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Impact of the pediatric 13-valent pneumococcal conjugate vaccine on serotype distribution and clinical characteristics of pneumococcal pneumonia in adults: The Japan Pneumococcal Vaccine Effectiveness Study (J-PAVE)

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ABSTRACT

Background: The pediatric 13-valent pneumococcal conjugate vaccine (PCV13) was included in the pediatric immunization programme in Japan in late 2013. The impact of vaccination on the serotype distribution and clinical characteristics of pneumococcal pneumonia has not been described.
Methods: The first phase of this multicentre prospective study was conducted at community-based hospitals in Japan from 2011 to 2014. The second phase was conducted from 2016 to 2017. Pneumococcal isolates and clinical data were collected from patients with community-acquired pneumonia who were ≥15 years of age. Patients were classified by pneumococcal serotype to PCV13 serotype, 23-valent pneumococcal polysaccharide vaccine (PPV23) non-PCV13 serotype, and non-vaccine serotype.
Results: A total of 484 patients were enrolled, 241 in the first phase and 243 in the second. The proportion of PCV13 serotypes decreased from 53% to 33% ($p < 0.001$), whereas PPV23 non-PCV13 serotypes did not change ($p = 0.754$). PCV13 serotypes were associated with increased risk of elevated blood urea nitrogen (adjusted odds ratio 2.49; 95% confidence interval: 1.49–4.16) and hospitalization (adjusted odds ratio 1.74; 95% confidence interval: 1.02–2.95). These associations were not observed in patients with PPV23 non-PCV13 serotypes.
Conclusions: The occurrence of pneumococcal pneumonia caused by vaccine-covered serotypes dramatically decreased following the introduction of pediatric PCV13. The PCV13 serotypes were associated with pneumonia severity.

1. Introduction

Streptococcus pneumoniae, or pneumococcus, is the leading cause of bacterial pneumonia in adults [1,2]. As the incidence increases with age, the burden of pneumococcal pneumonia has been growing in Japan as the population ages [3]. There were an estimated 530,000 cases of adult pneumococcal pneumonia in Japan in 2012, and 74% of the patients were 65 years of age and older [3]. Two polyvalent pneumococcal vaccines are available for adults, a 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine (PCV13). PPV23 has been in use since the 1980s for people with high-risk conditions and in those ≥ 65 years of age. The vaccine reduces

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the risk of invasive pneumococcal disease (IPD) by 50% and its effectiveness against pneumococcal pneumonia caused by vaccine stereotypes is mild to moderate [4]. The CAPITA trial found that PCV13 reduced vaccine-serotype pneumococcal pneumonia in older people by 46% and IPD by 75% [5]. As of the end of 2018, both PPV23 and PCV13 are recommended for people ≥ 65 years of age in the USA, but only PPV23 is included in routine immunization in Japan and is recommended in other countries [6–8]. The PCV13 vaccine was approved for use in adults 65 years of age and older in Japan in 2014, but PCV13 has been routinely used in adults only in USA.

The assessment of adult pneumococcal vaccination programmes is complicated because the pneumococcal serotype distribution changes over time by the indirect effect of pediatric PCVs. Previous studies in the USA and Europe have shown that the proportion of vaccine-covered serotypes in adult IPD patients significantly decreased following the introduction of pediatric PCVs [9,10]. Considering the difference in transmissibility and virulence by pneumococcal serotypes, the distribution of serotypes may be different by IPD and pneumonia patients. However, only a few studies have demonstrated the change in the proportion of vaccine-covered serotypes in adult pneumococcal pneumonia patients [11,12]. Also the impact of paediatric PCVs on clinical characteristics of pneumococcal pneumonia has not been established. In Japan, PCV7 was adopted for vaccination of infants in 2010 and was replaced for routine vaccination by PCV 13 in 2013. We conducted this study to determine the impact of replacement of PCV7 with PCV13 on the serotype distribution and clinical characteristics of pneumococcal pneumonia in adults in Japan.

2. Methods

2.1. Study design and settings

This multicentre prospective study, the Japan Pneumococcal Vaccine Effectiveness Study (J-PAVE), was conducted at community hospitals in Japan. It collected pneumococcal isolates and clinical data from patients treated for community-onset pneumonia at five hospitals on the four main islands of Japan from 1 May 2016 through 30 April 2017. The isolates and clinical information of patients in the Adult Pneumonia Study Group-Japan (APSG-J) study conducted at four hospitals, all of which were included in the current study, from 28 September 2011, through 23 August 2014 have been described elsewhere [3]. This study included pneumonia patients with pneumococcal isolates that were available for serotyping.

2.2. Case enrolment and data collection

J-PAVE and APSG-J used the same community-onset pneumonia case definition. Eligible patients were ≥ 15 years of age, with symptoms compatible with pneumonia (i.e. fever, chills or rigors, cough, sputum, pleuritic chest pain, dyspnoea, dyspnoea and/or tachypnea), new pulmonary infiltrates on chest X-ray or computed tomography and pneumonia that developed within 48 h of admission. Demographic and clinical information including the pneumococcal vaccination history (PCV13/PPV23) were collected from patients and/or their guardians and medical records using a standardized data collection form.

2.3. Sample collection and microbiological testing

Sputum samples were collected from patients at their first visit or at the time of hospitalization. The sputum samples and pneumococcal isolates were frozen and stored at −80 °C. *S. pneumoniae* isolated from sputum, pleural effusions or blood was stored in cryotubes containing 1.0 ml STGG (Skim milk 2 g, Tryptone 3 g, Glucose 0.5 g, Glycerol 10 ml, distilled water 100 ml) medium (Streptococcus Laboratory Protocols-Centers for Disease Control and Prevention, https://www.cdc.gov/streplab/index.html) and stored frozen at −80 °C. The patient list and clinical specimens stored each participating institution were regularly shipped to the Institute of Tropical Medicine at Nagasaki University for serotyping by the capsular Quellung method.

2.4. Pneumococcal vaccination policy in Japan

PCV7 was adopted for vaccination of infants in Japan in 2010 and was replaced for routine vaccination by PCV 13 in November 2013. In June 2014, the PCV13 indication was extended to include people ≥ 65 years of age. PPV23 has been indicated for routine vaccination of people ≥ 65 years of age in October 2014. The estimated vaccination coverage of PCV7 in children was <10% in 2010, 50–60% in 2011, 80–90% in 2012 [13] and 97.4% in 2016 [14]. The estimated vaccination coverage of PPV23 in people aged 65 years was approximately 40% in 2015 [15].

2.5. Statistical analysis

The distribution of pneumococcal serotypes was monitored in two study periods. The first was from September 2011 through February 2014, which was the post-PCV7 period. The second was from May 2016 through April 2017, or the post-PCV13 period. Pneumococcal isolates were grouped as PCV13 serotypes, PPV23 non-PCV13 serotypes and non-vaccine serotypes. Baseline characteristics were compared with chi-square or Fisher's exact tests for categorical variables. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CI) were estimated by logistic regression. Study site, patient sex, age, pre-hospital antibiotic treatment, underlying disorder, nursing home residence and history of PPV23 vaccination were potential confounders and were included in the final multiple regression models. Statistical analyses were conducted with STATA version 14.0 (Stata Corp., College Station, TX, USA).

2.6. Ethics

The study was approved by the Institutional Review Boards of the Institute of Tropical Medicine, Nagasaki University, Kameda Medical Center, Chikamori Hospital, Juzenkai Hospital and Nagasaki Rosai Hospital. In Ebetsu City Hospital, approval was given by the hospital director. The study was conducted following the Ministry of Health, Labour and Welfare 2008 Ethical Guidelines for Epidemiological Studies. The requirement for obtaining written consent from all participants was waived because of the study's observational nature without any deviation from the current practice.

3. Results

3.1. Baseline characteristics

A total of 484 patients with pneumococcal pneumonia were enrolled, 241 in the first study phase and 243 in the second. Seventeen first-phase patients were excluded, 16 for a non-pneumonia diagnosis and one for refusal to participate. Twenty-eight second-phase patients were excluded, 14 for a non-pneumonia diagnosis, 10 for hospital-acquired pneumonia, 3 for refusal to participate and 1 for lack of data. One patient in the first study phase was serotyped as 3 or 22F and was excluded from the analysis.

Serotype 22F is included in PPV23 but not in PCV13, but serotype 3 is included in both vaccines. The remaining 223 patients in the first phase and 215 in the second were eligible for analysis. The demographic characteristics of patients did not differ between the pre- and post-PCV13 periods except that the proportion of nursing home residents was lower in the post-PCV13 period (Supplementary Table 1). Twenty-eight (6.4%) of the 438 included patients were positive for blood culture.

3.2. Pneumococcal serotype distribution

Fig. 1 shows the distribution of pneumococcal serotypes. In the first phase, which was the post-PCV7 period, the most frequent serotype was 3 (22%), followed by 11A (10%), 19F and 19A (7%). In the second phase, the post-PCV13 period, the most frequent serotype was 35B (12%), followed by 3 (10%). The degree of decline was different by PCV13 serotypes; the decline was substantial for serotypes 3, 19F, and 14 but marginal for serotypes 19A, 6B, 6A, and 23F. The proportion of vaccine-covered serotypes included in each study period is shown in Table 1. The proportion of PCV13 serotypes decreased from 53% to 33% (difference −20%; 95% CI, −29 to −11; $p < 0.001$); the declines in the proportion of PCV7 serotypes and PCV13 non-PCV7 serotypes were −11% (95%CI, −18 to −4; $p = 0.002$) and −9% (−17 to −1; $p = 0.035$), respectively. The proportion of PPV23 non-PCV13 serotypes did not change over the study period (−1%; −8 to 6; $p = 0.754$). These trends were observed in home residents, but the changes were marginal in nursing home residents.

3.3. Characteristics of pneumococcal pneumonia by serotype

The patient characteristics and pneumococcal pneumonia serotypes are shown in Table 2. Overall, 39% of the patients were women and the median age was 73 (interquartile range 63–83) years. The proportion of women ≥ 65 years of age and comorbidities in the three groups did not differ. The proportions of patients being nursing home residents, inpatients, have altered mental status, elevated blood urea nitrogen, CURB-65 pneumonia severity score ≥ 3, and PPV23 vaccination history were different between the three groups. The 30-day mortality of pneumococcal pneumonia was 3%; no significant difference was observed among the three groups. Approximately 1% of patients had been vaccinated with PCV13. Bacteraemia occurred in 7.9% of patients with PCV13 serotypes, 7.5% of those with PSV23 non-PCV13 serotypes and 4.1% of those with non-vaccine serotypes; the occurrence did not differ between the three groups ($p = 0.309$).

Univariate analyses found that PCV13 serotypes were associated with elevated blood urea nitrogen, hospitalization, nursing home residence, having a CURB-65 score ≥ 3 and having hypoxemia (Table 3). In multivariate analysis, the association of elevated blood urea nitrogen (adjusted OR 2.49, 95% CI: 1.49 to 4.16), nursing home residence (adjusted OR 1.93, 95%CI: 1.04 to 3.59) and hospitalization (adjusted OR 1.74, 95% CI: 1.02 to 2.95) with PCV13 serotypes remained significant. PPV23 non-PCV13 serotypes were associated with a decreased risk of altered mental status (adjusted OR 0.32, 95% CI: 0.12 to 0.83). We also compared PCV13 serotypes and PPV23 non-PCV13 serotypes (Supplementary Table 2). Univariate analyses revealed that PCV13 serotypes were associated with altered mental status and elevated blood urea nitrogen. These associations were also seen in the multivariate analysis.

4. Discussion

The proportion of vaccine-covered serotypes causing pneumococcal pneumonia in adults in Japan has significantly decreased following the introduction of pediatric PCV13 vaccination. Patients with pneumonia caused by PCV13 serotypes were more likely to be nursing home residents, hospital inpatients, or to have elevated blood urea nitrogen. The characteristics of patients with pneumonia caused by PPV23 non-PCV13 serotypes or non-vaccine serotypes did not differ except for a decreased risk of having altered mental status in those with PPV23 non-PCV13 serotypes.

The occurrence of PCV13 serotypes decreased by 19.7% and that of PPV23 serotypes decreased by 22.2% from the post-PCV7 to the post-PCV13 period because of the indirect effect of pediatric PCV vaccination. A substantial impact of PCV13 vaccination on the occurrence of adult pneumococcal pneumonia in the Japanese population has also been seen in other high-income countries [16]. The incidence of IPD in the USA caused by PCV13 non-PCV7 serotypes declined by 58–72% following the introduction of the pediatric PCV13 [17]. The incidence of pneumococcal pneumonia caused by PCV13 non-PCV7 serotypes in the UK declined by 30% in the 2 years following the introduction of the pediatric PCV13 [18]. A systematic review by Katoh et al. reported that the proportion of adult pneumonias caused by PCV7 serotypes decreased by 18.1%,

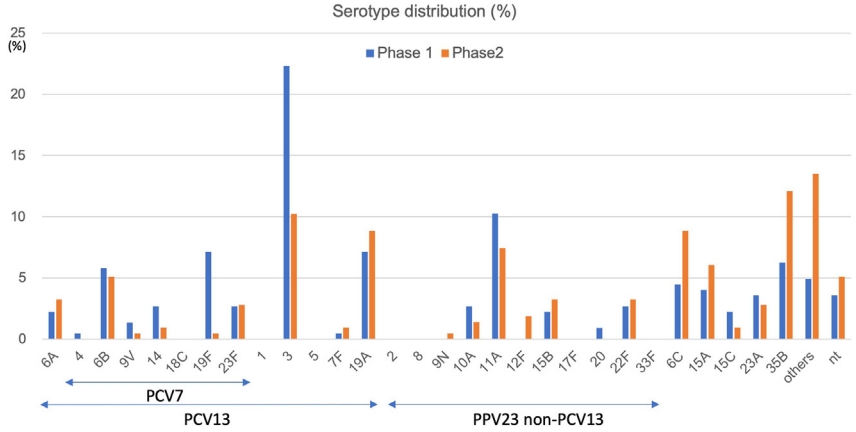

Fig. 1. Serotype distribution in the first and second study phases. nt, non-typable; PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), PCV13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), PPV23 non-PCV13 serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F), and non-vaccine types (NVT; non-PCV-13 and non-PPV23 serotypes). Phase 1, is shown in blue, the first study phase was from September 2011 through February 2014; Phase 2, is shown in orange, the second study phase was from May 2016 through April 2017. Y axis: Isolated proportion (%) of serotype positive among pneumococcal isolates.

Table 1
Proportions of vaccine serotypes in the first and second study phases.

Total (N = 438)	Phase 1 (N)	(%)	Phase 2 (N)	(%)	Difference (95% CI)	p-value
PCV13 serotypes	118/223	53%	71/215	33%	−20% (−29.0 to −10.8)	<0.001
PCV7 serotypes	46/223	21%	21/215	10%	−11% (−17.5 to −4.2)	0.002
PCV13 non-PCV7 serotypes	72/223	32%	50/215	23%	−9% (−17.4 to −0.7)	0.035
PPV23 non-PCV13 serotypes	42/223	19%	38/215	18%	−1% (−8.4 to 6.1)	0.754
NVT	63/223	28%	106/215	49%	21% (12.1 to 30.0)	<0.001
Home residents (N = 361)						
PCV13 serotypes	88/171	52%	58/190	31%	−21% (−30.9 to −11.0)	<0.001
PCV7 serotypes	36/171	21%	16/190	8%	−13% (−19.9 to −5.4)	0.001
PCV13 non-PCV7 serotypes	52/171	30%	42/190	22%	−8% (−17.3 to 0.8)	0.073
PPV23 non-PCV13 serotypes	34/171	20%	33/190	17%	−3% (−10.6 to 5.5)	0.539
NVT	49/171	29%	99/190	52%	23% (13.6 to 33.3)	<0.001
Nursing home residents (N = 77)						
PCV13 serotypes	30/52	58%	13/25	52%	−6% (−29 to 18)	0.638
PCV7 serotypes	10/52	19%	5/25	20%	1% (−18.2 to 19.8)	0.936
PCV13 non-PCV7 serotypes	20/52	38%	8/25	32%	−6% (−29 to 16)	0.581
PPV23 non-PCV13 serotypes	8/52	15%	5/25	20%	5% (−13.9 to 23.1)	0.613
NVT	14/52	27%	7/27	28%	1% (−20.3 to 22.4)	0.921

N, number of patients; PPV23 serotypes, 23-valent pneumococcal polysaccharide vaccine serotypes; PCV13 serotypes, 13-valent pneumococcal conjugate vaccine serotypes; PCV7 serotypes, 7-valent pneumococcal conjugate vaccine serotypes; Non-vaccine serotypes, non-PPV23 plus non-PCV13 serotype; 95% CI, 95% confidence intervals. Phase 1, the first study phase was from September 2011 through February 2014; Phase 2, the second study phase was from May 2016 through April 2017.

Table 2
Patient characteristics of pneumococcal pneumonia by serotype groups.

			PPV23 serotypes + 6A			p-value[a]
		Total (%) n = 438	PCV13 serotypes (%) n = 189	PPV23 non-PCV13 serotypes (%) n = 80	Non-vaccine serotypes (%) n = 169	
Sex	Female	171 (39)	74 (39)	33 (41)	64 (38)	0.877
	Male	267 (61)	115 (61)	47 (59)	105 (62)	
Age years	>65	314 (72)	139 (74)	61 (76)	114 (67)	0.268
	0–64	124 (28)	50 (26)	19 (24)	55 (33)	
Comorbidities	Yes	378 (86)	168 (89)	69 (86)	141 (83)	0.325
	No	60 (14)	21 (11)	11 (14)	28 (17)	
Nursing home resident	Nursing home	77 (18)	43 (23)	13 (16)	21 (12)	0.035
	Home	361 (82)	146 (77)	67 (84)	148 (88)	
Smoking	Yes	240 (55)	102 (54)	49 (61)	89 (53)	0.474
	No	173 (40)	73 (39)	29 (36)	71 (42)	
	Unknown	25 (6)	14 (7)	2 (3)	9 (5)	
Pre-hospital antibiotics	Yes	61 (14)	32 (17)	11 (14)	18 (11)	0.156
	No	370 (84)	154 (81)	66 (83)	150 (89)	
	Unknown	7 (2)	3 (2)	3 (4)	1 (1)	
Hospitalization	Inpatient	306 (70)	146 (77)	58 (73)	102 (60)	0.002
	Outpatient	132 (30)	43 (23)	22 (28)	67 (40)	
Altered mental status	Yes	83 (19)	46 (24)	7 (9)	30 (18)	0.010
	No	355 (81)	143 (76)	73 (91)	139 (82)	
Systolic blood pressure (mmHg)	0–100	59 (13)	26 (14)	9 (11)	24 (14)	0.589
	>100.1	361 (82)	158 (84)	68 (85)	135 (80)	
	Unknown	18 (4)	5 (3)	3 (4)	10 (6)	
SPO_2 < 90% or oxygen supply	Yes	206 (47)	100 (53)	40 (50)	66 (39)	0.057
	No	226 (52)	87 (46)	40 (50)	99 (59)	
	Unknown	6 (1)	2 (1)	0 (0)	4 (2)	
Blood urea nitrogen (mg/dL)	≥20	181 (41)	100 (53)	32 (40)	49 (29)	<0.001
	<20	242 (55)	85 (45)	47 (59)	110 (65)	
	Unknown	15 (3)	4 (2)	1 (1)	10 (6)	
CURB65	>3	138 (32)	72 (38)	24 (30)	42 (25)	0.039
	0–2	268 (61)	107 (57)	52 (65)	109 (65)	
	Unknown	32 (7)	10 (5)	4 (5)	18 (11)	
Bacteremia	Yes	28 (6)	15 (8)	6 (8)	7 (4)	0.309
	No	410 (94)	174 (92)	74 (93)	162 (96)	
Mortality ≤ 30 days	Yes	14 (3)	7 (4)	1 (1)	6 (4)	0.676
	No	424 (97)	182 (96)	79 (99)	163 (96)	
PPV23 vaccination	Vaccinated ≤ 5 years	83 (19)	25 (13)	15 (19)	43 (25)	0.02
	Vaccinated > 5 years	12 (3)	3 (2)	4 (5)	5 (3)	
	Not-vaccinated	232 (53)	112 (59)	45 (56)	75 (44)	
	Unknown	111 (25)	49 (26)	16 (20)	46 (27)	

Data are n (%). PPV23, 23-valent pneumococcal polysaccharide vaccine, Non-vaccine serotypes, non-PPV23 plus non-PCV13 serotype.
[a] Compared between the three groups: PCV13 serotypes, PPV23 non-PCV13 serotypes, and non-vaccine serotypes.

Table 3
Patient characteristics associated with PCV13 and PPV23 non-PCV13 pneumococcal serotypes.

		PCV13 serotypes vs non-vaccine serotypes						PPV23 non-PCV13 serotypes vs non-vaccine serotypes					
		uOR	95% CI	p-value	aOR[a]	95% CI	p-value	uOR	95% CI	p-value	aOR[a]	95% CI	p-value
Sex	Female	0.95	(0.62 to 1.45)	0.803	0.99	(0.63 to 1.56)	0.968	0.87	(0.50 to 1.49)	0.610	0.84	(0.48 to 1.50)	0.559
	Male	Ref						Ref					
Age years	>65	1.34	(0.85 to 2.12)	0.207	0.98	(0.43 to 2.21)	0.952	1.55	(0.84 to 2.84)	0.158	0.71	(0.24 to 2.07)	0.528
	0–64	Ref						Ref					
Comorbidities	Yes	1.59	(0.86 to 2.92)	0.136	1.52	(0.77 to 3.03)	0.225	1.25	(0.59 to 2.65)	0.568	0.97	(0.39 to 2.41)	0.944
	No	Ref						Ref					
Nursing home resident	Nursing home	2.08	(1.17 to 3.67)	0.012	1.93	(1.04 to 3.59)	0.037	1.37	(0.65 to 2.89)	0.413	1.16	(0.50 to 2.70)	0.722
	Home	Ref						Ref					
Smoking	Yes	1.11	(0.72 to 1.72)	0.623	1.58	(0.92 to 2.72)	0.101	1.35	(0.77 to 2.35)	0.292	1.99	(0.95 to 4.16)	0.069
	No	Ref						Ref					
	Unknown	1.51	(0.62 to 3.72)	0.367	1.35	(0.52 to 3.53)	0.537	0.54	(0.11 to 2.67)	0.454	0.39	(0.06 to 2.35)	0.304
Pre-hospital antibiotics	Yes	1.73	(0.93 to 3.22)	0.082	1.51	(0.78 to 2.92)	0.220	1.39	(0.62 to 3.10)	0.423	1.60	(0.67 to 3.86)	0.291
	No	Ref						Ref					
	Unknown	2.92	(0.30 to 28.41)	0.355	1.79	(0.17 to 18.45)	0.625	6.82	(0.70 to 66.77)	0.099	7.65	(0.71 to 82.55)	0.094
Hospitalization	Inpatient	2.23	(1.41 to 3.53)	0.001	1.74	(1.02 to 2.95)	0.041	1.73	(0.97 to 3.09)	0.063	1.39	(0.71 to 2.74)	0.333
	Outpatient	Ref						Ref					
Altered mental status	Yes	1.49	(0.89 to 2.50)	0.129	1.11	(0.63 to 1.98)	0.717	0.44	(0.19 to 1.06)	0.068	0.32	(0.12 to 0.83)	0.019
	No	Ref						Ref					
Systolic blood pressure (mmHg)	0–100	0.93	(0.51 to 1.69)	0.801	0.99	(0.52 to 1.88)	0.971	0.74	(0.33 to 1.69)	0.480	0.75	(0.31 to 1.79)	0.517
	>100.1	Ref						Ref					
	Unknown	0.43	(0.14 to 1.28)	0.129	0.55	(0.17 to 1.78)	0.319	0.60	(0.16 to 2.24)	0.443	0.63	(0.14 to 2.83)	0.550
SPO_2 < 90% or oxygen supply	Yes	1.72	(1.13 to 2.63)	0.012	1.36	(0.85 to 2.17)	0.203	1.50	(0.88 to 2.57)	0.139	1.32	(0.71 to 2.48)	0.383
	No	Ref						Ref					
	Unknown	0.57	(0.10 to 3.18)	0.521	0.68	(0.11 to 4.08)	0.677	1.00					
Blood urea nitrogen (mg/dL)	≥20	2.64	(1.69 to 4.12)	<0.001	2.49	(1.49 to 4.16)	<0.001	1.53	(0.87 to 2.68)	0.139	1.14	(0.58 to 2.25)	0.710
	<20	Ref						Ref					
	Unknown	0.52	(0.16 to 1.71)	0.280	0.57	(0.16 to 2.02)	0.385	0.23	(0.03 to 1.88)	0.172	0.27	(0.03 to 2.28)	0.229
CURB65	>3	1.75	(1.10 to 2.78)	0.019	1.30	(0.75 to 2.24)	0.350	1.20	(0.66 to 2.18)	0.556	0.79	(0.37 to 1.66)	0.528
	0–2	Ref						Ref					
	Unknown	0.57	(0.25 to 1.28)	0.172	0.61	(0.26 to 1.46)	0.267	0.47	(0.15 to 1.45)	0.186	0.46	(0.13 to 1.58)	0.215
Bacteremia	Yes	2.00	(0.79 to 5.01)	0.142	1.76	(0.66 to 4.73)	0.261	1.88	(0.61 to 5.78)	0.273	2.54	(0.74 to 8.74)	0.141
	No	Ref						Ref					
Mortality ≤ 30 days	Yes	1.04	(0.34 to 3.17)	0.938	0.67	(0.20 to 2.24)	0.516	0.34	(0.04 to 2.91)	0.327	0.25	(0.02 to 3.56)	0.304
	No	Ref						Ref					
PPV23 vaccination	vaccinated ≤ 5 years	0.39	(0.22 to 0.69)	0.001	0.35	(0.19 to 0.64)	0.001	0.58	(0.29 to 1.16)	0.126	0.49	(0.23 to 1.07)	0.072
	vaccinated > 5 years	0.40	(0.09 to 1.73)	0.221	0.33	(0.07 to 1.52)	0.154	1.33	(0.34 to 5.22)	0.680	1.16	(0.27 to 4.94)	0.838
	Not-vaccinated	Ref						Ref					
	Unknown	0.71	(0.43 to 1.17)	0.183	0.63	(0.36 to 1.10)	0.102	0.58	(0.29 to 1.14)	0.115	0.51	(0.24 to 1.07)	0.075

[a] Adjusted by study site, sex, age, pre-hospital antibiotic treatment, underlying disorder, nursing home residence and history of PPV23 vaccination; uOR, unadjusted odds ratio; aOR, adjusted odds ratio; Ref, reference; PPV23, 23-valent pneumococcal polysaccharide vaccine; Non-vaccine serotypes, non-PPV23 plus non-PCV13 serotype.

from 44.7% to 26.6%, following the introduction of pediatric PCV7 vaccination [11]. The review indicated that the reduction in the proportion of pneumonias caused by PCV13 observed in our study may be explained by the combination of long-term effect of PCV7 and short-term effect of PCV13. In fact, the decline in the proportion of some PCV13 non-PCV7 serotypes such as serotypes 19A and 6A was not observed during our study period probably because of the short time interval since introduction of PCV13; and these serotypes are expected to decrease in the coming years. The change in serotype distribution differed with patient residential status. In patients ≥ 65 years of age, the reduction in the proportion of PCV13 serotypes was larger in community dwellers (54–30%, $p < 0.001$) than in nursing home residents (61–46%, $p = 0.473$; Supplementary Table). This finding may be explained by more contact of community dwellers than nursing home residents with smaller children and a stronger indirect effect of pediatric PCV vaccination. However, this difference in the proportion of PCV13 serotypes by residential status might diminish over time.

In this study, PCV13 serotypes were associated with severe pneumonia with hospitalization and elevated blood urea nitrogen in comparison with non-vaccine serotypes. However, the mortality of PCV13 and non-vaccine serotypes did not differ. Few previous studies investigated the association of patient characteristics and pneumococcal pneumonia serotypes, and the findings are inconsistent. Our findings are in line with those of a multicentre study conducted in patients ≥ 16 years of age in Denmark. In those patients, invasive serotypes such as 1 and 7F, both are the PCV13 serotypes, were seen in 33% of bacteraemic and in 5% of non-bacteraemic pneumococcal pneumonias [19]. A study conducted in the UK reported that the CURB65 scores and mortality of patients with PCV13 serotypes and non-PCV13 serotypes were not different. However, the study included only hospitalized patients. The finding may not apply to outpatients [20]. A Swedish study of a series of patients with IPD found that the mortality of PCV13 serotypes was lower than that of non-PCV13 serotypes [21]. The inconsistent findings might be partially the result of differences in the distribution of PCV13 serotypes. The severity of PCV13 serotypes varies, and specific serotypes may be associated with severe disease. Associations of patient characteristics and pneumococcal serotypes were found. Serotype 6A had a higher mortality (25%) compared with other serotypes (3%, $p = 0.005$) and serotype 6C was associated with nursing home residence, comorbidities and CURB65 scores > 2. Previous studies found that serotype 35B was associated with penicillin and carbapenem resistance [22], and 12F was associated with local outbreaks [23,24]. Further studies are needed to establish clinical characteristics of individual serotypes.

The PPV23 was added to the Japanese national immunization programme for older people in 2014. Approximately 20% of the study patients ≥ 65 years of age had received a PPV23 vaccination. PCV13 has been commercially available since 2014, but only 0.6% of patients ≥ 65 years of age had received the PCV13. In 2018, Japanese public health authorities chose not to include PCV13 in the national immunization programme for older adults. The substantial reduction in the proportion of PCV13 serotypes observed in our study may support this decision. We compared the two phases, after introducing PCV7 (phase 1) and PCV13 (phase 2) for children, the latter phase may reflect an indirect effect by PCV13 minus PCV7 because of its short period after PCV13 introduction. Our finding also shows that the indirect effect of pediatric PCV13 vaccination had less impact on nursing home residents than community dwellers. Introducing PCV13 for specific high-risk groups such as those in nursing homes may be worth considering. Non-vaccine serotypes were associated with less severe disease, but 60% of patients with those serotypes were hospitalized. That finding indicates the potential benefit of novel increased valency vaccines or serotype-independent vaccines. To help guide the development of future pneumococcal vaccine programmes, we need to monitor the serotype distribution of pneumococcal infections and their clinical features.

The study limitations include enrolment of pneumococcal pneumonia patients whose isolates were available for serotyping. The findings may not apply to patients who are culture-negative but PCR-positive or positive by urinary antigen assays. The sample size of our study was too small to investigate the association of clinical characteristics and individual serotypes. In our hospital-based study, we did not estimate the incidence of pneumococcal pneumonia by serotypes. The observed increase in the proportion of NVT may be simply due to the decrease in the proportion of vaccine-types and not be reflecting true serotype replacement (i.e., the increase in the incidence of NVT). Moreover, our single-year observation in the post-PCV13 period did not allow us to account for secular trends. Despite the limitations, we conclude that the change of serotype distribution has occurred in adult pneumococcal pneumonia after introducing pediatric PCV13 vaccination in Japan. PCV13 serotypes were associated with more severe clinical manifestations than the non-vaccine serotypes were. Further studies including population-based studies are needed to monitor the overall impact of pediatric PCV13 vaccination on adult pneumococcal diseases.

5. Collaborators

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Conflict of interest

KM reports receiving speaker fees from Pfizer. All other authors declare no competing interests.

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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.2019.04.009.

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