PPSV23 vaccination only, administered in the previous 5 years for all-cause CAP, after 28 who had PCV immunization and 18 with missing information on PPSV23 vaccination in the previous 5 years were excluded. Finally, 158 participants (31 cases and 127 controls) were included in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years for pneumococcal CAP. Of the 31 cases of pneumococcal pneumonia, 8 were diagnosed based on pneumococcal urinary antigen and sputum culture, 18 were diagnosed based on pneumococcal urinary antigen alone, and 5 were diagnosed based on sputum culture alone.

The characteristics of the cases and controls included in the analysis of the effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) for all-cause pneumonia are shown in Table 1. The combined pneumococcal vaccination rate for PPSV23 only, PCV13 only, both vaccines, and unknown was 58% among cases and 56% among controls, and the influenza vaccination rate was 42% among cases and 44% among controls. The classification of the pneumococcal vaccine in cases and controls was as follows: only PPSV23 in 79 cases (56%) and 310 controls (52%); only PCV13 in 0 cases (0%) and 10 controls (2%); both PPSV23 and PCV13 in 2 cases (1%) and 11 controls (2%); and unknown in 2 cases (1%) and 4 controls (1%). The percentage of patients with a BMI < 18.5 kg/m^2 was significantly greater in the cases than in the controls (23% vs. 11%, $p < 0.001$). The frequency of dyslipidemia was significantly greater in the controls than in the cases (19% vs. 29%, $p = 0.016$). Loss of independence (10% vs. 5%, $p = 0.012$) and living with children aged < 6 years (15% vs. 3%, $p < 0.001$) were significantly more frequent in the cases than in the controls. Respiratory disease (48% vs. 41%, $p = 0.144$) and diabetes mellitus (25% vs. 23%, $p = 0.691$), which are established risk factors for pneumonia and potential confounders, were more frequent among cases than among controls. Other variables with a p-value of < 0.20, which was a criterion for inclusion as an adjustment factor in the adjusted analysis, including hypertension (47% vs. 54%, $p = 0.174$), digestive disease (9% vs. 14%, $p = 0.110$), and liver disease (2% vs. 5%, $p = 0.170$), were more frequent among controls than among cases. The causative pathogen in 32 (23%) out of the 142 patients with CAP was pneumococcus.

The crude and adjusted ORs for all-cause CAP for each variable are shown in Table 2. The adjusted OR for pneumococcal vaccination was 1.31 (95% CI: 0.84–2.06); the effectiveness of the pneumococcal vaccine for all-cause CAP was not detected. The adjusted OR for influenza vaccination against pneumonia decreased to 0.77 (95% CI: 0.47–1.26), but the difference was not significant. The

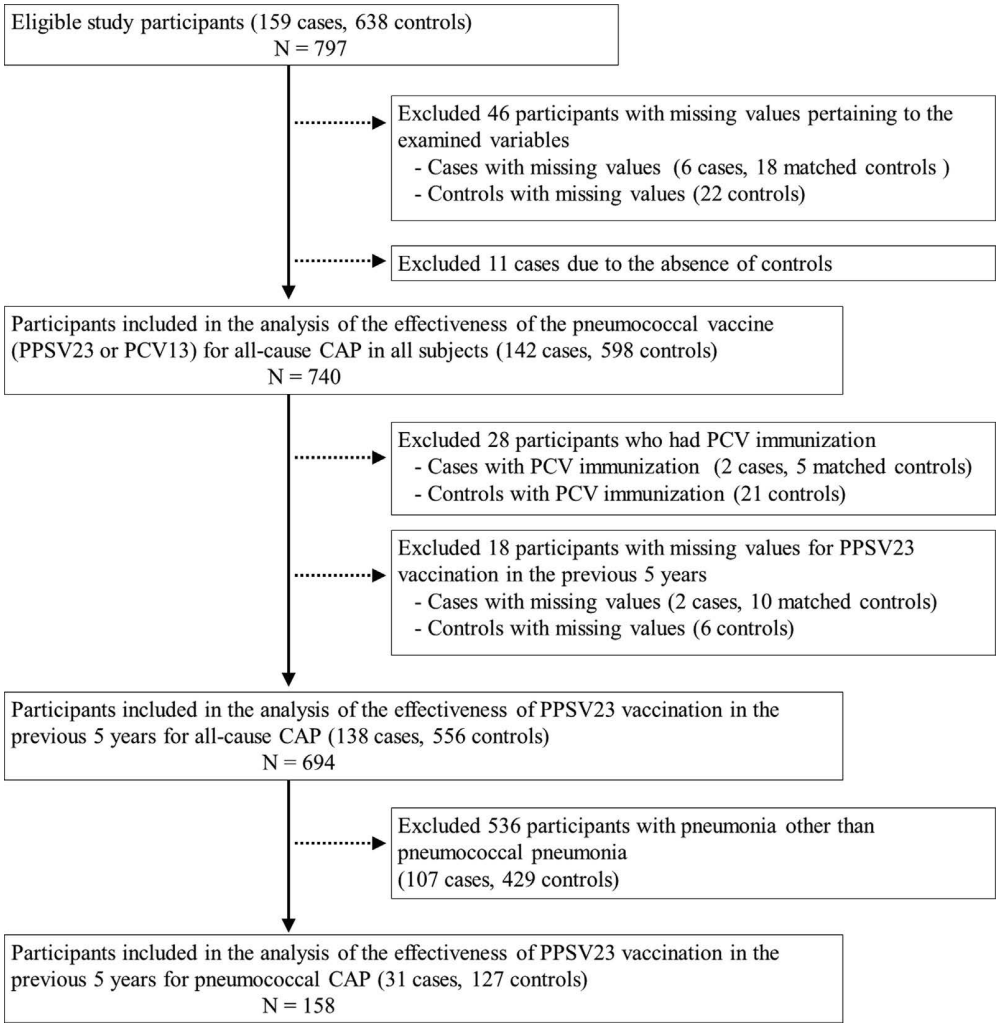

Fig. 2. Flowchart of the enrollment of the study population for conditional logistic regression analysis. CAP, community-acquired pneumonia; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

adjusted ORs for a BMI < 18.5 kg/m^2, inability to independently perform ADL, and living with children aged < 6 years were 1.92 (95% CI: 1.10–3.35), 2.33 (95% CI: 1.09–4.98), and 6.14 (95% CI: 2.87–13.14), respectively, showing a significant increase.

The characteristics of the cases and controls included in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years for all-cause CAP are shown in Supplementary Table 1. The proportion of individuals with PPSV23 vaccination in the previous 5 years among cases and controls was 51% and 48%, respectively; whereas the proportion among those with influenza vaccination was 41% and 42%, respectively. The crude and adjusted ORs for all-cause CAP for each variable are presented in Table 3. The adjusted OR for all-cause CAP in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years was 1.33 (95% CI: 0.85–2.09), whereas that for influenza vaccination was 0.79 (95% CI 0.48–1.31). The adjusted ORs for a BMI < 18.5 kg/m^2, inability to independently perform ADL, and living with children aged < 6 years were 1.97 (95% CI: 1.11–3.49), 2.61 (95% CI: 1.20–5.68), and 7.17 (95% CI: 3.19–16.12), respectively, showing a significant increase.

Group comparisons of characteristics included in the analysis of the effectiveness of PPSV23 vaccination administered in the previous 5 years for pneumococcal CAP are shown in Supplementary Table 2. The proportion of individuals with PPSV23 vaccination in the previous 5 years among cases and controls was 42% and 43%, respectively; while among those with influenza vaccination, the proportion was 35% and 33%, respectively. The crude and adjusted ORs for pneumococcal CAP for each variable are presented in Table 4. The adjusted OR for pneumococcal CAP in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years was 0.93 (95% CI: 0.35–2.50); significant effectiveness of PPSV23 for pneumococcal CAP was not detected, although the OR was less than unity. The adjusted OR for living with children aged < 6 years showed a significant increase of 10.94 (95% CI: 1.97–60.70).

4. Discussion

In this study, we evaluated the effectiveness of the pneumococcal vaccine for all-cause CAP and pneumococcal CAP in the elderly population aged ≥ 65 years after vaccination with PPSV23 was included in the national immunization program and in the era of childhood PCV13 immunization in Japan. The effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) against all-cause CAP in the elderly population was not detected. The preventive effect against all-cause CAP could not be detected even in the analysis of the effectiveness of PPSV23 vaccination in the previous

Table 1
The characteristics of cases and controls included in the analysis of the effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) (N = 740).

Characteristics	Cases	Controls	*P**
	n = 142	n = 598	
Age (years)			
Median (range)	75 (65–90)	75 (65–91)	0.987
Sex			
Male	79 (56)	317 (53)	0.573
Female	63 (44)	281 (47)	
Pneumococcal vaccine			
Unvaccinated	59 (42)	263 (44)	0.600
Vaccinated	83 (58)	335 (56)	
PPSV23 only	79 (56)	310 (52)	
PCV13 only	0 (0)	10 (2)	
Both	2 (1)	11 (2)	
Unknown	2 (1)	4 (1)	
Influenza vaccine			
Unvaccinated	83 (58)	335 (56)	0.600
Vaccinated	59 (42)	263 (44)	
Body mass index (kg/m^2)			
< 18.5	33 (23)	64 (11)	< 0.001
18.5–24.9	87 (61)	374 (63)	
≥ 25.0	22 (15)	160 (27)	
Underlying disease			
Respiratory disease	68 (48)	246 (41)	0.144
Hypertension	67 (47)	320 (54)	0.174
Dyslipidemia	27 (19)	174 (29)	0.016
Heart disease	19 (13)	103 (17)	0.267
Stroke	6 (4)	27 (5)	0.881
Renal disease	9 (6)	54 (9)	0.302
Digestive disease	13 (9)	85 (14)	0.110
Diabetes mellitus	35 (25)	138 (23)	0.691
Liver disease	3 (2)	28 (5)	0.170
Activities of daily living			
Independent	128 (90)	571 (95)	0.012
Not independent	14 (10)	27 (5)	
Living with children aged < 6 years			
No	121 (85)	582 (97)	< 0.001
Yes	21 (15)	16 (3)	
Pneumococcal pneumonia	32 (23)		

All data except age are expressed as n (%). Some total percentages are not equal to 100% because of rounding.
*Wilcoxon rank-sum test, chi-square test, or Fisher's exact test was performed as appropriate.
PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

5 years. In addition, the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years for pneumococcal pneumonia did not show a significant decrease in the adjusted OR of PPSV23 vaccination, although the OR was less than unity. Although we did not reach our pre-calculated target sample size of 1,200 subjects, 834 (159 Cases and 675 controls) participants were finally enrolled. Given the results of our previous case-control study in which we showed effectiveness against pneumococcal pneumonia with 161 cases and 308 controls, we considered that 834 participants are an adequate number of participants [10]. Although the insufficient number of participants may have affected the study results, even if we were to increase the number of cases to 1,200, we would expect the point estimate of the OR to remain unchanged, with only a somewhat narrower confidence interval.

In Japan, from October 2010 to September 2014, we previously examined the effectiveness of pneumococcal vaccines for pneumonia in older adults before vaccination with PPSV23 was included in the national immunization program after the introduction of childhood PCV7 and before the introduction of childhood PCV13 [10]. The preventive effect of pneumococcal vaccination against all-cause CAP was not demonstrated; however, when the cases were limited to pneumococcal CAP, the preventive effect of pneumococcal vaccination was noted [10]. In this study, however, we were unable to demonstrate the effectiveness of PPSV23 for all-cause and pneumococcal CAP. The reason could be related to the herd immunity effect of regular vaccination with PCV13 in children [14,25]. The transmission of pneumococcus from children is considered one of the causes of pneumococcal infection in the elderly [26]. Widespread use of PCV13 among children has reduced the pneumococcal colonization rate in the upper respiratory tract among children and has had the indirect effect of reducing pneumococcal infections in adults [11]. In addition, according to a recent study in Japan, the non-vaccine serotypes (non-PPSV23 and non-PCV13 serotypes) increased from 28% (September 2011 to August 2014) to 49% (May 2016 to April 2017) after the introduction of childhood PCV13 on November 2013; serotype replacement has been reported worldwide [12,14,27], thus it is possible that serotype replacement of *Streptococcus pneumoniae* makes it difficult to detect the preventive effect on pneumonia. Another possible reason why the effectiveness of PPSV23 could not be detected in this study is the difference of methodology between the current study and the previous study [10]. We have made changes in our methodology compared to the previous study, such as increasing the number of participating sites (from 24 to 41 medical institutions), limiting the maximum number of cases per site up to five matched sets (up to 5 cases and 25 controls) in a year, and increasing the maximum number of controls per case from two to five. We cannot rule out the possibility that these methodological changes may have led to different results from those of the previous study. Further, we cannot deny the possibility that there may be an important underlying difference that cannot be offset by adjustment in the statistical analysis considering the difference in BMI distribution between cases and controls and failure to obtain the socioeconomic information of the participants.

There remains controversy surrounding the effectiveness of PPSV23 against CAP. The reported VE of pneumococcal immunization differs across previous studies. As we mentioned in the Introduction section, in Japan, an RCT conducted by Kawakami et al. [7] reported the significant efficacy of PPSV23 for preventing all cause pneumonia in a population aged over 75 years (41.5%) with difficulty walking (62.7%). In the same period, another RCT conducted by Maruyama et al. reported the significant efficacy of PPSV23 for all cause (44.8%) and pneumococcal pneumonia (63.8%) in nursing home residents in the period before the introduction of childhood PCV7 [8]. A reduction in both invasive and non-invasive pneumococcal pneumonia following PPSV23 was reported in a Cochrane *meta*-analysis of 18 randomized trials including the Maruyama's and Kawakami's studies [2]. In addition, a recent test-negative case-control study reported that the VE of PPSV23 was 27.4% (95% CI: 3.2%–45.6%) against pneumococcal pneumonia and 33.5% (95% CI: 5.6%–53.1%) against PPSV23-serotype CAP in adults aged ≥ 65 years in Japan after the introduction of childhood PCV7 and before the introduction of childhood PCV13 [9]. In contrast, another test-negative case-control study in England, from 2013 to 2018 after the introduction of childhood PCV13, did not find a significant VE of PPSV23 against hospitalization with PPSV23-serotype CAP in adults aged ≥ 65 years (adjusted VE 20%, 95% CI: −5% to 40%); however this study showed a significant VE of PPSV23 against hospitalization in individuals aged ≥ 16 years (adjusted VE 24%, 95% CI: 5%–40%) [28]. Additionally, a recent matched case-control study performed in Korea did not detect a significant VE of PPSV23 against IPD (adjusted VE 28.5%, 95% CI: −5.8% to 51.6%) or nonbacteremic pneumococcal pneumonia (adjusted VE 10.2%, 95% CI: −15.1% to 30.0%) in the elderly aged ≥ 65 years in the development of ongoing herd immunity from the national pediatric PCV immunization program [29]. Nevertheless, in that study, a protective effectiveness against IPD (VE 57.4%, 95% CI: 19.4%–77.5%) and nonbacteremic pneumococcal pneumonia (VE 35.0%, 95% CI: 2.3%–56.7%) was identified in the subgroup analysis of the elderly aged 65–74 years [29]. Finally, a

Table 2
ORs for all-cause CAP in the analysis of the effectiveness of the pneumococcal vaccine (PPSV23 and/or PCV13) (N = 740).

		Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
Pneumococcal vaccine					
	Unvaccinated	1		1	
	Vaccinated	1.18 (0.79–1.76)	0.424	1.31 (0.84–2.06)	0.234
Influenza vaccine					
	Unvaccinated	1		1	
	Vaccinated	0.83 (0.53–1.30)	0.414	0.77 (0.47–1.26)	0.299
Body mass index (kg/m^2)					
	< 18.5	2.12 (1.30–3.47)	0.003	1.92 (1.10–3.35)	0.021
	18.5–24.9	1		1	
	≥25.0	0.55 (0.33–0.93)	0.030	0.55 (0.32–0.96)	0.037
Respiratory disease					
	No	1		1	
	Yes	1.31 (0.84–2.04)	0.243	1.13 (0.69–1.85)	0.626
Hypertension					
	No	1		1	
	Yes	0.77 (0.52–1.14)	0.184	0.89 (0.58–1.37)	0.591
Dyslipidemia					
	No	1		1	
	Yes	0.59 (0.35–0.98)	0.040	0.76 (0.44–1.30)	0.311
Digestive disease					
	No	1		1	
	Yes	0.58 (0.30–1.11)	0.101	0.58 (0.29–1.15)	0.119
Diabetes mellitus					
	No	1		1	
	Yes	1.04 (0.8–1.60)	0.862	1.33 (0.83–2.13)	0.234
Liver disease					
	No	1		1	
	Yes	0.41 (0.12–1.43)	0.164	0.37 (0.10–1.36)	0.135
Activities of daily living					
	Independent	1		1	
	Not independent	2.12 (1.04–4.32)	0.039	2.33 (1.09–4.98)	0.029
Living with children aged < 6 years					
	No	1		1	
	Yes	6.66 (3.23–13.7)	< 0.001	6.14 (2.87–13.14)	< 0.001

* Model included all variables in the Table.
ORs, odds ratios; CAP, community-acquired pneumonia; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; CI, confidence interval.

recent prospective test-negative study in South Korea, conducted from September 2015 to September 2017 after the introduction of childhood PCV13, assessing the effectiveness of PCV13, PPSV23, and sequential PCV13/PPSV23 against pneumococcal pneumonia did not find a statistically significant VE of PPSV23 against hospitalization with pneumococcal CAP in older adults aged ≥ 65 years (adjusted VE 11.0%, 95% CI: −26.4% to 37.3%) [30]. The different results among these studies could be because of the differences in study design, distributions of pneumococcal serotypes during the study period, characteristic of the study population, level of herd protection owing to childhood PCV immunization, methods for identifying vaccination status, types of primary outcomes, and diagnostic methods of pneumococcal pneumonia [30]. The effectiveness of PPSV23 against pneumococcal pneumonia could be declining because of the PCV immunization and serotype replacement in children, although the protective effectiveness against IPD was maintained in most recent studies [29,31,32].

Regarding the evaluated variables, there were significant differences between cases and controls for dyslipidemia, ADL, and living with children aged < 6 years, whereas no significant differences were noted for these variables between cases and controls in our previous study [10]. As for ADL and living with children aged < 6 years, in the previous study, we observed a tendency toward increased ORs for all-cause pneumonia, although this increase was not significant [10]. In the current study, the number of controls per case was increased to a maximum of five, which may have narrowed the confidence interval and allowed us to detect significant differences. In the present study, the percentage of controls with a BMI of ≥ 25 kg/m^2 was 27%, which is higher than the 22% of controls with a BMI of ≥ 25 kg/m^2 in the previous study. Therefore, it is possible that the proportion of controls with dyslipidemia was higher, resulting in a significant difference between cases and controls. In addition, in our previous study, we reported a difference between cases and controls for diabetes mellitus, which was not found in the current study [10]. It is difficult to speculate why in the previous study there were more cases of diabetes among controls than among cases (27% vs. 14%). However, since diabetes is considered a risk factor for pneumonia, a higher frequency of diabetes would have been expected among cases in the current study.

In most countries, vaccination with PPSV23 is recommended for the elderly population, with the optional administration of PCV13 after PPSV23 [32,33]. Unlike PPSV23, PCVs promote robust long-term protection with functional antibody responses by inducing T-cell–dependent immunity [3]. A previous study reported that the sequential administration of PCV13/PPSV23 vaccination is a more effective alternative for preventing pneumococcal CAP among the elderly aged 65–74 years than the single dose administration of PCV13 or PPSV23 [30]. Considering the ongoing serotype replacement of *Streptococcus pneumoniae*, further studies are needed to clarify the effectiveness of PPSV23, PCV13, or sequential PCV13/PPSV23 in relation to various outcomes—such as death, hospitalization due to pneumonia, all-cause CAP, pneumococcal CAP, and vaccine-type pneumococcal CAP—and patient characteristics, including age, sex, country, and ongoing herd immunity from childhood PCV13 immunization.

Our study has several limitations. First, as we mentioned earlier, the number of cases did not reach the pre-calculated sample size of 1,200 participants, as we enrolled only 834 participants. However,

Table 3
ORs for all-cause CAP in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years (N = 694).

		Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
PPSV23 in the previous 5 years					
	Unvaccinated	1		1	
	Vaccinated	1.24 (0.83–1.85)	0.303	1.33 (0.85–2.09)	0.212
Influenza vaccine					
	Unvaccinated	1		1	
	Vaccinated	0.87 (0.55–1.37)	0.549	0.79 (0.48–1.31)	0.360
Body mass index (kg/m^2)					
	< 18.5	2.20 (1.33–3.63)	0.002	1.97 (1.11–3.49)	0.020
	18.5–24.9	1		1	
	≥25.0	0.57 (0.34–0.97)	0.039	0.60 (0.34–1.05)	0.073
Respiratory disease					
	No	1		1	
	Yes	1.36 (0.87–2.13)	0.176	1.23 (0.75–2.01)	0.419
Heart disease					
	No	1		1	
	Yes	0.61 (0.34–1.10)	0.101	0.56 (0.30–1.04)	0.068
Dyslipidemia					
	No	1		1	
	Yes	0.56 (0.34–0.95)	0.030	0.68 (0.39–1.19)	0.179
Digestive disease					
	No	1		1	
	Yes	0.60 (0.31–1.16)	0.131	0.58 (0.29–1.17)	0.127
Diabetes mellitus					
	No	1		1	
	Yes	1.07 (0.68–1.67)	0.774	1.45 (0.89–2.37)	0.135
Liver disease					
	No	1		1	
	Yes	0.42 (0.12–1.45)	0.167	0.35 (0.10–1.29)	0.115
Activities of daily living					
	Independent	1		1	
	Not independent	2.19 (1.07–4.51)	0.033	2.61 (1.20–5.68)	0.015
Living with children aged < 6 years					
	No	1		1	
	Yes	7.67 (3.56–16.53)	< 0.001	7.17 (3.19–16.12)	< 0.001

* Model included all variables in the Table.
ORs, odds ratios; CAP, community-acquired pneumonia; PPSV23, 23-valent pneumococcal polysaccharide vaccine; ORs, odds ratios.

Table 4
ORs for pneumococcal CAP in the analysis of the effectiveness of PPSV23 vaccination in the previous 5 years (N = 158).

		Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
PPSV23 in the previous 5 years					
	Unvaccinated	1		1	
	Vaccinated	0.97 (0.41–2.29)	0.942	0.93 (0.35–2.50)	0.885
Influenza vaccine					
	Unvaccinated	1		1	
	Vaccinated	0.92 (0.33–2.62)	0.881	1.18 (0.36–3.84)	0.788
Respiratory disease					
	No	1		1	
	Yes	1.71 (0.67–4.36)	0.262	2.33 (0.86–6.33)	0.096
Dyslipidemia					
	No	1		1	
	Yes	0.40 (0.12–1.32)	0.132	0.43 (0.11–1.67)	0.223
Diabetes mellitus					
	No	1		1	
	Yes	0.97 (0.40–2.34)	0.947	1.04 (0.40–2.73)	0.932
Living with children aged < 6 years					
	No	1		1	
	Yes	10.25 (1.95–53.85)	0.006	10.94 (1.97–60.70)	0.006

*Model included all variables in the Table.
ORs, odds ratios; CAP, community-acquired pneumonia; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

as already mentioned, even if the number of participants was increased, the OR would not change. The 95% CI would only become narrower. Thus, we believe that the conclusion would not change. Second, we could not evaluate the serotype-specific effectiveness of PPSV23 because we did not evaluate the serotype of pneumococcal pneumonia. Third, we were unable to confirm the validity of the information regarding the vaccination status obtained from each patient's questionnaire. Fourth, there might have been a selection bias because our cases did not include patients who died of pneumonia outside hospitals. Fifth, we did not examine sociodemographic factors in this study. We could not adjust for socioeconomic status, which is unfortunate, considering that poverty is an important confounding factor in pneumococcal disease [34].

5. Conclusions

We could not detect the effectiveness of PPSV23 against all-cause CAP and pneumococcal CAP in the study population after the introduction of childhood PCV13 in Japan. Nonetheless, additional studies are needed to validate these results.

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Data statement

All datasets generated and analyzed during the study are available from the corresponding author upon request.

CRediT authorship contribution statement

Kei Nakashima: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Kanzo Suzuki:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Masahiro Aoshima:** Investigation, Resources, Writing – review & editing. **Mayumi Murabata:** Investigation, Resources, Writing – review & editing. **Kyoko Kondo:** Conceptualization, Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Satoko Ohfuji:** Conceptualization, Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Wakaba Fukushima:** Conceptualization, Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Akiko Maeda:** Conceptualization, Methodology, Writing – review & editing. **Yoshio Hirota:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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