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Note

Distribution and annual changes in the proportion of *Streptococcus pneumoniae* serotypes in Japanese adults with pneumococcal pneumonia from 2011 to 2017☆

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ABSTRACT

In 2014, vaccinations with 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13) were implemented in Japan for all adults aged ≥65 years. We previously clarified reductions in the proportions of PCV7-, PCV13-, and PPSV23-covered serotypes in patients with pneumococcal pneumonia after the initiation of PCV7 and PCV13 vaccinations for Japanese children; however, information about the annual changes in the proportion of *Streptococcus pneumoniae* serotypes in patients with pneumococcal pneumonia after the initiation of routine PPSV23 vaccinations remains unclear. We retrospectively studied 229 adults with pneumococcal pneumonia which *S. pneumoniae* was cultured from their lower respiratory tract samples between 2011 and 2017 and investigated the annual changes in the proportion of *S. pneumoniae* serotypes. The proportion of PPSV23-covered serotypes decreased from 71.4% in 2011 to 52.2% in 2014, but it remained essentially unchanged from 2015 to 2017. The proportions of PCV7-covered serotypes decreased from 46.4% in 2011 to 4.3% in 2014; however, this rate increased beginning in 2015 and reached 20.6% in 2017. Among the PCV7-covered serotypes, the proportion of the 19F serotype increased from 2015 to 2017. In conclusion, there were no obvious changes in the proportion of PPSV23-covered and PCV13-covered serotypes in patients with pneumococcal pneumonia after the initiation of routine PPSV23 vaccinations.

Streptococcus pneumoniae is one of the most common bacteria implicated in community-onset pneumonia. In Japan, the estimated incidence of adult pneumococcal pneumonia is 473 cases per 100,000 person-years [1], to date, over 90 capsular serotypes of *S. pneumoniae* have been identified. After the initiation of 7-valent pneumococcal conjugate vaccine (PCV7) and/or PCV13 vaccinations for children [2,3], a decrease in the proportion of PCV7-covered *S. pneumoniae* serotypes in adults has been reported [1,4].

The Japanese Ministry of Health, Labour and Welfare implemented routine vaccinations with 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults aged ≥65 years in October 2014, and PCV13 was also licensed for use in adults aged ≥65 years in June 2014. Although the protective effects of PPSV23 against pneumococcal pneumonia remain controversial [5,6], a previous study indicated its moderate effectiveness against PPSV23-covered serotypes that cause pneumococcal pneumonia in patients aged ≥65 years in Japan [7]. But the annual changes in the proportion of *S. pneumoniae* serotypes that cause pneumococcal pneumonia after the initiation of routine PPSV23 vaccinations in Japan remain unknown.

This retrospective observational study was performed at the University of Occupational and Environmental Health, Japan from January 2016 to December 2017 using data previously collected from January 2011 to December 2015 [8]. This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (No. H26-226). Written informed consent was waived because of the retrospective design of the study and an absence of personal information. Pneumococcal

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pneumonia was suspected when it was cultured in sputum, intratracheal samples and bronchoalveolar lavage fluid, and the diagnosis of pneumococcal pneumonia was made when all of the following factors were fulfilled; at least one relevant respiratory symptoms, the presence of new infiltration on chest radiograph, and elevated white blood cell count ($\geq$10,000/μL), as used in our previous reports [8]. In addition, *S. pneumoniae* strain was cultivated by horse blood agar, and the identification of its serotyping was performed with Quellung reaction using antisera from Statens Serum Institute (SSI; Copenhagen, Denmark) [8].

We analyzed a total of 229 patients with pneumococcal pneumonia including 24 and 34 patients encountered in 2016 and 2017, in addition to the data of 171 patients treated between January 2011 and December 2015 [8]. The clinical characteristics of these 229 patients are summarized in Table 1. The 36 patients (15.7%) had been vaccinated with PPSV23 before the onset of pneumococcal pneumonia, and the ratio of patients with previous PPSV23 vaccination increased in 2016–2017 (25.0% in 2016 and 38.2% in 2017) compared with those in 2011–2015 (10.7% in 2011, 6.5% in 2012, 20.0% in 2013, 6.5% in 2014, and 8.3% in 2015). Conversely, the number (ratio) of patients complicated with invasive pneumococcal disease (IPD) decreased from 2011–2014 to 2015–2017, 2011–2014 were 11.1% (1/9) in 2011, 4.8% (1/21) in 2012, 16.7% (3/18) in 2013 and 9.1% (2/22) in 2014, respectively, and 2015–2017 were 0% in 2015 and 2016, and 3.7% (1/27) in 2017, respectively. The overall pneumonia mortality rate was 3.9%, and 3.6% (1/28) in 2011, 6.5% (2/31) in 2012, 3.3% (1/30) in 2013, 4.3% (2/46) in 2014, 0.0% (0/36) in 2015 and 2016 and 8.8% (3/34) in 2017.

Fig. 1 shows the annual changes in the distribution of *S. pneumoniae* serotypes. The proportion of PCV7-covered serotypes decreased annually from 46.4% in 2011 to 4.3% in 2014 and increased from 4.3% in 2014 to 20.6% in 2017. The proportion of PCV13-covered serotypes decreased annually from 71.4% in 2011 to 33.3% in 2015, but it did not change significantly between 2015 and 2017. Moreover, the proportion of PPSV23-covered serotypes decreased from 71.4% in 2011 to 50.0% in 2015, but it remained almost unchanged between 2015 and 2017. Further, the proportion

Table 1
Clinical characteristics of 229 patients with pneumococcal pneumonia.

	Total (n = 229)		2011 (n = 28)		2012 (n = 31)		2013 (n = 30)		2014 (n = 46)		2015 (n = 36)		2016 (n = 24)		2017 (n = 34)	
Age (yrs), mean ± SD	67.0 ± 13.6		64.6 ± 14.6		68.5 ± 14.4		66.8 ± 12.4		68.9 ± 15.1		68.7 ± 13.3		72.7 ± 14.1		68.1 ± 13.8	
Male; n (%)	140	(61.1)	18	(64.3)	21	(67.7)	19	(63.3)	27	(58.7)	18	(50.0)	15	(62.5)	22	(64.7)
Type of pneumonia; n (%)																
CAP	126	(55.0)	15	(53.6)	17	(54.8)	16	(53.3)	25	(54.3)	17	(47.2)	14	(58.3)	22	(64.7)
HCAP	48	(21.0)	2	(7.1)	10	(32.3)	3	(10.0)	12	(26.1)	7	(19.4)	4	(16.7)	10	(29.4)
HAP	55	(24.0)	11	(39.3)	4	(12.9)	11	(36.7)	9	(19.6)	12	(33.3)	6	(25.0)	2	(5.9)
Invasive pneumococcal disease; n (%)	8	(6.6)	1	(11.1)	1	(4.8)	3	(16.7)	2	(9.1)	0	(0.0)	0	(0.0)	1	(3.7)
Histories of use of PPSV23; n (%)																
Received	36	(15.7)	3	(10.7)	2	(6.5)	6	(20.0)	3	(6.5)	3	(8.3)	6	(25.0)	13	(38.2)
Not received	163	(71.2)	25	(89.3)	27	(87.1)	22	(73.3)	35	(76.1)	26	(72.2)	12	(50.0)	16	(47.1)
Unknown	30	(13.1)	0	(0.0)	2	(6.5)	2	(6.7)	8	(17.4)	7	(19.4)	6	(25.0)	5	(14.7)
Current smoking; n (%)	31	(13.5)	0	(0.0)	3	(9.7)	6	(20.0)	9	(19.6)	8	(22.2)	2	(8.3)	3	(8.8)
ECOG PS; n (%)																
3	33	(14.4)	8	(28.6)	6	(19.4)	1	(3.3)	8	(17.4)	6	(16.7)	2	(8.3)	2	(5.9)
4	27	(11.8)	3	(10.7)	2	(6.5)	5	(16.7)	5	(10.9)	6	(16.7)	3	(12.5)	3	(8.8)
Comorbidity; n (%)																
Malignancy	43	(18.8)	5	(17.9)	8	(25.8)	13	(43.3)	5	(10.9)	5	(13.9)	2	(8.3)	5	(14.7)
Cerebrovascular disease	51	(22.3)	12	(42.9)	7	(22.6)	7	(23.3)	10	(21.7)	5	(13.9)	4	(16.7)	6	(17.6)
Chronic cardiac disease	48	(21.0)	3	(10.7)	3	(9.7)	8	(26.7)	12	(26.1)	12	(33.3)	1	(4.2)	9	(26.5)
Chronic respiratory disease	58	(25.3)	15	(53.6)	16	(51.6)	15	(50.0)	1	(2.2)	5	(13.9)	3	(12.5)	3	(8.8)
Chronic liver disease	16	(7.0)	2	(7.1)	1	(3.2)	1	(3.3)	5	(10.9)	2	(5.6)	1	(4.2)	4	(11.8)
Chronic kidney disease	15	(6.6)	0	(0.0)	2	(6.5)	4	(13.3)	3	(6.5)	3	(8.3)	0	(0.0)	3	(8.8)
Diabetes mellitus	54	(23.6)	7	(25.0)	5	(16.1)	12	(40.0)	9	(19.6)	6	(16.7)	6	(25.0)	9	(26.5)
Collagen disease	22	(9.6)	2	(7.1)	5	(16.1)	1	(3.3)	3	(6.5)	4	(11.1)	3	(12.5)	4	(11.8)
Dementia	17	(7.4)	2	(7.1)	1	(3.2)	5	(16.7)	5	(10.9)	0	(0.0)	3	(12.5)	1	(2.9)
Glucocorticoids (PSL $\geq$ 5 mg/day)	29	(12.7)	6	(21.4)	8	(25.8)	3	(10.0)	4	(8.7)	5	(13.9)	2	(8.3)	1	(2.9)
Immunosuppressive agent	22	(9.6)	3	(10.7)	5	(16.1)	6	(20.0)	2	(4.3)	1	(2.8)	0	(0.0)	5	(14.7)
Clinical parameters; n (%)																
Orientation disturbance (confusion)	35	(15.3)	5	(17.9)	5	(16.1)	6	(20.0)	4	(8.7)	5	(13.9)	3	(12.5)	7	(20.6)
Body temperature <35 °C or >40 °C	4	(1.7)	0	(0.0)	0	(0.0)	2	(6.7)	0	(0.0)	1	(2.8)	0	(0.0)	1	(2.9)
Systolic BP < 90 mmHg	17	(7.4)	2	(7.1)	4	(12.9)	4	(13.3)	2	(4.3)	2	(5.6)	0	(0.0)	3	(8.8)
Pulse rate $\geq$ 125 beats/min	22	(9.6)	1	(3.6)	2	(6.5)	4	(13.3)	4	(8.7)	6	(16.7)	2	(8.3)	3	(8.8)
Respiratory failure	89	(38.9)	10	(35.7)	12	(38.7)	11	(36.7)	20	(43.5)	20	(55.6)	6	(25.0)	10	(29.4)
Laboratory findings																
BUN $\geq$ 10.7 mmol/L	34	(14.8)	2	(7.1)	6	(19.4)	7	(23.3)	6	(13.0)	6	(16.7)	3	(12.5)	4	(11.8)
Glucose $\geq$ 13.9 mmol/L	7	(3.1)	1	(3.6)	0	(0.0)	3	(10.0)	0	(0.0)	1	(2.8)	1	(4.2)	1	(2.9)
Hematocrit < 30%	26	(11.4)	2	(7.1)	2	(6.5)	1	(3.3)	9	(19.6)	5	(13.9)	3	(12.5)	4	(11.8)
Albumin, g/dl, mean ± SD	3.2 ± 0.60		3.06 ± 0.60		3.17 ± 0.49		3.11 ± 0.61		3.39 ± 0.53		3.05 ± 0.63		3.36 ± 0.54		3.22 ± 0.71	
PSI score; n (%)																
Mild (I–III)	100	(43.7)	14	(50.0)	14	(45.2)	10	(33.3)	19	(41.3)	12	(33.3)	16	(66.7)	15	(44.1)
Moderate (IV)	96	(41.9)	10	(35.7)	13	(41.9)	14	(46.7)	21	(45.7)	18	(50.0)	7	(29.2)	13	(38.2)
Severe(V)	33	(14.4)	4	(14.3)	4	(12.9)	6	(20.0)	6	(13.0)	6	(16.7)	1	(4.2)	6	(17.6)
The mortality by pneumonia	9	(3.9)	1	(3.6)	2	(6.5)	1	(3.3)	2	(4.3)	0	(0.0)	0	(0.0)	3	(8.8)

The blood culture was performed in 121 patients (9, 21, 18, 22, 13, 11, 27 patients for 2011, 2012, 2013, 2014, 2015, 2016, 2017, respectively).
Abbreviations: CAP, community acquired pneumonia; HCAP, healthcare associated pneumonia; HAP, hospital acquired pneumonia; PPSV23, 23-valent pneumococcal polysaccharide vaccine; ECOG-PS, eastern cooperative oncology group performance status; PSL, prednisolone; BP, blood pressure; BUN, blood urea nitrogen; PSI, pneumonia severity index.

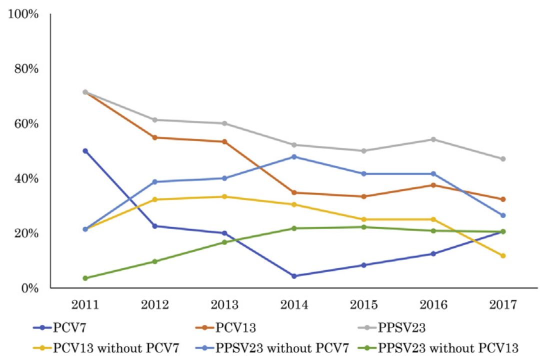

Fig. 1. Annual changes in the proportion of the vaccine and non-vaccine serotypes in patients with *Streptococcus pneumoniae*.

of PPSV23-covered without PCV13-covered serotypes remained almost unchanged between 2014 and 2017.

Next, the annual changes in the distribution of each serotype are shown in Fig. 2. The proportion of most PCV7-, PCV13-, and/or PPSV23-covered serotypes remained almost unchanged or decreased between 2011 and 2017. The proportion of the 19F serotype increased from 0.0% to 14.7% between 2014 and 2017, instead of the downward trend observed from 2011 to 2014. The 19F serotype was detected in 3 (8.3%) of 36 patients with pneumococcal pneumonia vaccinated with PPSV23 and 14 (8.6%) of 163 patients who were not vaccinated with PPSV23. In addition, the proportion of the 11A/E serotype increased from 2.2% in 2014 to 14.7% in 2017, and it was detected in 4 (11.1%) of 36 patients vaccinated with PPSV23 and 9 (5.5%) of 163 patients who were not vaccinated with PPSV23.

The proportion of non-PPSV23-covered serotypes (others) increased from 25.0% in 2011 to 44.4% in 2015, with proportions of 41.7% in 2016 and 47.1% in 2017 (Fig. 2). Among the 89 patients with *S. pneumoniae* caused by a non-PPSV23-covered serotype, the most frequently detected serotype was 35B (16.9%), followed by 6C (13.5%), 15A (13.5%), and 34 (12.4%).

We investigated the differences in terms of clinical background, laboratory findings, and prognosis between patients with pneumococcal pneumonia caused by PPSV23-covered serotypes (n = 93) and non-PPSV23-covered serotypes (n = 70). These cases were identified from the 163 patients who did not receive PPSV23 to avoid the influence of PPSV23 inoculation. Notably, we observed no

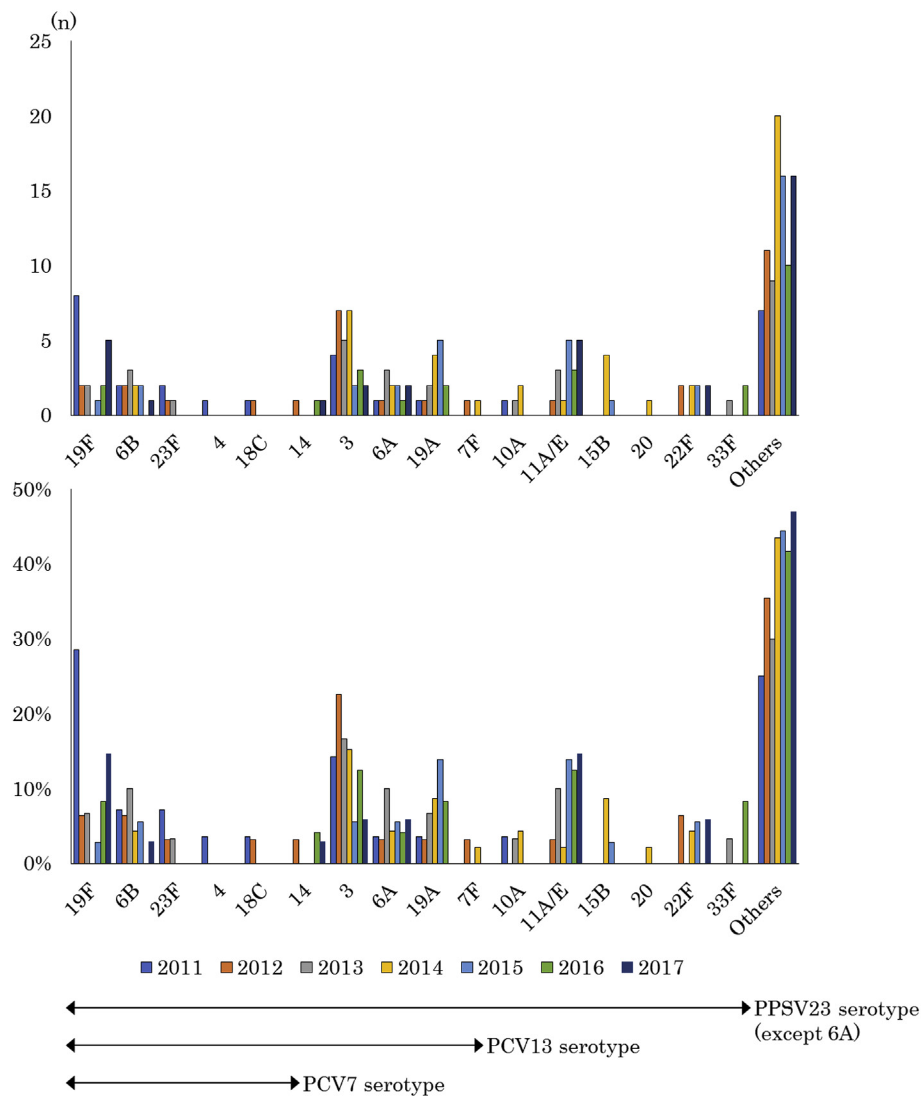

Fig. 2. Annual changes in the distribution of each *Streptococcus pneumoniae* serotype in patients with pneumococcal pneumonia.

significant differences in terms of clinical background, laboratory findings, and prognosis between patients with pneumococcal pneumonia with PPSV23 vaccination and those without PPSV23 vaccination (Supplemental Table A.1).

In our present study, we found no changes in the proportion of PPSV23-covered serotypes between 2014 and 2017 after the initiation of routine PPSV23 vaccinations in 2014. So far, there have been reports of increasing proportions of PPSV23 without PCV13-covered serotypes in adults with pneumococcal pneumonia [1,9], but no study has explained the relationship between the initiation of PPSV23 vaccinations for adults and annual changes in the proportion of the *S. pneumoniae* serotypes identified among those with pneumococcal pneumonia.

In contrast, the proportion of PCV7-covered serotypes gradually increased since 2014. The increase in the proportion of PCV7-covered serotypes and slowing downward trend of the proportions of PCV13- and PPSV23-covered serotypes between 2011 and 2017 might be explained by increases in the proportions of the 19F between 2015 and 2017 and 11A/E serotypes between 2014 and 2017. The 19F serotype is covered in PCV7, PCV13, and PPSV23 and the reasons for the increase of 19F serotype are unclear. Basically, PPSV23 vaccination increases the levels of the IgG antibody to the 19F serotype [10], on the other hand, it was also reported that the vaccine failure for the 19F serotype due to resistance to complement deposition and lower sensitivity to opsonophagocytic killing [11,12]. In addition, pneumococcal serotypes may be partially affected by regional outbreaks of a certain pneumococcal serotype such as a local outbreak of IPD patients with serotype 12F in Tsuruoka city, Japan [13]. On the other hand, regarding the increase of 11A/E, we found it difficult to evaluate the increases in the proportion of the 11A serotype (PPSV23-covered) because our serotyping method does not facilitate distinction between the 11A and 11E (non-PPSV23-covered) serotypes.

Our study has shown that these percentages of non-PPSV23-covered pneumococcal serotypes were approximately 30% in 2012 and 2013 [8] and 40% in 2014–2017 and that they showed no obvious changes between 2014 and 2017. Generally, pneumococcal pneumonia caused by the 3, 6A, 6B, 9N, 14 and 19F serotypes, including PCV13- and/or PPSV23-covered serotypes, are associated with increased risk of mortality and bacteremia [14]. Whereas, the 35B, 6C, and 15A serotypes were frequently detected in patients with pneumococcal pneumonia caused by non-PPSV23-covered serotypes in Japan [4], similar to our results, and, for example, it was reported that the 35B serotype comprised a non-invasive *S. pneumoniae* capsule [15]. Therefore, increases in the incidence of pneumococcal pneumonia caused by non-PPSV23-covered serotypes may help reduce the number of critically ill patients with pneumococcal pneumonia, but the differences between pneumococcal pneumonia caused by PPSV23-covered and non-PPSV23-covered serotypes remain poorly understood. Similar to Suzuki et al. [7], we found no obvious differences between patients with pneumococcal pneumonia caused by PPSV23-covered and non-PPSV23-covered serotypes.

There are several limitations to this study. First, this was a retrospective study conducted at a single institution; therefore, the number of cases in each year was relatively small. Second, we could not determine the history related to PPSV23 vaccination in approximately 10% of patients and could not evaluate the influence of PCV13 vaccination because there were no participants with previous history of PCV13 vaccination, although PCV13 vaccinations for adults were initiated in 2014 in Japan.

In conclusion, we found that there were no obvious changes in the proportion of PPSV23 after the initiation of routine PPSV23 vaccinations in adults, and the proportion of specific serotypes such as 19F and 11A/E increased between 2014 and 2017.

Authors' contributions

SN (designed experiments, analyzed the data, wrote the first draft), KY (designed experiments, wrote the first draft), KA (designed experiments, analyzed the data), BC (analyzed the data, intellectual contributions), HI (analyzed the data), RH (analyzed the data), KY (intellectual contributions), TK (intellectual contributions), HM (conceived and designed experiments, intellectual contributions).

Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.07.007.

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