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Long-term impact of pneumococcal conjugate vaccines for children on adult pneumococcal pneumonia in Japan: Two multicenter observational studies from 2011 to 2020

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ABSTRACT

Background: Pediatric pneumococcal conjugate vaccines (PCVs) introduction has directly and indirectly reduced pneumococcal pneumonia and invasive disease caused by PCV-covered serotypes among children and adults globally. In Japan, both PCV7 and PCV13 were introduced into the national immunization program (NIP) for children in 2013. However, the long-term impact of PCV use in children on adult pneumococcal pneumonia in Japan remains unclear.

Methods: We assessed serotypes isolated from adult pneumococcal pneumonia patients (in- and outpatients) in two multicenter observational studies in Japan: 2011–2014 and 2016–2020. The latter study period was divided into two periods to evaluate changes after PCV introduction in children. The Quellung reaction was used to determine serotypes. We evaluated trends of individual and vaccine-covered serotypes over three periods and assessed the difference in changes by patient group before and after the introduction of pediatric PCVs.

Results: A total of 650 patients were enrolled: 224, 322, and 104 in 2011–2014, 2016–2017, and 2018–2020, respectively. The median age was 73 years; 59.7% (388/650) were male; 86.9% (565/650) had comorbidities; and 10.2% (66/650) were nursing-home residents. The proportion of PCV13 serotypes decreased from 52.7% in 2011–2014 to 30.4% in 2016–2017 ($p < 0.001$) after PCV13 introduction for children. However, PCV13, PCV15, and PCV20 serotypes still accounted for 38.5, 43.3, and 59.6% of total pneumococcal pneumonia in 2018–2020, respectively. Decline of PCV13 serotypes was more marked in patients aged ≥65 (-23.5%; $p < 0.001$) than those aged <65 (-12.3%; $p = 0.104$) from 2011–2014 to 2016–2020. The proportion of PPSV23 non-PCV13 serotypes didn't change over time.

Conclusions: The proportion of adult pneumococcal pneumonia caused by PCV13 serotypes in Japan declined after pediatric PCVs introduction into NIP, possibly due to indirect effects of pediatric PCVs. However, use of new PCVs in Japanese adults may potentially prevent additional pneumococcal pneumonia cases. Now, pneumococcal vaccination strategy for older adults requires discussion.

Abbreviations: CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; NIP, national immunization program; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; IQR, interquartile range; CI, confidence interval; PCR, polymerase chain reaction.

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1. Introduction

Community-acquired pneumonia (CAP) has been a significant cause of mortality and morbidity globally, especially among older adults [1]. The rapid aging of the Japanese society has led to an increasing burden of CAP [2]. One study estimated that the number of adult CAP patients in Japan was 1,880,000 in 2012, and 69.4% were aged ≥65 years [2]. *Streptococcus pneumoniae* is a common microorganism that causes pneumonia, reportedly responsible for 17.1 to 23.2% of CAP in Japan [2–4]. *S. pneumoniae* also causes invasive pneumococcal diseases (IPD), including bacteremia or meningitis, associated with higher mortality rates than pneumococcal pneumonia [5,6]. However, the incidence of pneumococcal pneumonia is 100 times higher than that of IPD in Japan [2,7,8], which means that studies on pneumococcal pneumonia are necessary from a public health perspective when considering the burden of pneumococcal diseases on society.

The introduction of pediatric pneumococcal conjugate vaccines (PCVs) has directly and indirectly reduced IPD and pneumococcal pneumonia caused by PCV-covered serotypes among children and adults in many countries [9–11]. Since 2010, the 7-valent pneumococcal conjugate vaccine (PCV7) has been available for children in Japan [12]. The Japanese government incorporated PCV7 into the national immunization program (NIP) for children in April 2013, and it was replaced by the 13-valent pneumococcal conjugate vaccine (PCV13) in November 2013. Following this introduction, reductions in IPD and pneumococcal pneumonia caused by PCV serotypes were observed among adults in Japan [6,13–17]. To assess the effects of these vaccines and determine optimal vaccination programs, domestic data on the latest serotype distribution are essential.

Recently, PCV15 and PCV20 were newly developed; PCV15 includes PCV13 serotypes, 22F and 33F; and PCV20 includes PCV15 serotypes, 8, 10A, 11A, 12F, and 15B. Both PCV15 and PCV20 were proved to be safe and show immunogenicity [18]. Considering the epidemiology of pneumococcal diseases caused by PCV15 or PCV20 serotypes is also necessary when discussing the inclusion of PCV15 or PCV20 in the routine vaccination for older adults in Japan.

Since 2011, we have conducted observational studies on adult pneumonia and followed the serotype trends of adult pneumococcal pneumonia in Japan [2,15,19]. In the present study, we aimed to assess the changes in serotype distribution and patients' clinical characteristics of adult pneumococcal pneumonia between 2011 and 2020 in Japan, and evaluate the extent of changes stratified by patient groups, such as age group, sex, and pneumococcal vaccination status.

2. Methods

2.1. Study design

We conducted two multicenter observational studies on CAP. From September 2011 to August 2014, the Adult Pneumonia Study Group-Japan (APSG-J) conducted the first study on adult pneumonia at four community-based hospitals on Japan's four main islands [2,19]. Study sites included hospitals in Hokkaido, Chiba, Kochi, and Nagasaki Prefectures (Supplementary Fig. 1). From May 2016 to October 2020, the Japan Pneumococcal Vaccine Effectiveness Study (J-PAVE) conducted the second study on culture-positive adult pneumococcal pneumonia at the same four hospitals as in APSG-J and one additional hospital in Nagasaki Prefecture [15] (Supplementary Fig. 1). Two of the same four hospitals did not participate after 2018. In the present study, we evaluated serotypes isolated from sputum or blood culture-positive adult pneumococcal pneumonia patients from these two studies.

APSG-J and J-PAVE enrolled both in- and outpatients aged ≥15 years with CAP, which was defined as having signs or symptoms consistent with pneumonia (i.e., fever, chills or rigors, cough, sputum, pleuritic chest pain, dyspnea, or tachypnea) and new pulmonary infiltrates on chest X-ray or computed tomography. Patients who developed pneumonia 48 h after admission were excluded. Clinical specimens were collected from patients and cultured as a standard of care at the first visit or on admission. Pneumococcal pneumonia was defined as pneumonia with isolation of *S. pneumoniae* from sputum or blood culture obtained in clinical practice. Demographic and clinical information was collected from medical records using a standardized data collection form. Pneumococcal vaccination history was obtained from patients and/or their family members or medical records.

2.2. Pneumococcal vaccination policy and coverage in Japan

The Japanese government started health insurance-based coverage of PPSV23 for asplenic or splenectomized patients aged ≥2 years in 1992 and then introduced it into the NIP for older adults aged ≥65 years in 2014. PCV13 became available for older adults aged ≥65 years in 2014, but it has not been included in the NIP for older adults aged ≥65 years (Supplementary Fig. 2) [12]. For children, PCV13 has been included in the NIP since 2013. The routine pediatric schedule for PCV13 consists of a three-dose primary series and a booster dose given between two months and five years old. The recommended schedule includes a three-dose series at two, three, and four months old and a booster dose between 12 and 15 months old.

Vaccination coverage with PCV13 of children, including a booster dose, was from 91 to 100% in 2014–2019 [20], and that with PPSV23 of older adults aged ≥65 years was about 30 to 40% in 2014–2018 [20,21]. Vaccination coverage with PCV13 of older adults aged ≥65 years was estimated to be <5% in 2016–2019, based on the number of PCV13 vaccinations and vaccination coverage with PCV13 of children [20,22,23].

2.3. Microbiological testing

S. pneumoniae isolates were stored in a cryotube containing 1.0 mL STGG (skim milk: 2 g, tryptone: 3 g, glucose: 0.5 g, glycerol: 10 mL, distilled water: 100 mL) medium at −80℃ [24]. The isolates were transported regularly from each study site to the Institute of Tropical Medicine, Nagasaki University. Optochin-sensitivity tests and bile solubility tests were used to identify *S. pneumoniae*, and serotyping was performed by the Quellung reaction (ImmuLex Pneumotest, SSI Diagnostica, Hillerod, Denmark) [25].

2.4. Definitions

Pneumococcal serotypes were categorized as follows: 4, 6B, 9 V, 14, 18C, 19F, and 23F were defined as PCV7 serotypes; 1, 3, 5, 6A, 7F, and 19A as PCV13 non-PCV7 serotypes; 2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F as PPSV23 non-PCV13 serotypes; PCV13 serotypes plus 22F and 33F as 15-valent pneumococcal conjugate vaccine (PCV15) serotypes; PCV15 serotypes plus 8, 10A, 11A, 12F, and 15B as 20-valent pneumococcal conjugate vaccine (PCV20) serotypes; PCV7 serotypes plus 1, 2, 3, 5, 7F, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, 33F as PPSV23 serotypes; and other serotypes as non-vaccine serotypes. Based on possible cross-protection conferred by serotype 6A [26], a secondary analysis was also performed, including serotype 6C in PCV13 serotypes. The study was divided into three periods: first period, from 2011 to 2014; second period, from 2016 to 2017; and third period, from 2018 to 2020. Since we have already described the changes in serotype distribution between 2011–2014 and 2016–2017 [15], and

because one of the purposes of the present study was to describe the long-term changes in serotype distribution after the introduction of PCVs in 2013, we divided the period after the introduction of PCVs into two phases: 2016–2017 and 2018–2020. To calculate the CURB-65 score [27], SpO2 <90% or oxygen administration was used instead of respiratory rates, and severe pneumonia was defined as having CURB-65 scores ≥3. The PPSV23-vaccinated group was defined as a group of patients who had received PPSV23 within the five years prior to the first hospital visit for pneumonia, and the non-vaccinated group was defined as a group of patients who had not received any pneumococcal vaccines prior to the first hospital visit for pneumonia.

2.5. Data analysis

When we evaluated the trends in demographic and clinical information of patients and the changes in individual and vaccine-covered serotypes over time, we divided the entire study period into three periods: 2011–2014, 2016–2017, and 2018–2020. On the other hand, when we assessed the extent of changes in vaccine-covered serotypes depending on the hosts before and after the introduction of pediatric PCVs, we divided the entire study period into two periods: 2011–2014 and 2016–2020. Continuous variables are expressed as medians (with interquartile ranges [IQR]), and categorical variables are summarized as numbers and proportions. Patients' characteristics in each study period were compared using the Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables. The proportions of individual and vaccine-covered serotypes in each study period are given with 95% confidence intervals (CIs). Statistical analyses were conducted with STATA version 16.0 (Stata Corp., College Station, TX, USA).

2.6. Ethics

APSG-J and J-PAVE were approved by the Institutional Review Board of the Institute of Tropical Medicine, Nagasaki University and the study hospitals (approval no. 110630070 and 160303150, respectively). APSG-J was conducted following the 2008 Ethical Guidelines for Epidemiological Studies, and J-PAVE was carried out following the 2014 Ethical Guidelines for clinical studies provided by the Ministry of Health, Labour and Welfare.

3. Results

3.1. Baseline characteristics

Table 1 summarizes the demographic characteristic and clinical information of the study patients divided into three periods. Overall, 650 pneumococcal pneumonia patients were enrolled: 224, 322, and 104 patients in the first, second, and third periods (2011–2014, 2016–2017, and 2018–2020), respectively. The median age was 73 years (IQR: 64–84 years); 59.7% (388/650) were male; 86.9% (565/650) had comorbidities; and 10.2% (66/650) were nursing- home residents. The proportion of patients with severe pneumonia (CURB-65 ≥3) was 22.0% (143/650). Thirty-seven patients (5.7%) had positive blood culture results. PPSV23 and PCV13 vaccination status was available for 68.6% (446/650) and 76.5% (497/650) patients, respectively; 26.9% (120/446) had received PPSV23, and 2.8% (14/497) had received PCV13 within the past five years in patients with known pneumococcal vaccination history. Supplementary Table 1 shows the patient characteristics categorized by PPSV23 vaccination status. The PPSV23-vaccinated group was more likely to be older and to have comorbidities compared to the non-vaccinated group (p <0.001). Over the periods, the median age and proportions of men, people with comorbidities, and nursing- home residents did not change significantly. However, the proportion with severe pneumonia (CURB-65 ≥3) decreased from 29.9% in 2011–2014 to 16.8% in 2016–2017 and 21.2% in 2018–2020.

3.2. Trends in proportions of individual serotypes

Fig. 1 and Supplementary Table 2 show individual pneumococcal serotype distributions in each study period divided into three periods. In the first period, serotype 3 was the most common (22.7% [51/225]), followed by 11A (10.7% [24/225]), and then 19A/19F (7.1% [16/225]). In the second period, serotype 3 was the most common (9.9% [32/322]), followed by 35B (8.7% [28/322]), and then 15A (8.1% [26/322]). In the third period, serotype 3 was the most common (11.5% [12/104]), followed by 6B (10.6% [11/104]), and then 11A (8.7% [9/104]). Although serotype 3 was the most common in all periods, the proportion of patients with serotype 3 in the second and third periods declined to approximately half of that in 2011–2014. Additionally, among PCV13 serotypes, the proportion of 19F and 14 decreased significantly after the introduction of PCV13 for children.

3.3. Trends in proportions by vaccine-covered serotypes

Table 2 and Supplementary Fig. 3 show the proportions of adult pneumococcal pneumonia patients with vaccine-covered serotypes divided into three periods. From the first to second periods, the proportions of patients with PCV7 and PCV13 non-PCV7 serotypes decreased from 20.1% (95% CI: 15.0–25.9%) to 8.4% (95% CI: 5.6–12.0%) and from 32.6% (95% CI: 26.5–39.2%) to 22.0% (95% CI: 17.6–27.0%), respectively. However, the proportion of patients with PCV13 serotypes has not continued to decrease from the second (30.4%; 95% CI: 25.5–35.8%) to the third (38.5%; 95% CI: 29.1–48.5%) periods based on the 95% CI. Even after the proportion of patients with PCV13 serotypes declined, PCV13 serotypes still accounted for 38.5% of the total pneumococcal pneumonia patients in the third period. On the other hand, the proportion of PPSV23 non-PCV13 serotypes showed no change over the three periods. PCV15 and PCV20 serotypes accounted for 43.3 and 59.6%, respectively, of the total pneumococcal pneumonia patients in the third period. Supplementary Table 7 and Supplementary Fig. 4 show the results of the secondary analysis of trends in serotype proportions of vaccine-covered serotypes by study periods, including serotype 6C in PCV13 serotypes based on possible cross-protection conferred by serotype 6A. PCV13 serotypes accounted for 41.3% (95% CI: 31.8–51.4%) of the total pneumococcal pneumonia patients in the third period in the secondary analysis.

3.4. Trends in proportions of vaccine-covered serotypes stratified by patient groups

Table 3 shows the extent of changes in the proportion of vaccine-covered serotypes by patient characteristics divided into two periods: 2011–2014 and 2016–2020, specifically before and after the introduction of pediatric PCVs into the NIP in Japan, respectively. Patient characteristics included sex, age group, residence, presence of respiratory diseases or malignancy, and pneumococcal vaccination status. Overall, the proportion of PCV13 serotypes decreased significantly by 20.3% in the post-PCV13 period; however, the decrease was statistically significant only for older adults aged ≥65 years (p <0.001). The difference in reduction of the proportion of PCV13 serotypes among female patients (-29.7%) was higher than that of male patients (-13.8%), and the differences between female and male patients were more marked among those aged ≥65 years (Supplementary Table 4). However,

Table 1
Baseline characteristics, disease severity, and vaccination status by study periods.

	Total n = 650	2011–2014 n = 224	2016–2017 n = 322	2018–2020 n = 104	P-value*
Age, years (IQR)	73 (64–84)	74 (63.5–83.5)	73 (63–83)	74.5 (65.5–84.5)	0.741
Age group, no. (%)					0.675
15–64	179 (27.5)	64 (28.6)	90 (28.0)	25 (24.0)	
≥65	471 (72.5)	160 (71.4)	232 (72.0)	79 (76.0)	
Sex, no. (%)					0.762
Male	388 (59.7)	136 (60.7)	194 (60.2)	58 (55.8)	
Female	261 (40.2)	88 (39.3)	127 (39.5)	46 (44.2)	
Unknown	1 (0.2)	0	1 (0.3)	0	
Comorbidity, no. (%)					
Any	565 (86.9)	200 (89.3)	279 (86.6)	86 (82.7)	0.307
Respiratory diseases	151 (23.2)	45 (20.1)	81 (25.2)	25 (24.0)	0.393
Malignancy	78 (12.0)	30 (13.4)	38 (11.8)	10 (9.6)	0.555
Residence, no. (%)					0.975
Living at home	584 (89.8)	202 (90.2)	289 (89.8)	93 (89.4)	
Living at nursing-home	66 (10.2)	22 (9.8)	33 (10.2)	11 (10.6)	
Smoking history, no. (%)					0.011
Yes	347 (53.4)	130 (58.0)	163 (50.6)	54 (51.9)	
No	257 (39.5)	87 (38.8)	125 (38.8)	45 (43.3)	
Unknown	46 (7.1)	7 (3.1)	34 (10.6)	5 (4.8)	
Pre-hospital antibiotics, no. (%)					0.029
Yes	80 (12.3)	39 (17.4)	29 (9.0)	12 (11.5)	
No	562 (86.5)	181 (80.8)	289 (89.8)	92 (88.5)	
Unknown	8 (1.2)	4 (1.8)	4 (1.2)	0	
PPSV23 vaccination within the past five years, no. (%)					<0.001
Yes	120 (18.5)	49 (21.9)	60 (18.6)	11 (10.6)	
No	326 (50.2)	126 (56.3)	155 (48.1)	45 (43.3)	
Unknown	204 (31.4)	49 (21.9)	107 (33.2)	48 (46.2)	
PCV13 vaccination within the past five years**, no. (%)					<0.001
Yes	14 (2.2)	0	8 (2.5)	6 (5.8)	
No	483 (74.3)	224 (100)	209 (64.9)	50 (48.1)	
Unknown	153 (23.5)	0	105 (32.6)	48 (46.2)	
Altered mental status, no. (%)					0.210
Yes	114 (17.5)	41 (18.3)	61 (18.9)	12 (11.5)	
No	536 (82.5)	183 (81.7)	261 (81.1)	92 (88.5)	
Systolic blood pressure, no. (%)					0.295
<90 mmHg	31 (4.8)	10 (4.5)	16 (5.0)	5 (4.8)	
≥90 mmHg	585 (90.0)	207 (92.4)	283 (87.9)	95 (91.3)	
Unknown	34 (5.2)	7 (3.1)	23 (7.1)	4 (3.8)	
SpO2 ≤90% or oxygen administration, no. (%)					<0.001
Yes	161 (24.8)	92 (41.1)	47 (14.6)	22 (21.2)	
No	460 (70.8)	126 (56.3)	255 (79.2)	79 (76.0)	
Unknown	29 (4.5)	6 (2.7)	20 (6.2)	3 (2.9)	
Blood urea nitrogen, no. (%)					0.004
≤20 mg/dL	381 (58.6)	121 (54.0)	203 (63.0)	57 (54.8)	
>20 mg/dL	245 (37.7)	98 (43.8)	101 (31.4)	46 (44.2)	
Unknown	24 (3.7)	5 (2.2)	18 (5.6)	1 (1.0)	
CURB-65, no. (%)					<0.001
0–2	486 (74.8)	155 (69.2)	251 (78.0)	80 (76.9)	
≥3	143 (22.0)	67 (29.9)	54 (16.8)	22 (21.2)	
Unknown	21 (3.2)	2 (0.9)	17 (5.3)	2 (1.9)	
In-hospital deaths, no. (%)					0.259
Yes	37 (5.7)	12 (5.4)	17 (5.3)	8 (7.7)	
No	598 (92.0)	208 (92.9)	294 (91.3)	96 (92.3)	
Unknown	15 (2.3)	4 (1.8)	11 (3.4)	0	
Bacteremia, no. (%)					0.338
Yes	37 (5.7)	16 (7.1)	14 (4.3)	7 (6.7)	

In Abbreviations: IQR, interquartile range; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
To calculate the CURB-65 score, SpO2 <90% or oxygen administration was used instead of respiratory rates.
*Compared among three periods: 2011–2014, 2016–2017, and 2018–2020.
**PCV13 became available for older adults aged ≥65 years from 2014 in Japan.

there was no significant difference between female and male patients based on the 95% CI. The proportion of PPSV23 serotypes in the PPSV23-vaccinated group was lower than that in the non-vaccinated group, both before and after the introduction of pediatric PCVs (specifically, 57.1% in the PPSV23-vaccinated group vs 77.3% in the non-vaccinated group before the introduction of pediatric PCVs, and 27.0% in the PPSV23-vaccinated group vs 50.0% in the non-vaccinated group after the introduction of

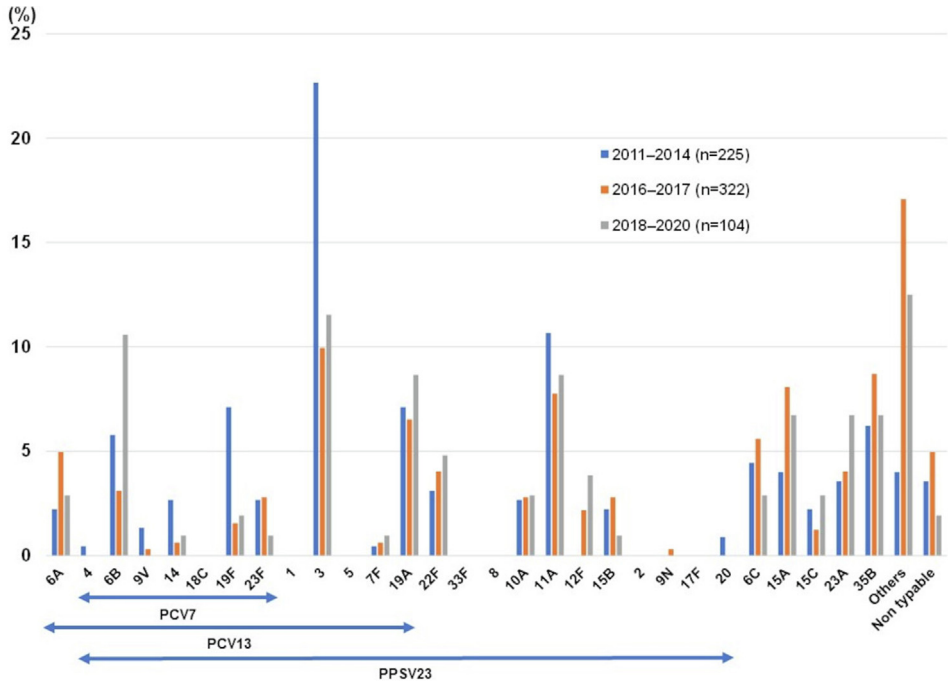

Fig. 1. Percentage of individual serotypes isolated from 650 adult pneumococcal pneumonia patients ≥15 years in Japan, from 2011–2014, 2016–2017, and 2018–2020. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine serotypes; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. Y-axis: individual serotypes as percentage (%) of the total pneumococcal isolates in each study period. One patient had two kinds of pneumococcal serotypes, 11A and 22F, analyzed as two isolates in the first period.

Table 2
Trends in proportions of vaccine-covered serotypes by study periods.

	2011–2014		2016–2017		2018–2020		P-value*
	no. 224	% (95% CI)	no. 322	% (95% CI)	no. 104	% (95% CI)	
PCV7 serotypes	45	20.1 (15.0–25.9)	27	8.4 (5.6–12.0)	15	14.4 (8.3–22.7)	<0.001
PCV13 non-PCV7 serotypes	73	32.6 (26.5–39.2)	71	22.0 (17.6–27.0)	25	24.0 (16.2–33.4)	0.020
PCV13 serotypes	118	52.7 (45.9–59.4)	98	30.4 (25.5–35.8)	40	38.5 (29.1–48.5)	<0.001
PCV15 serotypes	125	55.8 (49.0–62.4)	111	34.5 (29.3–39.9)	45	43.3 (33.6–53.3)	<0.001
PCV20 serotypes	159	71.0 (64.6–76.8)	161	50.0 (44.4–55.6)	62	59.6 (49.5–69.1)	<0.001
PPSV23 non-PCV13 serotypes	43	19.2 (14.3–25.0)	64	19.9 (15.7–24.7)	22	21.2 (13.8–30.3)	0.918
Non-vaccine serotypes	63	28.1 (22.3–34.5)	160	49.7 (44.1–55.3)	42	40.4 (30.9–50.5)	<0.001

Data are presented as numbers and proportions with 95% confidence intervals. PCV7 serotypes includes serotype 4, 6B, 9 V, 14, 18C, 19F, and 23F; PCV13 non-PCV7 serotypes serotype 1, 3, 5, 6A, 7F, and 19A; PCV15 serotypes PCV13 serotypes plus serotype 22F and 33F; PCV20 serotypes PCV15 serotypes plus serotype 8, 10A, 11A, 12F, and 15B; PPSV23 non-PCV13 serotypes serotype 2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F; and non-vaccine serotypes non-PCV13 and non-PPSV23 serotypes.
In Abbreviations: CI, confidence interval; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.
*Compared among three periods: 2011–2014, 2016–2017, and 2018–2020.

pediatric PCVs, respectively). However, after the introduction of PCVs for children, the proportion of PCV13 serotypes decreased similarly in the PPSV23-vaccinated group and non-vaccinated groups (specifically, from 38.8 to 17.5% in the PPSV23-vaccinated group, and from 59.7 to 36.6% in the non-vaccinated group). The same trend was observed in older adults aged ≥65 years with comorbidities (Supplementary Table 5).

4. Discussion

The key study findings were as follows: 1) the proportion of PCV13 serotypes in patients declined after pediatric PCV13 introduction into the NIP in 2013, but there has been no decrease since 2017; 2) the proportions of PCV13, PCV15, and PCV20 still accounted for 38.5, 43.3, and 59.6% of the total adult pneumococcal pneumonia, respectively, in 2018–2020; 3) the proportion of PPSV23 non-PCV serotypes did not change over time; 4) the reduction in the proportion of PCV13 serotypes differed by age group and sex; 5) the overall decline of the proportion of PCV13 serotypes was driven by serotypes 3, 19F, and 14; and 6) the severity of pneumococcal pneumonia decreased over time.

We showed that after the introduction of PCVs into the NIP for children in 2013, the proportion of adult pneumococcal pneumonia caused by PCV13 serotypes in Japan declined. This decline was possibly due to the indirect effects of the introduction of PCVs for children. Since 2017, however, the proportion of PCV13 serotypes among adult pneumococcal pneumonia has remained stable, showing no further decrease. PCV13 serotypes still accounted for 38.5% in 2018–2020. However, over the study period, the proportion of PPSV23 non-PCV13 serotypes did not change, and the proportions of PCV15 and PCV20 serotypes were 43.3 and 59.6%, respectively, in 2018–2020. The proportions were almost the same as in older adults aged ≥65 years (Supplementary Table 3). These results indicate that introducing PCVs, including newly developed

Table 3
Changes in proportions of vaccine-covered serotypes before and after the introduction of PCV13 into the NIP for children in Japan.

	2011–2014		2016–2020		Difference (95% CI)	P-value*
	no.	% (95% CI)	no.	% (95% CI)		
Total (n = 650)	224		426			
PCV7 serotypes	45	20.1 (15.0 to 25.9)	42	9.9 (7.2 to 13.1)	-10.2 (-16.2 to -4.3)	<0.001
PCV13 non-PCV7 serotypes	73	32.6 (26.5 to 39.2)	96	22.5 (18.7 to 26.8)	-10.1 (-17.4 to -2.7)	0.005
PCV13 serotypes	118	52.7 (45.9 to 59.4)	138	32.4 (28.0 to 37.1)	-20.3 (-28.2 to -12.4)	<0.001
PCV15 serotypes	125	55.8 (49.0 to 62.4)	156	36.6 (32.0 to 41.4)	-19.2 (-27.1 to -11.2)	<0.001
PCV20 serotypes	159	71.0 (64.6 to 76.8)	223	52.3 (47.5 to 57.2)	-18.7 (-26.2 to -11.0)	<0.001
PPSV23 non-PCV13 serotypes	43	19.2 (14.3 to 25.0)	86	20.2 (16.5 to 24.3)	1.0 (-5.4 to 7.4)	0.763
PPSV23 serotypes	156	69.6 (63.2 to 75.6)	205	48.1 (43.3 to 53.0)	-21.5 (-29.2 to -13.9)	<0.001
Non-vaccine serotypes	63	28.1 (22.3 to 34.5)	202	47.4 (42.6 to 52.3)	19.3 (11.7 to 26.9)	<0.001
Age group						
Aged ≥65 years (n = 471)	160		311			
PCV13 serotypes	89	55.6 (47.6 to 63.5)	100	32.2 (27.0 to 37.7)	-23.5 (-32.8 to -14.2)	<0.001
PPSV23 non-PCV13 serotypes	30	18.8 (13.0 to 25.7)	61	19.6 (15.3 to 24.5)	0.9 (-6.6 to 8.4)	0.822
PPSV23 serotypes	116	72.5 (64.9 to 79.3)	144	46.3 (40.7 to 52.0)	-26.2 (-35.1 to -17.3)	<0.001
Non-vaccine serotypes	41	25.6 (19.1 to 33.1)	150	48.2 (42.6 to 53.9)	22.6 (13.9 to 31.4)	<0.001
Aged <65 years (n = 179)	64		115			
PCV13 serotypes	29	45.3 (32.8 to 58.3)	38	33.0 (24.6 to 42.5)	-12.3 (-27.2 to 2.7)	0.104
PPSV23 non-PCV13 serotypes	13	20.3 (11.3 to 32.2)	25	21.7 (14.6 to 30.4)	1.4 (-11.0 to 13.8)	0.823
PPSV23 serotypes	40	62.5 (49.5 to 74.3)	61	53.0 (43.5 to 62.4)	-9.5 (-24.4 to 5.5)	0.221
Non-vaccine serotypes	22	34.4 (22.9 to 47.3)	52	45.2 (35.9 to 54.8)	10.8 (-3.9 to 25.6)	0.158
Sex						
Men (n = 388)	136		252			
PCV13 serotypes	69	50.7 (42.0 to 59.4)	93	36.9 (30.9 to 43.2)	-13.8 (-24.1 to -3.5)	0.008
PPSV23 non-PCV13 serotypes	23	16.9 (11.0 to 24.3)	49	19.4 (14.7 to 24.9)	2.5 (-5.4 to 10.5)	0.540
PPSV23 serotypes	89	65.4 (56.8 to 73.4)	126	50.0 (43.7 to 56.3)	-15.4 (-25.5 to -5.3)	0.004
Non-vaccine serotypes	44	32.4 (24.6 to 40.9)	110	43.7 (37.4 to 50.0)	11.3 (1.3 to 21.3)	0.030
Women (n = 261)	88		173			
PCV13 serotypes	49	55.7 (44.7 to 66.3)	45	26.0 (19.6 to 33.2)	-29.7 (-41.9 to -17.4)	<0.001
PPSV23 non-PCV13 serotypes	20	22.7 (14.5 to 32.9)	37	21.4 (15.5 to 28.3)	-1.3 (-12.0 to 9.3)	0.804
PPSV23 serotypes	67	76.1 (65.9 to 84.6)	79	45.7 (38.1 to 53.4)	-30.5 (-42.1 to -18.9)	<0.001
Non-vaccine serotypes	19	21.6 (13.5 to 31.6)	91	52.6 (44.9 to 60.2)	31.0 (19.6 to 42.4)	<0.001
Residence						
Living at home (n = 584)	202		382			
PCV13 serotypes	103	51.0 (43.9 to 58.1)	119	31.2 (26.5 to 36.1)	-19.8 (-28.2 to -11.5)	<0.001
PPSV23 non-PCV13 serotypes	41	20.3 (15.0 to 26.5)	81	21.2 (17.2 to 25.6)	0.9 (-6.0 to 7.8)	0.798
PPSV23 serotypes	139	68.8 (61.9 to 75.1)	186	48.7 (43.6 to 53.8)	-20.1 (-28.2 to -12.0)	<0.001
Non-vaccine serotypes	58	28.7 (22.6 to 35.5)	182	47.6 (42.5 to 52.8)	18.9 (10.9 to 26.9)	<0.001
Nursing-home residents (n = 66)	22		44			
PCV13 serotypes	15	68.2 (45.1 to 86.1)	19	43.2 (28.3 to 59.0)	-25.0 (-49.4 to -0.6)	0.055
PPSV23 non-PCV13 serotypes	2	9.1 (1.1 to 29.2)	5	11.4 (3.8 to 24.6)	2.3 (-13.0 to 17.5)	0.777
PPSV23 serotypes	17	77.3 (54.6 to 92.2)	19	43.2 (28.3 to 59.0)	-34.1 (-56.9 to -11.3)	0.009
Non-vaccine serotypes	5	22.7 (7.8 to 45.4)	20	45.5 (30.4 to 61.2)	22.7 (-0.1 to 45.6)	0.073
Comorbidity						
Respiratory diseases (n = 151)	45		106			
PCV13 serotypes	22	48.9 (33.7 to 64.2)	24	22.6 (15.1 to 31.8)	-26.2 (-42.9 to -9.6)	0.001
PPSV23 non-PCV13 serotypes	9	20.0 (9.6 to 34.6)	22	20.8 (13.5 to 29.7)	0.8 (-13.3 to 14.8)	0.916
PPSV23 serotypes	30	66.7 (51.0 to 80.0)	43	40.6 (31.1 to 50.5)	-26.1 (-42.7 to -9.5)	0.003
Non-vaccine serotypes	14	31.1 (18.2 to 46.6)	60	56.6 (46.6 to 66.2)	25.5 (9.0 to 42.0)	0.004
Malignancy (n = 78)	30		48			
PCV13 serotypes	16	53.3 (34.3 to 71.7)	12	25.0 (13.6 to 39.6)	-28.3 (-50.0 to -6.7)	0.011
PPSV23 non-PCV13 serotypes	3	10.0 (2.1 to 26.5)	14	29.2 (17.0 to 44.1)	19.2 (2.4 to 35.9)	0.046
PPSV23 serotypes	19	63.3 (43.9 to 80.1)	24	50.0 (35.2 to 64.8)	-13.3 (-35.6 to 9.0)	0.249
Non-vaccine serotypes	11	36.7 (19.9 to 56.1)	22	45.8 (31.4 to 60.8)	9.2 (-13.1 to 31.4)	0.425
Pneumococcal vaccination status						
PPSV23-vaccinated group ** **(n = 112)**	49		63			
PCV13 serotypes	19	38.8 (25.2 to 53.8)	11	17.5 (9.1 to 29.1)	21.3 (-37.9 to -4.8)	0.012
PPSV23 non-PCV13 serotypes	9	18.4 (8.8 to 32.0)	8	12.7 (5.6 to 23.5)	-5.7 (-19.3 to 7.9)	0.407
PPSV23 serotypes	28	57.1 (42.2 to 71.2)	17	27.0 (16.6 to 39.7)	-30.2 (-47.8 to -12.5)	0.001
Non-vaccine serotypes	21	42.9 (28.8 to 57.8)	44	69.8 (57.0 to 80.8)	27.0 (9.1 to 44.9)	0.004

(*continued on next page*)

Table 3 (*continued*)

	2011–2014		2016–2020		Difference (95% CI)	P-value*
	no.	% (95% CI)	no.	% (95% CI)		
Non-vaccinated group* (n = 291)**	119		172			
PCV13 serotypes	71	59.7 (50.3 to 68.6)	63	36.6 (29.4 to 44.3)	-23.0 (-34.4 to -11.7)	<0.001
PPSV23 non-PCV13 serotypes	24	20.2 (13.4 to 28.5)	34	19.8 (14.1 to 26.5)	-0.4 (-9.7 to 8.9)	0.933
PPSV23 serotypes	92	77.3 (68.7 to 84.5)	86	50.0 (42.3 to 57.7)	-27.3 (-37.9 to -16.7)	<0.001
Non-vaccine serotypes	24	20.2 (13.4 to 28.5)	75	43.6 (36.1 to 51.4)	23.4 (13.1 to 33.8)	<0.001

Data are presented as numbers and proportions with 95% confidence intervals. PCV7 serotypes includes serotype 4, 6B, 9 V, 14, 18C, 19F, and 23F; PCV13 non-PCV7 serotypes serotype 1, 3, 5, 6A, 7F, and 19A; PCV15 serotypes PCV13 serotypes plus serotype 22F and 33F; PCV20 serotypes PCV15 serotypes plus serotype 8, 10A, 11A, 12F, and 15B; PPSV23 non-PCV13 serotypes serotype 2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F; PPSV23 serotypes PCV7 serotypes plus serotype 1, 2, 3, 5, 7F, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, 33F; and non-vaccine serotypes non-PCV13 and non-PPSV23 serotypes.

In Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; NIP, national immunization program; PCV7, 7-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

*Comparing 2011–2014 and 2016–2020 periods.

** PPSV23-vaccinated group was defined as a group of patients who had received PPSV23 within the five years prior to the first hospital visit for pneumonia.

*** Non-vaccinated group was defined as a group of patients who had not received any pneumococcal vaccines prior to the first hospital visit for pneumonia.

PCVs, to older adults aged ≥65 years could prevent additional pneumococcal pneumonia cases in adults. Based on our data, it is time to consider the next Japanese pneumococcal vaccination policy for older adults. However, studies from other points of view are also needed when discussing vaccination policy, including cost-effectiveness analysis. Prior to the discussion of future pneumococcal vaccination policy, further studies are required.

The reduction in the proportion of PCV13 serotypes after introducing PCVs for children differed depending on the hosts. The decline in women was more marked than that in men even though there was no statistically significant difference; one of the plausible reasons could be that women typically have more contact with children than men, as parents or grandparents. Therefore, there is a high probability that similar serotypes may pass between women and children. This result is consistent with a previous study in the United States: the number of IPD caused by serotypes frequently detected among children increased among older adults, especially older women, after holidays [28]. Indirect effects caused by pediatric vaccination as well as transmission of *S. pneumoniae* from children are likely to occur more markedly among women. As for the pneumococcal vaccination status, the proportion of PPSV23 serotypes was lower in the PPSV23-vaccinated group compared with the non-vaccinated group, irrespective of being before or after the introduction of pediatric PCVs (specifically, 57.1% in the PPSV23-vaccinated group vs 77.3% in the non-vaccinated group before the introduction of pediatric PCVs, and 27.0% in the PPSV23-vaccinated group vs 50.0% in the non-vaccinated group after the introduction of pediatric PCVs, respectively). One of the reasons for the differences in the proportion of PPSV23 serotypes between the PPSV23-vaccinated group and the non-vaccinated group could possibly be the direct effects of PPSV23.

Decreases in serotypes 3, 19F and 14 largely drove the reduction in PCV13 serotypes in our study. The overall proportion of serotype 3 has decreased significantly since the introduction of pediatric PCV13 (from 22.7 to 10.3%, p <0.001), although serotype 3 remains the most common serotype. Serotypes that contributed to the overall decline in PCV13 serotypes varied depending on the country. In the United States and Canada, serotypes 19A and 7F contributed to the reduction. Still, serotype 3 has been dominant and increasing among both IPD and pneumococcal pneumonia patients even after the introduction of PCVs for children [29–33]. In England and Wales, serotypes 3 and 19A initially declined and contributed to the reduction in PCV13 serotypes, but both have been increasing since 2013 [34–37]. In France and Korea, serotypes 3, 19A, and 7F contributed to the decline [38,39]. Since future serotype changes cannot be predicted and will vary by geographical area, it will be essential to keep following the local data to determine the appropriateness of vaccination policies.

The severity of pneumococcal pneumonia decreased over time despite the fact that patient characteristics, such as age, sex, and presence of comorbidities, have not changed, and that the proportion of those vaccinated with PPSV23 within the past five years decreased. Some previous studies reported an association between specific serotypes and disease severity: serotypes 3, 8, 19A, and 7F were associated with severe pneumococcal pneumonia [40], and serotype 3 with septic shock [41]. In our study, the reduction in serotypes 3 and 19F may have contributed to the decline in disease severity since serotypes 3 and 19F were associated with severe diseases (CURB-65 ≥3) (Supplementary Table 6).

There were several limitations of our study. First, we did not estimate the incidence of pneumococcal pneumonia by serotypes or patient characteristics. We evaluated only the proportion as a percentage of the total pneumococcal pneumonia patients; the proportion of non-vaccine serotypes increased, but this does not mean that the incidence of non-vaccine pneumococcal pneumonia increased. It is essential to conduct further studies that aim to estimate the incidence of pneumococcal pneumonia by serotypes after the introduction of PCV13 for children. Second, our study only included pneumococcal patients whose isolates were available for serotyping. We did not include patients with culture-negative but polymerase chain reaction (PCR) or urinary assay-positive results. There is a possibility that applying other methods may lead to different results [42]. However, since the serotyping of culture-positive strains by the Quellung reaction has acceptable levels of sensitivity and specificity [43], we consider it reasonable to apply our study method to facilitate pneumococcal pneumonia serotype surveillance. Third, vaccination histories were unknown for 20–30% of the total study population and more than 40% of patients in the third period. Due to this uncertainty, it was unclear whether the changes of PCV13 serotypes over time were caused by the introduction of pediatric PCVs or the direct effects of PPSV23. However, the proportion of PCV13 serotypes in the PPSV23-vaccinated group and non-vaccinated groups showed a similar decline. Therefore, the decrease in PCV13 serotypes could have been caused by the introduction of pediatric PCVs. Fourth, although the reduction of PCV13 serotypes after pediatric PCVs introduction differed by patient group, we could not show any significant differences due to the small sample size.

In conclusion, after the introduction of PCVs into the NIP for children in 2013, the proportion of adult pneumococcal pneumonia caused by PCV13 serotypes in Japan declined. This decline was possibly due to the indirect effects of the introduction of PCVs into the NIP for children. However, PCV13 serotypes still accounted for 38.5% of the total. Now that new PCVs have been developed, it is time to consider the next pneumococcal vaccination strategy for older adults in Japan.

5. Collaborators

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Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

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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.2022.07.041.

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