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Safety and immunogenicity of sequential administration of PCV13 followed by PPSV23 in pneumococcal vaccine-naïve adults aged ≥ 65 years: Comparison of booster effects based on intervals of 0.5 and 1.0 year

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ABSTRACT

Objective: An open-label study was conducted to compare the safety and immunogenicity of a sequential administration of 13-valent pneumococcal conjugate vaccine (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) between an interval of 0.5 (0.5-y) and 1 year (1.0-y) in adults aged ≥ 65 years.

Methods: Pneumococcal vaccine-naïve adults aged ≥ 65 years (n = 129) received a sequential administration with an interval of 0.5-y or 1.0-y or received a single administration of PPSV23 (single PPSV23). We evaluated the immunogenicity before and 1 month after each vaccination and at 0.5-y intervals for 2 years. The primary endpoint was the increase in geometric mean fold rises (GMFRs) of immunoglobulin G (IgG) or opsonophagocytic activity (OPA) for eight common serotypes one month after one dose of PPSV23. The secondary endpoint was the safety profile for one dose of PPSV23.

Results: One month after administration of PPSV23, the GMFRs of IgG considerably increased for five of eight serotypes in the 1.0-y interval group, whereas the GMFRs of IgG considerably increased for two serotypes in the 0.5-y interval group. Furthermore, GMFRs of OPA markedly increased for all eight serotypes in the 1.0-y interval group, while GMFRs of OPA markedly increased for four serotypes in the 0.5-y interval group. At 2 years after initial vaccination, GMFRs of IgG or OPA were higher for all serotypes, except for serotype 3, than those in the single PPSV23 group irrespective of intervals. No significant difference was found in the frequencies of local reactions of all grades between the two intervals.

Conclusions: The 1.0-y interval provided better booster effects induced by PPSV23 than those of the 0.5-y interval in a sequential administration in pneumococcal vaccine-naïve adults aged ≥ 65 years. No difference was found in the safety profile between both intervals.

1. Introduction

Pneumococcal diseases, including invasive pneumococcal disease (IPD) and noninvasive disease, represent major causes of morbidity and mortality in elder individuals worldwide [1]. A 23-valent pneumococcal polysaccharide vaccine (PPSV23) was included in the national immunization program of Japan for adults aged ≥ 65 years who had not received PPSV23 previously in 2014.

Abbreviations: PCV, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; OPA, opsonophagocytic activity; GMFR, geometric mean fold rise; 0.5-y, 0.5-year interval; 1.0-y, 1-year interval; GMT, geometric mean titer; GMC, geometric mean concentration; IPD, invasive pneumococcal disease; VE, vaccine effectiveness.

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A 13-valent pneumococcal conjugate vaccine (PCV13) was licensed for inoculating adults aged ≥ 65 years in 2014, and the range of age for the use of PCV13 was expanded in 2020 to cover children and adults aged 6–64 years on a voluntary basis in Japan [2].

Studies have previously evaluated the immunogenicity of sequential administration of 7-valent conjugate vaccine (PCV7) or PCV13 followed by PPSV23 in elder individuals [3–8]. The rationale of this sequential administration of the two vaccines is that the memory B-cells generated by the prior PCV13 vaccination can induce booster responses to 12 shared serotypes after PPSV23 vaccination, although the main B-cell subset in humans involved in the immune response to PCVs is not fully understood [9]. Two studies have been conducted on the sequential administration of PCV13 followed by PPSV23 after 2 or 6 months in adults aged ≥ 50 years [3,4]. No significant increase in immune response to PPSV23 was found after either 2 or 6 months of subsequent vaccination in these studies. In contrast, two studies on sequential administration of PCV7 followed by PPSV23 after 6 months reported an enhanced immune response to PPSV23 in elder individuals [5,6]. When PPSV23 is administered 1 year after PCV13, the immune responses elicited by PPSV23 are considerably lower for 8 of 12 shared serotypes than those obtained following a single dose of PCV13 in adults aged 60–64 years [7]. In contrast, when PPSV23 is administered approximately 4 years after PCV13 vaccination, the immune responses elicited by subsequent PPSV23 vaccination are markedly higher than those elicited by the initial dose of PPSV23 for 10 of 13 serotypes in adults aged ≥ 50 years [8]. Collectively, the immune responses elicited by the sequential administration of PCV following PPSV23 are inconsistent based on different intervals and study settings. Therefore, the optimal interval required between two doses of vaccination for inducing booster responses remains unknown. In addition, a time interval of 4 years between PCV and PPSV23 administration may be too long for elder individuals who are at risk of developing various health conditions.

In this study, we aimed to determine an appropriate period of interval between PCV and PPSV23 administration and conducted a head-to-head comparison study on the safety profile and immunogenicity of the sequential administration of PCV13 followed by PPSV23 at intervals of 0.5 versus 1.0 year apart in a cohort of pneumococcal vaccine-naïve, immunocompetent adults aged ≥ 65 years in Japan.

2. Material and methods

2.1. Study design and participants

We conducted an open-label study between July 2015 and March 2017 at two clinical sites, Tokushima University Hospital and Hakuai Memorial Hospital in Tokushima city, Japan. In this study, pneumococcal vaccine-naïve adults aged ≥ 65 years (n = 129) were enrolled and randomly assigned to three groups (Fig. 1). The vaccinations evaluated included: sequential PCV13 (Prevnar 13; Pfizer, New York, NY, USA) – PPSV23 (Pneumovax 23; Merck & Co., Inc., Kenilworth, NJ, USA) with an interval of 0.5 years (the 0.5-y interval), sequential PCV13–PPSV23 with an interval of 1.0 year (1.0-y interval), and a single administration of PPSV23 (single PPSV23). While PCV13 contains purified capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F, PPSV23 contains purified capsular polysaccharides from all PCV13 serotypes, except 6A, and 11 additional serotypes including 2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. PCV13 and PPSV23 were administered intramuscularly at a dose of 0.5 mL.

Eligibility criteria included no history of previous pneumococcal vaccination and absence of protocol-defined known or suspected immunocompromising conditions, including generalized malignancy, poorly-controlled diabetes mellitus, and use of immunosuppressive agents. Informed consent was obtained from all participants. Blood samples were collected for evaluating the immunogenicity before and one month after each vaccination and at 0.5-y intervals for 2 years. This study was conducted with the approval of the Tokushima University School of Medicine Ethics Review Committee, based on the Declaration of Helsinki and each participating site.

2.2. Enzyme-linked immunosorbent assay (ELISA)

The concentrations of antipneumococcal IgG antibodies were measured using the World Health Organization (WHO)-approved ELISA protocol using standard reference serum (89-SF or 007sp) along with C-polysaccharide and 22F polysaccharide-binding, as previously described [10,11]. The concentrations of serotype-specific IgGs for serotypes 3, 4, 6B, 9 V, 14, 19A, 19F, and 23F were measured according to the WHO protocol. A detailed protocol is available at https://www.vaccine.uab.edu/uploads/mdocs/ELISAProtocol(007sp).pdf. Sera were collected from the participants before and one month after each vaccination and at 0.5-y intervals for 2 years. Coded serum samples were stored at −30 °C and sent to the Research Institute for Microbial Diseases, Osaka University (Osaka, Japan) for the measurement of antibody levels. Of twelve shared serotypes (1,3,4,5,6B, 7F, 9V,14, 18C, 19A, 19F, 23F) between PCV13 and PPSV23, we excluded serotypes 1, 5. 7F and 18C from the serotypes for analysis in this study because the prevalence of these serotypes was low in adult IPD during 2013 to 2015 and in adult pneumococcal pneumonia during 2011 to 2014 in Japan [12,13]. Antibody levels for eight serotypes, including 3, 4, 6B, 9V, 14, 19A, 19F, and 23F, in serum samples were measured at the following time points: baseline (prior to first vaccination), 1 month after vaccination, and at 0.5-y intervals for 2 years.

2.3. Multiplexed opsonophagocytic killing assay (MOPA)

A MOPA based on antibiotic-resistant target bacteria was performed at the Research Institute for Microbial Diseases, Osaka University. The serotype-specific opsonophagocytic assay (OPA) titer was determined using a MOPA for serotypes 3, 4, 6B, 9V, 14, 19A, 19F, and 23F, as previously described [14]. The quality control serum was prepared from the pooled sera of adults vaccinated with PPSV23 and was used in each assay. OPA titers in serum samples were measured at the following time points: baseline (prior to first vaccination), 1 month after vaccination, and at 0.5-y intervals for 2 years.

2.4. Study outcome

Primary endpoints were geometric mean fold rises (GMFRs) at 1 month after a sequential administration of PCV13 followed by PPSV23 with a 0.5-y or 1.0-y interval. We also evaluated GMFRs at 2 years after a sequential administration of PCV13 followed by PPSV23 with a 0.5-y or 1.0-y interval. The secondary endpoints were safety profiles of the sequential administration of PCV13 followed by PPSV23 with a 0.5-y or 1.0-y interval.

2.5. Safety profile

Local reactions (redness, swelling, and pain) and systemic events (example.g., fever, rash, malaise, headache, and vomiting) were monitored and recorded for 7 days in the participants. Redness and swelling were graded as mild (maximum diameter of 2.5–5.0 cm), moderate (maximum diameter of ≥5.0 cm), and severe (maximum diameter ≥ 10.0 cm). Pain was graded as mild

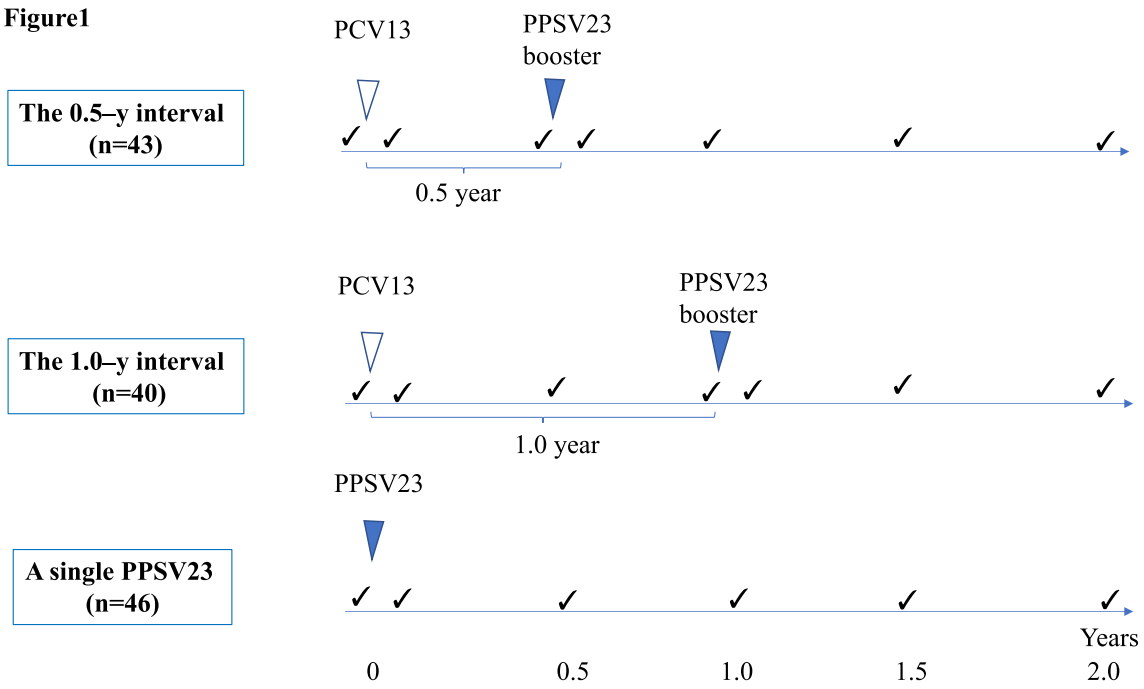


Fig. 1. Study design and disposition of participants. The 0.5-y interval: administration of PCV13 followed by PPSV23 0.5 years apart; the 1.0-y interval: administration of PCV13 followed by PPSV23 1 year apart; single PPSV23: administration of PPSV23 alone. Blood sampling (✓) was conducted for antibody level measurement before and 1 month after each vaccination and at 0.5-year intervals for 2 years. PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine.

(painful, but easily tolerated), moderate (discomfort causing interference with usual activity), and as severe (extremely distressed or unable to perform usual activities). We requested the study participants to record the local reactions and systemic events for 7 days after pneumococcal vaccinations in a record form and collected the record form from the participants and analyzed the data of safety profile. We also examined the health conditions of study participants every 6 months. Data on serious adverse events and deaths were collected from enrollment to the end of the study.

2.6. Statistical analysis

For each serotype, OPA titers and IgG concentrations were logarithmically transformed for analysis; geometric mean titers (GMTs) of OPA and geometric mean concentrations (GMCs) of IgG were calculated along with 95 % confidence intervals (CIs) at each time point. GMTs of OPA and GMCs of IgG were natural log-transformed. The two-sided 95 % CIs for mean OPA GMTs and IgG GMCs were calculated on the natural log scale and reference a *t*-distribution. The mean values and CIs were back-transformed to obtain the corresponding point estimates and 95 % CIs for GMTs of OPA and GMCs of IgG on the original scale. The same approach was used to estimate each GMFR. The Wilcoxon signed-rank tests, two paired groups; and Mann–Whitney U tests were used to compare and unpaired two groups. Local reactions and systemic events were compared among three groups with corresponding *p*-values in a chi-square test. This was an exploratory study to generate hypotheses; therefore, sample size was computed based on feasibility, and multiplicity adjustment for *p*-values was not attempted.

3. Results

3.1. Baseline characteristics of participants

The baseline characteristics of 129 participants are demonstrated in Table 1. Distribution of age, sex, and underlying chronic medical conditions were similar among the three groups and no significant difference was found among the groups. Baseline data for GMTs of OPA and GMCs of IgG among the three groups are demonstrated in Supplementary Table 1. No significant difference was found in baseline data among the three groups.

3.2. Kinetics of GMFR of IgG

The kinetics of GMFR of IgG in the 0.5-y interval, 1.0-y interval, and single PPSV23 groups are illustrated in Fig. 2. GMFRs of serotype-specific IgG were measured before and one month after each vaccination and at 0.5-y intervals for 2 years, and the baseline GMFR was considered as 1. Marked increases were found in GMFRs of IgG for all serotypes (except for serotype 3) one month after vaccination with PCV13 for the 0.5-y and 1.0-y intervals and with PPSV23. We compared the increases in GMFR of IgG before and 1 month after a booster dose of PPSV23 in a sequential PCV13–PPSV23 administration between the 0.5-y and 1.0-y interval groups. While the GMFRs of IgG considerably increased for two

Table 1
Baseline data of study subjects.

Factors	The 0.5–y interval (n = 43)	The 1.0–y interval (n = 40)	A single PPSV23 (n = 46)
Age (mean, range)	75 (71–94)	74 (65–89)	77 (65–95)
Male (%)	16 (37.2)	15 (37.5)	19 (41.3)
Underlying chronic conditions (%)	29 (67.5)	23 (57.5)	31 (67.3)
Chronic lung disease (%)	3 (6.9)	2 (5)	3 (6.5)
Chronic heart disease (%)	4 (6.9)	4 (7.5)	4 (8.3)
Diabetes millitus (%)	4 (9.3)	5 (12.5)	9 (19.5)
HbA1c (mean, range)	6.2 (5.2–7.5)	6.6 (6.2–7.3)	6.1 (5.4–7.0)
Other chronic conditions (%)	18 (62.0)	12 (52.2)	15 (48.4)

Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine.

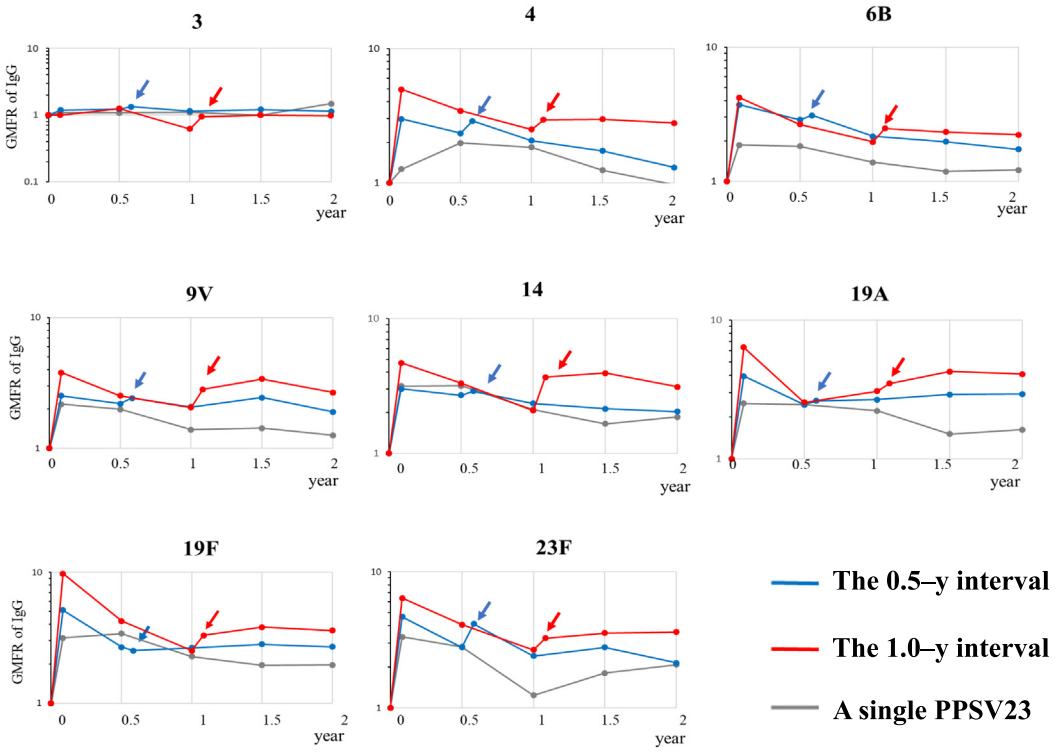


Fig. 2. Comparison of GMFRs of IgG between the 0.5-y and 1.0-y interval groups. Blue line: sequential administration of PCV13 followed by PPSV23 with an interval of 0.5 years; red line: serial administration of PCV13 followed by PPSV23 with an interval of 1 year; gray line: administration of PPSV23 alone. Arrows indicate the time points of 1 month after serial administration of PPSV23. PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; GMFR, geometric mean fold rise; 0.5-y, 0.5-year interval; 1.0-y, 1-year interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(6B and 23F) of the eight common serotypes in the 0.5-y interval group (Table 2), the GMFRs of IgG markedly increased for five (3, 6B, 9V, 14, and 19F) of the eight common serotypes in the 1.0-y interval group.

3.3. Kinetics of GMFRs of OPA

The kinetics of the GMFR of OPA in the 0.5-y interval, 1.0-y interval, and the single PPSV23 groups are illustrated in Fig. 3. GMFRs of serotype-specific OPA were measured before and 1 month after each vaccination and at 0.5-y intervals for 2 years, and the baseline GMFR was considered as 1. Considerable increases were found in the GMFRs of OPA for all serotypes 1 month after vaccination with PCV13 for the 0.5-y and 1.0-y intervals and for PPSV23. We compared the increases in GMFRs of OPA before and 1 month after a booster dose of PPSV23 in sequential PCV13–PPSV23 administration between the 0.5-y and 1.0-y interval groups. While the GMFRs of OPA considerably increased for four (3, 4, 19A, and 19F) of the eight common serotypes in the 0.5-y interval group (Table 3), the GMFRs of OPA markedly increased for all of the eight common serotypes in the 1.0-y interval group.

3.4. Immune response at 2 years after initial vaccination

We compared the GMFRs of IgG or OPA between the 0.5-y and the 1.0-y intervals at 2 years after the initial vaccination with PCV13 or PPSV23. GMFRs of IgG were higher in the 1.0-y interval group than in the 0.5-y interval group for all serotypes, except for serotype 3, and notable differences were found in GMFRs for serotypes 4, 14, 19F, and 23F (Supplementary Table 2). GMFRs of

Table 2
GMFRs of IgG 1 month after administration of PPSV23 between The 0.5–y interval group and The 1.0–y interval.

	The 0.5–y interval		Comparison Pre vs Post		The 1.0–y interval		Comparison Pre vs Post
	Pre PPSV23 (n = 35) GMFR from baseline	Post PPSV23 (n = 35) GMFR from baseline	*P* value		Pre PPSV23 (n = 34) GMFR from baseline	Post PPSV23 (n = 34) GMFR from baseline	*P* value
3	1.22 (0.98,1.52)	1.34 (1.05,1.72)	>0.05	3	0.62 (0.40, 0.96)	0.95 (0.61,1.47)	0.0017
4	2.34 (1.78, 3.08)	2.88 (2.16, 3.83)	>0.05	4	2.50 (1.81, 3.46)	2.95 (2.13, 4.11)	>0.05
6B	2.88 (1.98,4.20)	3.10 (2.15,4.46)	0.0022	6B	1.96 (1.33, 2.87)	2.48 (1.68, 3.67)	0.0337
9V	2.69 (2.05,3.52)	2.52 (1.87, 3.39)	>0.05	9V	2.52 (1.85, 3.44)	3.30 (2.28, 4.78)	0.0061
14	2.70 (1.91,3.83)	2.89 (2.10,3.98)	>0.05	14	2.07 (1.47,2.91)	3.67 (2.39, 5.62)	<0.0001
19A	2.45 (1.47, 4.09)	2.62 (1.62,4.23)	>0.05	19A	3.07 (2.06, 4.57)	3.49 (2.20,5.54)	>0.05
19F	2.20 (1.49,3.24)	2.42 (1.76,3.34)	>0.05	19F	2.05 (1.47, 2.86)	2.82 (1.94, 4.10)	0.0026
23F	2.79 (2.03, 3.83)	4.15 (3.08,5.57)	0.0074	23F	2.67 (1.91, 3.74)	3.25 (2.39, 4.41)	>0.05

Abbreviations: GMFRs; Geometric Mean of the Fold Rises, IgG; immunoglobulin G, PPSV23; 23-valent pneumococcal polysaccharide vaccine, PCV-13; 13-valent pneumococcal conjugate vaccine.

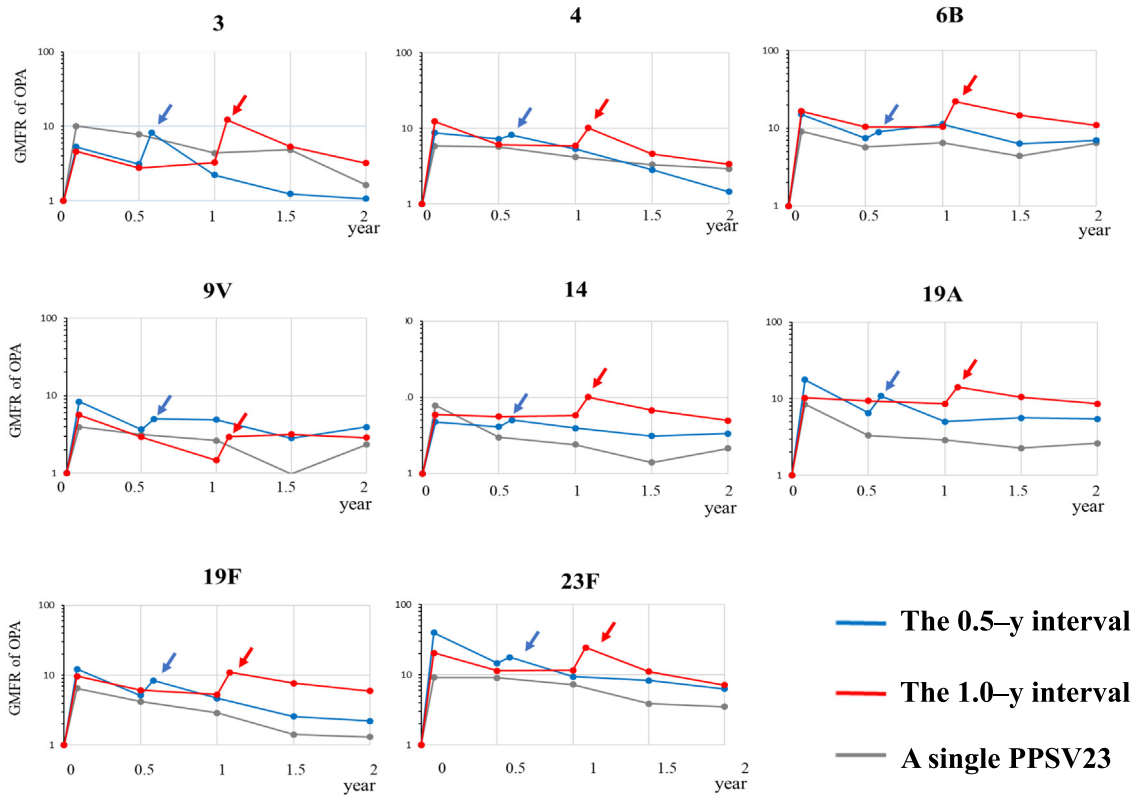


Fig. 3. Comparison of GMFRs of OPA between the 0.5-y and 1.0-y intervals. Blue line: sequential administration of PCV13 followed by PPSV23 with an interval of 0.5 years; red line: serial administration of PCV13 followed by PPSV23 with an interval of 1 year; gray line: administration of PPSV23 alone. Arrows indicate the time points of 1 month after serial administration of PPSV23. PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; GMFR, geometric mean fold rise; 0.5-y, 0.5-year interval; 1.0-y, 1-year interval; OPA, opsonophagocytic activity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
GMFRs of OPA 1 month after administration of PPSV23 between the 0.5–y interval group and the 1.0–y interval.

	The 0.5–y interval		Pre vs Post
	Pre PPSV23 (n = 35) GMFR from baseline (95 %CI)	Post PPSV23 (n = 35) GMFR from baseline (95 %CI)	*P* value
3	3.12 (1.53,6.39)	8.17 (3.87, 17.26)	**0.001**
4	7.23 (3.08, 16.94)	8.22 (3.24,20.89)	**0.0484**
6B	7.47 (4.15,13.45)	8.93 (4.97,16.05)	0.0548
9V	3.65 (1.71, 7.79)	4.99 (2.42,10.30)	0.1478
14	4.12 (2.28, 7.47)	5.06 (3.00, 8.53)	0.1965
19A	6.54 (3.29, 12.97)	10.85 (5.45, 21.61)	**0.011**
19F	5.15 (2.25,11.78)	8.39 (3.71,18.99)	**0.0025**
23F	14.06 (6.74, 31.86)	17.78 (8.44, 37.46)	0.5888
	The 1.0–y interval		Pre vs Post
	Pre PPSV23 (n = 35) GMFR from baseline (95 %CI)	Post PPSV23 (n = 35) GMFR from baseline (95 %CI)	*P* value
3	3.26 (1.42,7.50)	12.30 (5.89, 25.67)	**0.001**
4	5.87 (2.12, 16.23)	10.13 (3.08, 33.39)	**<0.0001**
6B	10.39 (4.72, 22.87)	22.09 (10.67, 45.76)	**<0.0001**
9V	1.46 (0.73, 2.92)	2.97 (1.48, 5.81)	**0.0033**
14	5.78 (2.70,12.38)	10.11 (4.72, 21.67)	**0.0009**
19A	8.57 (4.50,16.35)	14.22 (8.05,25.12)	**0.0249**
19F	5.35 (2.43, 11.75)	11.03 (5.94, 20.50)	**0.0343**
23F	11.66 (4.77,28.46)	24.44 (10.59,56.42)	**0.0003**

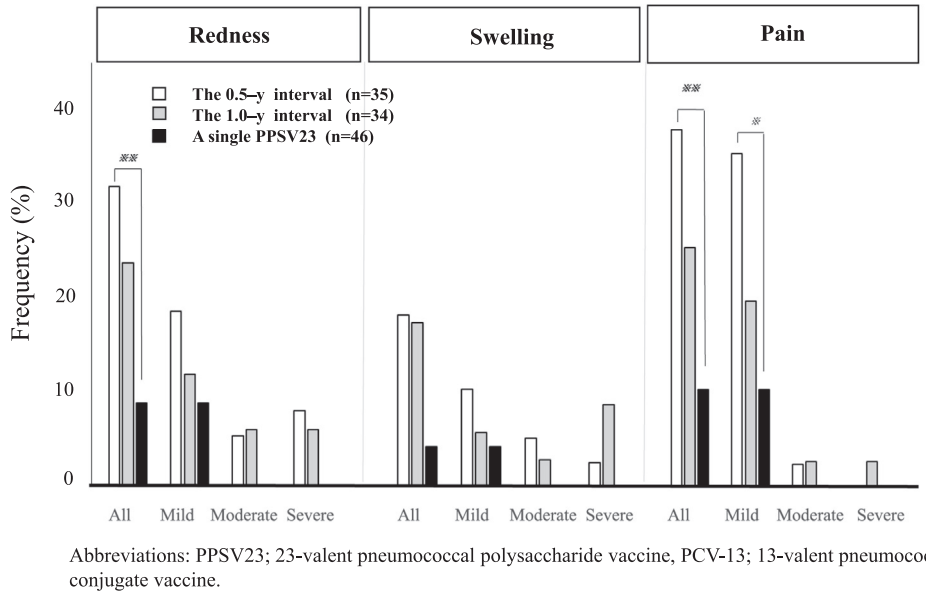
Abbreviations: GMFRs; Geometric Mean of the Fold Rises, OPA; opsonophagocytic activity, PPSV23; 23-valent pneumococcal polysaccharide vaccine, PCV-13; 13-valent pneumococcal conjugate vaccine.

OPA were higher in the 1.0-y interval group than in the 0.5-y interval group for all serotypes, except for serotype 9V, and a marked difference was found in GMFRs for serotype 19F (Supplementary Table 3). GMFRs of IgG were higher for all serotypes, except for serotype 3, in the 0.5-y and 1.0-y interval groups than those in the single PPSV23 group (Supplementary Table 2). GMFRs of OPA were also higher for all serotypes in the 0.5-y and 1.0-y interval groups than those in the single PPSV23 group (Supplementary Table 3).

3.5. Safety profile

The frequencies of local and systemic reactions occurring 7 d after administration of PPSV23 were analyzed in 115 participants among the three groups (Fig. 4). Eight participants in the 0.5-y interval group and six participants in the 1.0-y interval group dropped out of the study at the time of this analysis. The main reason was that participants had relocated to distant locations, making it difficult to participate in this study. Three deaths were reported during this study, which were not related to the vaccine.

Local reactions were generally mild in all three groups. The frequency of redness of all grades was the highest in the 0.5-y interval group, followed by the 1.0-y interval and the single PPSV23 groups. A significant difference was found in the frequencies of redness of all grades between the 0.5-y interval and single PPSV23 groups (p = 0.005), and no difference was found between the 0.5-y and 1.0-y interval groups. The frequencies of pain of all grades or mild grade were the highest in the 0.5-y interval group, followed by those in the 1.0-y interval and single PPSV23 groups. Significant differences were found in the frequencies of pain of all grades (p = 0.005) and mild grade (p = 0.003) between the 0.5-y interval



Abbreviations: PPSV23; 23-valent pneumococcal polysaccharide vaccine, PCV-13; 13-valent pneumococcal conjugate vaccine.

Fig. 4. Frequency of adverse events occurring within 1 week after administration of PPSV23 in each group. Open, gray, and closed bars show the frequency of AEs in the 0.5-y interval, 1.0-y interval, and single PPSV23 groups, respectively. PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; AE, adverse event; 0.5-y, 0.5-year interval; 1.0-y, 1-year interval.

and single PPSV23 groups, although no difference was found between the 0.5-y and 1.0-y interval groups. In contrast, the frequency of systemic reactions, such as high fever, general fatigue, headache, and nausea, were <5 %, and most of these reactions improved within 2–3 d. No vaccine-related serious events or deaths were reported.

4. Discussion

The optimal interval required between two doses of vaccination for inducing booster responses against pneumococcal diseases remains unknown. This is the first head-to-head study that compares the safety and immunogenicity of a sequential administration of PCV13 followed by PPSV23 with 0.5-y vs 1.0-y interval. Marked increases in GMFRs of IgG were found 1 month after administration of PPSV23 for five of eight serotypes in the 1.0-y interval group, whereas the GMFRs increased for only two of the eight serotypes in the 0.5-y interval group. Marked increases in GMFRs of OPA were found for all serotypes after administering PPSV23 with an interval of 1.0-y, whereas the GMFRs increased for only four of the eight common serotypes with 0.5-y interval. While the GMFR of IgG the 1.0–y interval was low as 0.95 for serotype 3, the GMFR of OPA was 12.3 for serotype 3 (Tables 2 and 3). This discrepancy between the GMFRs of IgG and OPA for serotype 3 may be explained by an improved efficiency of killing activity of serotype- specific IgG after vaccination with PPSV23 as previously reported [15]. This study clearly demonstrated that efficiency of killing activity of serotype- specific IgG for serotypes 6B, 14, 19F and 23F after primary and secondary vaccination with PPSV23.

At 2 years after the initial vaccination, the GMFRs of IgG were higher for all serotypes (except for serotype 3) in the 1.0-y interval group than in the 0.5-y interval group, and GMFRs of OPA were higher for all serotypes (except for serotype 9V) in the 1.0-y interval group than in the 0.5-y interval group. Furthermore, the GMFRs of IgG and OPA were higher in serial administration with intervals of 0.5–y and 1.0–y for all serotypes, except for serotype 3, than in the single PPSV23 group at the endpoint of this study.

The present study showed that booster doses of PPSV23 at 1.0-y interval could provide an immunological advantage over those administered at 0.5-y interval. This finding suggests that a shorter interval between PCV13 and PPSV23 led to a low antibody response elicited by PPSV23 vaccination for eight common serotypes. When PPSV23 is administered shortly after PCV13, the anti-polysaccharide antibodies induced by PCV13 may bind to PPSV23 polysaccharide antigens, and the immune complexes formed subsequently may reduce antigen presentation to B-cells and reduce antibody production [16]. We found no difference in the frequencies of adverse events between sequential administration at intervals of 0.5-y and 1.0-y.

Two previous studies on sequential administration of PCV7 or PCV13 following PPSV23 comparing intervals ranging from 8 weeks (or 2 months) to 26 weeks (or 6 months) reported that the reactogenicity tends to be relatively higher in shorter intervals [3,4]. Based on these findings, short intervals of <6 months between two vaccines may be associated with an increased local reactogenicity, although the frequency of the local adverse events after a dose of PPSV23 did not differ between the 0.5-y and 1.0-y interval groups in our study.

A prospective, test-negative study recently reported the real-world vaccine effectiveness of a sequential administration of PCV13 followed by PPSV23 against pneumococcal community-acquired pneumonia (CAP) in pneumococcal vaccine-naïve elder adults [17]. The adjusted vaccine effectiveness (VE) of the sequential administration of two vaccines was found to be 80.3 % in adults aged 65–74 years, although the adjusted VE was not significant (-14.8 %) in adults aged ≥75 years. This study adopted the KSID guideline for the interval between two vaccinations [18], and consequently, the intervals of the two vaccinations varied from 4 weeks to 5 years in this study. These findings of VE prompted us to compare the immune responses between two age groups. However, we found no difference in the GMFRs of IgG or OPA 2 years after the initial vaccination between age groups of 65–74 years and ≥75 years, except for GMFRs of OPA for serotypes 3, 4 and 6B in age ≥75 years of the 0.5–y interval group, in our study (Supplementary Tables 4, 5). A lack of VE against pneumococcal CAP in adults aged ≥75 years may be attributed to factors other than declined immune response by the booster dose of PPSV23. Further studies are needed to validate the VE of the sequential administration of PCV13–PPSV23 in pneumococcal vaccine-naïve elder adults.

A 15-valent pneumococcal conjugate vaccine (PCV15) was licensed in the United States in 2021, and the ACIP recommends the use of PCV15 in series with PPSV23 for all adults aged ≥65 years and in adults aged 19–64 years with certain chronic medical conditions who have not received a PCV previously or with unknown vaccination history [19]. A previous study compared the safety and immunogenicity of PCV15, which covers the unique serotypes 22F and 33F, with that of PCV13 in healthy adults [20]. The authors reported that the immune responses to serotypes 3, in addition to two unique serotypes, are higher in the individuals receiving PCV15 than in those receiving PCV13. This finding agrees with that of a phase 3 clinical trial on PCV15 which compared the immunogenicity of PCV13 in adults aged ≥50 years including Japanese participants aged ≥65 years [21,22]. The GMFRs of IgG for serotype 3 after a dose of PPSV23 followed by PCV13 were lower than those in the single PPSV23 group, and the GMFRs of OPA followed by PCV13 for serotype 3 were higher than those in the single PPSV23 group in our study; however, these trends were not significant. Therefore, it may be possible to achieve enhanced booster responses of IgG or OPA for serotype 3 after a dose of PPSV23 followed by PCV15 with an interval of 1.0-y, although a recent study reported that a sequential administration of PCV15–PPSV23 induces comparable antibody levels to those obtained via a sequential administration of PCV13–PPSV23 for common serotypes including serotype 3 [23].

As several recent studies reported serotype 3 as one of the highly prevalent serotypes associated with nonbacteremic pneumonia and IPD in Europe, United States, and Japan [2,24–27], an improved protection against diseases caused by serotype 3 is anticipated after clinical application of PCV15 in elder individuals. However, the mechanisms via which an improved immunogenicity to serotype 3 induced by PCV15 contribute to further protection against pneumococcal diseases caused by serotype 3 in elder individuals remain unknown.

Our study has several limitations. First, the immunogenicity data cannot be interpreted directly for providing protection against pneumococcal infections, because the threshold of immunological levels for protection have not been established for pneumococcal diseases in adults. Second, the number of participants may be insufficient to support the data on safety and immunogenicity for an appropriate interval of sequential vaccination. Third, the immune responses induced by pneumococcal vaccination were measured for only 8 of the 13 serotypes unique to PCV13 in this study. Finally, we were not able to evaluate the long-term persistence of immune responses after 2 years.

5. Conclusion

In a sequential administration of PCV13 followed by PPSV23, the GMFRs of IgG markedly increased for five of eight serotypes, and the GMFRs of OPA markedly increased for all eight serotypes in the 1.0-y interval group compared with those in the 0.5-y interval group. No significant difference was found in the frequencies of local adverse events between the 0.5-y and 1.0-y interval groups. The 1.0-y interval may be more effective than the 0.5-y interval in enhancing booster responses induced by sequential administration of PCV13 followed by PPSV23 in pneumococcal vaccine-naïve adults aged ≥65 years.

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Author contributions

M Azuma, M Hamaguchi and Y Nishioka conceived the idea of the study. M Azuma designed the trial and study protocol, coordinated study implementation, analyzed the data, and led the writing of the report. K Oishi designed the study and supervised the study. M Azuma, Y Motoki contributed patient management, and provided patient samples. Y Akeda, S Morino performed the immunological analysis. All authors have critically revised the paper for important intellectual content and approved the final version for submission.

Data availability

I have shared the data at the attach File step

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.12.060.

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