

Original Article

Serotype Replacement in Adult Pneumococcal Pneumonia after the Introduction of Seven-Valent Pneumococcal Conjugate Vaccines for Children in Japan: a Systematic Literature Review and Pooled Data Analysis

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SUMMARY: *Streptococcus pneumoniae* is the major causative agent for adult pneumonia. Following the introduction of pneumococcal conjugate vaccines (PCV) for children, serotype replacement has been reported in adult invasive pneumococcal diseases but has not been well studied for cases of pneumococcal pneumonia in adults in Asia. To investigate serotype replacement in adult pneumococcal pneumonia in Japan, we conducted a systematic review of the literature across 5 databases using terms, including pneumococcus, serotype, their synonyms, and derivatives. After the assessment of the identified articles, data on the pneumococcal serotype distribution among adult pneumonia cases were extracted from relevant studies. Twenty-two studies were reviewed, and 4 relevant articles were included in the pooled data analysis. The proportion of the 7-valent PCV (PCV7)-covered serotypes from before and after the introduction of PCV7 for children (-18.1% , $p < 0.001$) significantly decreased; moreover, the proportions of serotypes covered by PCV13 but not PCV7 ($+9.9\%$, $p = 0.003$) and those covered by the 23-valent polysaccharide vaccine but not PCV7 ($+9.4\%$, $p = 0.007$) significantly increased. Serotype replacement occurred in adult cases of pneumococcal pneumonia following vaccination of children with PCV7 in Japan. Further nationwide surveillance is warranted to investigate serotype replacement in the post-PCV13 phase.

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is one of the most common causative agents for adult pneumonia (1–4). Recent studies from Europe reported that approximately 30% of pneumonia cases resulted from a pneumococcal infection (2,4). Our previously published multicenter prospective study showed that pneumococcus was detected in 26.2% of all community-onset pneumonia cases, and the estimated incidence of adult pneumococcal pneumonia in Japan was 473 cases per 100,000 person-years (PYs) (1). However, in our study population, the proportion of cases of bacteremic pneumococcal pneumonia was less than 5% of the pneumococcal pneumonia cases, which was much lower than the 24.8% estimated by a meta-analysis based on multi-country studies (3), and the estimated incidence was only 12 cases per 100,000 PYs (1).

Currently available pneumococcal vaccines are effective against specific serotypes; thus, it is essential to monitor the latest serotype distribution when establishing vaccine policies. Pneumococci are categorized into more than 95 serotypes, of which 23-valent pneumococcal polysaccharide vaccine (PPV23) are used for

23 serotypes, and poly-valent pneumococcal conjugate vaccines PCV7, PCV10, and PCV13 are used for 7, 10, or 13 serotypes, respectively. Numerous studies have reported that the serotype distribution among adult invasive pneumococcal disease (IPD) cases is influenced by the introduction of PCV vaccination in children (5–7), which is called “serotype replacement.” However, few studies have shown serotype replacement in cases of adult pneumococcal pneumonia, all of which were from Europe (8–10). Because serotype distribution differs between pneumonia cases and IPD cases (8,10), it is crucial to clarify the impact of PCV introduction in children on the serotype distribution in adult pneumonia, which has a far greater disease burden than does IPD. Furthermore, there is a geographic difference in the serotype distribution of adult pneumococcal pneumonia, even among European countries including the United Kingdom, Spain, and Portugal (8–10). Serotype replacement in adult pneumococcal pneumonia has not been well studied in Asia, including in Japan.

In Japan, PCV7 became commercially available in February 2010 and was widely employed through a subsidiary from the local government, which increased the estimated vaccination rate among infants to approximately 50% in 2011 and to over 80% in 2012 (11). PCV7 was then incorporated into the routine immunization schedule for children in April 2013, and it was replaced by PCV13 in November 2013. However, the estimated proportion of PPV23-vaccinated elderly was as low as 25% by 2013 (12). Thereafter, the Japanese Ministry of Health, Labour and Welfare initiated a routine vaccination program using PPV23 for adults aged ≥ 65 years in October 2014. Despite recent changes in

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circumstances regarding pneumococcal vaccination, the serotype distribution and its changes in adult pneumococcal pneumonia are still poorly understood in Japan.

Hence, the present systematic review of the literature and meta-analysis aimed to investigate the serotype replacement in adult pneumococcal pneumonia following the PCV vaccination of children in Japan.

METHODS

We referred to a checklist from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13). The eligibility criteria were determined before surveying the literature to allow the systematic search to be comprehensive. We included all studies describing the serotype/serogroup distribution of pneumococcus that affected adult patients in Japan for study selection and quality assessment regardless of clinical manifestation and methods for serotyping. We included reviews, interventional studies, cohort studies, case-control studies, cross-sectional studies, and case series that presented original data; however, news, letters, conference reports, or any other studies without a description of materials, methods, and serotype/serogroup distribution were excluded from the meta-analysis.

Based on the eligibility criteria, we conducted a systematic review of the literature across 5 databases: MEDLINE®, Academic Search Premier®, Scopus®, ICHUUSHI®, and CiNii® (the first 2 originated from EBSCOhost® [EBSCO industries, Inc., Birmingham, AL, USA], and the last 2 are Japanese major databases for medicine and science). We used English search terms in MEDLINE®, Academic Search Premier® and Scopus®, and we employed both Japanese and English search terms in ICHUUSHI® and CiNii® to identify as many relevant articles as possible (Fig. 1). Our search was limited to studies published in English or Japanese and those about non-pediatric subjects in Japan. We searched the database for articles published any time prior to March 24, 2016.

After the literature search was conducted, the search results were transferred to EndNote™ version X7.5 (Thomson Reuters, New York, NY, USA). We scanned the titles and abstracts of the search results to exclude articles that were incompatible with the eligibility criteria. When it was difficult to judge eligibility by title and abstract, we skimmed the full text to determine eligibility. We also scanned the references of the included articles to identify studies that were compatible with the eligibility criteria but not identified in the systematic search. The literature search and selection were performed individually by SK and MS, and any discordance was confirmed by KM and KA. To assess the quality of the studies included, we referred to the guidelines for reporting observational studies as developed by the Strengthening the Reporting of Observational Studies in Epidemiology Initiative (14). Based on the assessment and our study objectives, we categorized the studies into 3 grade of relevance: “relevant” that indicates well-described multicenter prospective studies of community acquired pneumonia (CAP) reporting serotype distribution of all pneumococcal pneumonia cases in the study, “largely relevant” that indicates multicenter prospective studies of pneumonia or lower respiratory tract infec-

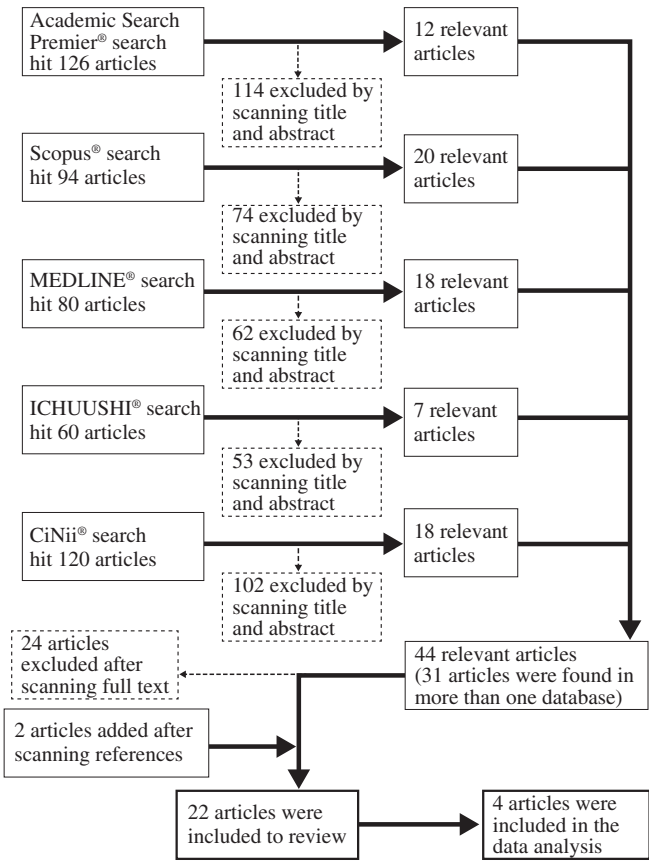


Fig. 1. Flow chart for the systematic literature search.

tion (LRTI) reporting serotype distribution of more than 70% of pneumococcal pneumonia cases in the study, and “partially relevant” that indicates studies reporting pneumococcal serotypes without sufficient information about the association between the pneumococcal strains and pneumonia cases. Studies based on retrospectively collected cases at a single tertiary hospital were also classified as “partially relevant” because of the biased patient population.

After the study appraisal, we conducted a narrative synthesis of the studies included. In addition, using the all published data in the “relevant” and “largely relevant” studies, we pooled data on the pneumococcal serotype distribution of adult pneumonia or LRTI. We also divided the pooled data into periods before and after 2010, which is the year of when PCV7 became commercially available for vaccinating children in Japan. In this analysis, the proportions of serotype 6A and 6C were combined, because serotype 6C was not differentiated from 6A in some of the studies that were conducted before 2008. To compare the proportions, we used Fisher’s exact test and a 2-sample test of proportions (z-test) for calculating the 95% confidence interval (CI) of the difference in proportions by using Stata®/IC 13.1 (StataCorp LP, College station, TX, USA). To assess the impact of different diagnostic criteria on our pooled estimates, a sensitivity analysis was conducted. We considered a *p*-value of < 0.05 statistically significant. Micro soft Excel® 2013 was used to create all of the datasets and graphics.

RESULTS

The results of the systematic search are summarized in Fig. 1. We identified a total of 480 articles during the primary search of the 5 databases, and we excluded 405 by scanning the titles and abstracts. We collected 44 articles from the 5 databases, of which 31 articles were found in more than one database. After scanning the references of the articles collected, we identified 2 more articles to include. We read a total of 46 articles thoroughly and excluded 24 irrelevant articles. Finally, we reviewed 22 articles, of which 4 were included in the data analysis.

We summarized the variety of the 22 studies in Table 1. All of the studies were performed in the pre-PCV13 period. The study designs could be categorized into case series of pneumococcal LRTI (15,16), prospective surveillance of pneumococcal LRTI or IPD cases

(1, 17–20), and laboratory-based pneumococcal strain surveillance (21–35). One of the prospective surveillance studies of the LRTI referred to the Japanese Respiratory Society (JRS) guidelines for the management of community-acquired pneumonia in adults (36) as diagnostic criteria for LRTI (17). Another 3 prospective surveillance studies of pneumonia also used similar case definitions to the JRS guidelines (1,18,19). All the laboratory-based pneumococcal strain surveillance studies were designed to test the collected pneumococcal strains from various specimens such as sputum, respiratory tract aspirates, nasopharyngeal swabs, eye or ear discharge, blood, cerebrospinal fluid, and pleural fluid. In these laboratory-based strain surveillances, we could not identify which serotypes were isolated from cases of adult pneumonia or LRTI, and the pathogenicity of the isolated pneumococcus was unclear because of the lack of case definitions. The serotyping methods were the

Table 1. Summary of the 22 studies in the review

Study period ¹⁾	–1988	1989–2009	2010–2013	2014–
	1	15	7	0
Study design	Laboratory-based pneumococcal strain surveillance		Case series of pneumococcal LRTI	
Single hospital-based	3		2	
	Laboratory-based pneumococcal strain surveillance		Prospective surveillance of pneumococcal CAP or LRTI cases	
Multicenter	4		4	
Nationwide	8		1	
Limited region				
Serotyping method	Quellung reaction	Glass slide agglutination	Multiplex PCR	Not described
	16 ²⁾	6 ²⁾	2 ²⁾	1
	< 100	100–199	200–299	300 <
Number of serotyped strains	8	5	3	6 ³⁾

¹⁾ One article reported 2 study periods, 2006 and 2012.

²⁾ In addition to the Quellung reaction, multiplex PCR was used in one study and glass slide agglutination was used in 2 studies.

³⁾ Two studies tested 300–399 strains. Each of the remaining studies tested 590, 715, 1,199, and 1,061 strains, respectively. LRTI, lower respiratory tract infection; CAP, community acquired pneumonia.

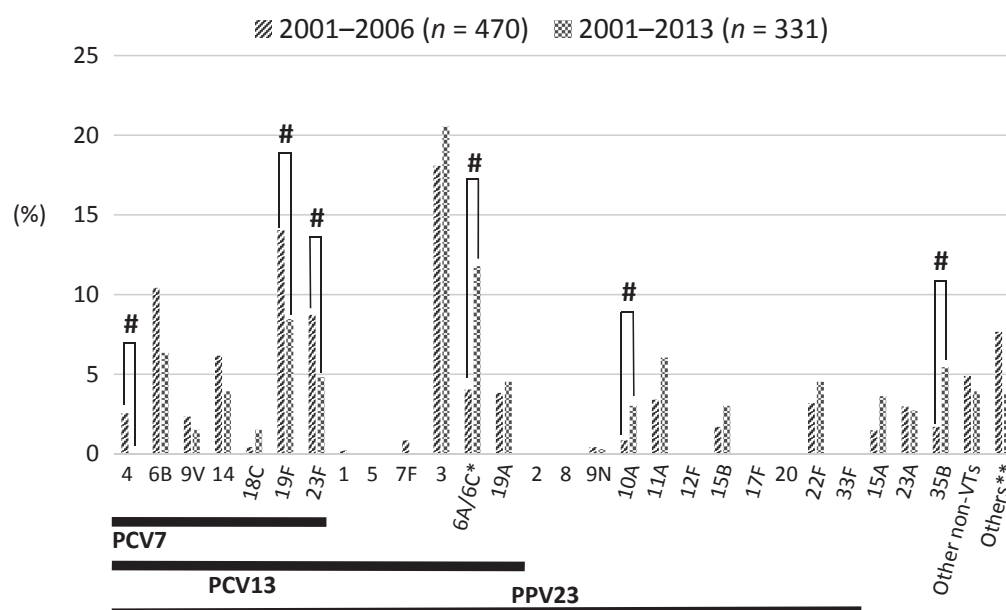


Fig. 2. Pooled serotype distribution of vaccine-covered serotypes and non-vaccine types among pneumococcal pneumonia. *, Serotype 6A is not included in PPV23, 6C was not differentiated from 6A. **, Others include the strains reported as non-typeable and indeterminable serogroups whether they were VT or non-VT. #, $P < 0.05$ by Fisher's exact test. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; and VT, vaccine type.

conventional Quellung reaction in 16 studies, glass slide agglutination in 6 studies, multiplex polymerase chain reaction (PCR) in 2 studies. The sample sizes varied considerably among the 22 studies.

For pooled analysis, we identified 2 “relevant” studies (18,19) and 2 “largely relevant” studies (1,17). One of the “largely relevant” studies reported combined serotype distribution of pneumococcal isolates from CAP cases (62.0% in 2006 and 70.1% in 2012), nosocomial pneumonia cases (13.0% in 2006 and 8.2% in 2012), cases of acute exacerbation of chronic bronchitis (13.5% in 2006 and 10.4% in 2012), and other LRTI cases (11.5% in 2006 and 10.3% in 2012) (17). The study reported the serotype data for 431 LRTI cases including 100 non-pneumonia LRTI cases ($n = 50/200$ in 2006 and $n = 50/231$ in 2012), but the pneumonia-specific

data were unavailable. However, all the isolates were cultured from good quality sputum and samples of the trans-tracheal aspiration or bronchoscopy. We therefore included all their data in our pooled analysis. The other “largely relevant” study included 1,200 CAP cases and 572 healthcare-associated pneumonia cases. This study reported the pneumococcal serotype of 100 strains out of a total of 142 isolates of pneumococcus (1).

With respect to the serotype distribution during the pre-PCV7 period, of the total 470 strains, 114 were extracted from the study conducted by Qin between 2001 and 2003 (19); 156, Isozumi between 2003 and 2005 (18); 200, Shoji in 2006 (17). For the post-PCV7 period, of the 331 total strains, 100 were extracted from the study conducted by Morimoto between 2011 and 2013 (1); 231, Shoji in 2012 (17) (Fig. 2, Table 2). The most

Table 2. Pooled dataset of serotype distribution

Serotype		Qin (19)		Isozumi (18)		Shoji, 2006 (17)		Pooled by 2006		Shoji, 2012 (17)		Morimoto (1)		Pooled 2011-2013	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
PCV7	4			4	2.6	8	4.0	12	2.6						
	6B	14	12.3	11	7.1	24	12.0	49	10.4	17	7.4	4	4.0	21	6.3
	9V	5	4.4	5	3.2	1	0.5	11	2.3	2	0.9	3	3.0	5	1.5
	14	9	7.9	8	5.1	12	6.0	29	6.2	10	4.3	3	3.0	13	3.9
	18C	1	0.9			1	0.5	2	0.4	5	2.2			5	1.5
	19F	25	21.9	21	13.5	20	10.0	66	14.0	20	8.7	8	8.0	28	8.5
	23F	15	13.2	14	9.0	12	6.0	41	8.7	11	4.8	5	5.0	16	4.8
PCV13	1					1	0.5	1	0.2						
	5														
	7F	1	0.9			3	1.5	4	0.9						
	3	13	11.4	42	26.9	30	15.0	85	18.1	46	19.9	22	22.0	68	20.5
	6A ¹⁾	7	6.1	4	2.6	4	2.0	15	3.2	14	6.1	3	3.0	17	5.1
PCV23	19A	5	4.4	5	3.2	8	4.0	18	3.8	9	3.9	6	6.0	15	4.5
	2														
	8														
	9N			1	0.6	1	0.5	2	0.4	1	0.4			1	0.3
	10A					4	2.0	4	0.9	8	3.5	2	2.0	10	3.0
	11A	5	4.4	6	3.8	5	2.5	16	3.4	10	4.3	10	10.0	20	6.0
	12F														
	15B					8	4.0	8	1.7	9	3.9	1	1.0	10	3.0
	17F														
	20														
	22F	1	0.9	6	3.8	8	4.0	15	3.2	12	5.2	3	3.0	15	4.5
Non-VT	12F/20/33F														
	6C ¹⁾					4	2.0	4	0.9	13	5.6	9	9.0	22	6.6
	7 ³⁾			1	0.6			1	0.2						
	9A	1	0.9			3	1.5	4	0.9	1	0.4			1	0.3
	9 ³⁾					1	0.5	1	0.2						
	10 ³⁾			2	1.3			2	0.4						
	11F/B			1	0.6			1	0.2						
	13					1	0.5	1	0.2						
	15A	1	0.9			6	3.0	7	1.5	8	3.5	4	4.0	12	3.6
	15C	2	1.8			2	1.0	4	0.9	2	0.9	1	1.0	3	0.9
	15 ³⁾			2	1.3			2	0.4						
	18A	1	0.9					1	0.2						
	18 ³⁾			1	0.6			1	0.2						
	22A											1	1.0	1	0.3
	23A	1	0.9	8	5.1	5	2.5	14	3.0	6	2.6	3	3.0	9	2.7
	24A or 24B									1	0.4			1	0.3
	25A or 38					1	0.5	1	0.2	1	0.4			1	0.3
	29	1	0.9					1	0.2						
	29 or 35 ²⁾					1	0.5	1	0.2						
	31									1	0.4			1	0.3
	33 ³⁾									1	0.4			1	0.3
	35B					8	4.0	8	1.7	10	4.3	8	8.0	18	5.4
	38														
	6D/7C/16F/18B/24F/34/37	5	4.4			4	2.0	9	1.9	5	2.2			5	1.5
	NT	1	0.9	14	9.0	14	7.0	29	6.2	8	3.5	4	4.0	12	3.6
Total		114	100	156	100	200	100	470	100	231	100	100	100	331	100

¹⁾: Serotype 6A is not included in PPV-23, 6C was not differentiated from 6A in studies by Qin (19) and Isozumi (18).

²⁾: Only serogroup was identified.

³⁾: Unclear either VT or Non-VT.

PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23: 23-valent pneumococcal.

prevalent serotypes during the pre-PCV7 and post-PCV7 periods was serotype 3 (18.1 and 20.5%, respectively), followed by serotype 19F (14.0 and 8.5%, respectively), and serotype 6B (10.4 and 6.3%, respectively). Serotype 6C (6.6%) was differentiated from 6A (5.1%) only in the post-PCV7 period. Overall, 7.7% of the strains were non-typeable or not determined to be either vaccine type (VT) or non-VT, but their serogroups were identified during the pre-PCV7 period, and 3.9% were identified in the post-PCV7 period. The percentages of the 3 serotypes covered by PCV7 significantly decreased between the 2 study periods by -2.6% in serotype 4 ($p = 0.002$, 95% CI of the difference: -4.0 , -1.1%), -5.5% in serotype 19F ($p = 0.019$, 95% CI of the difference: -9.9 , -1.2%), and -3.9% in serotype 23F ($p = 0.037$, 95% CI of the difference: -7.3 , -0.4%). Conversely, the percentages of 3 non-PCV7-covered serotypes significantly increased by $+7.8\%$ in serotype 6A/6C ($p < 0.001$, 95% CI of the difference: 3.8 , 11.6%), $+3.7\%$ in serotype 35B ($p = 0.004$, 95% CI of the difference: 1.0 , 6.4%), and $+2.1\%$ in serotype 10A ($p = 0.027$, 95% CI of the difference: 0.1 , 4.2%).

There was a significant decrease in the total proportion of PCV7-covered serotypes from 44.7 to 26.6% (difference: -18.1% , 95% CI: -24.6 , -11.5% ; $p < 0.001$) (Fig. 3). By contrast, the proportion of PCV13-covered but not PCV7-covered serotypes (PCV13-PCV7), PPV23-covered but not PCV7-covered serotypes (PPV23-PCV7), and PPV23-covered but not PCV13-covered serotypes (PPV23-PCV13) significantly increased from 27.0 to 36.9% (difference: $+9.9\%$, 95% CI: 3.3 , 16.4% ; $p = 0.003$), from 32.6 to 42.0% (difference: $+9.4\%$, 95% CI: 2.6 , 16.2% ; $p = 0.007$), and from 9.6 to 16.9% (difference: $+7.3\%$, 95% CI: 2.5 , 12.2% ; $p = 0.002$), respectively. There was a trend in which the pro-

portion of non-VTs increased from 11.1 to 15.7% (difference: $+4.6$, 95% CI: -0.2 , 9.5% ; $p = 0.056$). To assess the potential impact of non-pneumonia LRTI cases included in the study by Shoji et al. (17), we conducted a sensitivity analysis by excluding their data. The changes among the proportions of PCV7-covered serotypes (48.9% vs 23.0%, $p < 0.001$), PCV13-PCV7 (28.5% vs 40.0%, $p = 0.044$), PPV23-PCV7 (31.5% vs 44.0%, $p = 0.027$), PPV23-PCV13 (7.0% vs 16.0%, $p = 0.015$), and non-VTs (7.8% vs 17.0%, $p = 0.012$) were highly similar to those observed in the primary analysis.

DISCUSSION

This study is the first meta-analysis based on a systematic review of the literature on serotype distribution and its changes in adult pneumococcal pneumonia in Japan. Using 5 major databases, we comprehensively conducted systematic literature survey to identify studies that reported on the serotype distribution of adult pneumococcal pneumonia. In our pooled data analysis of the 4 studies (1, 17–19), the proportion of PCV7-covered serotypes decreased significantly and the proportions of serotypes of PCV13-PCV7, PPV23-PCV7, PPV23-PCV13, and non-VTs increased significantly. In summary, the decrease of the proportion of PCV7-covered serotype led to the increase of the proportion of non-PCV7-covered strains. Serotype replacement among adult pneumococcal pneumonia after the vaccination of children with PCV7 was evident in the Japanese population.

However, the study periods for the 4 studies do not encompass the period after PCV13 replaced PCV7 for routine child vaccination in Japan in November 2013. One study in the United Kingdom reported the decline

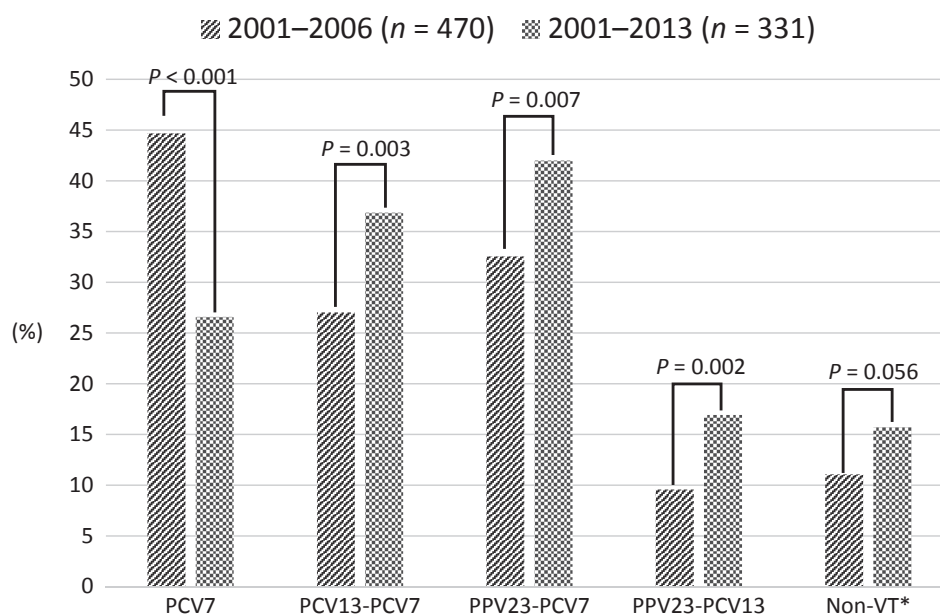


Fig. 3. Proportions of vaccine-covered serotypes among pneumococcal pneumonia before and after the introduction of PCV7. PCV13-PCV7 indicates serotypes covered by PCV13 but not PCV7. PPV23-PCV7 indicates serotypes covered by PCV23 but not PCV7. PPV23-PCV13 indicates serotypes covered by PCV23 but not PCV13. *, Non-VT does not include the strains reported as non-typeable and indeterminable serogroups whether they were the vaccine type or non-vaccine type. All P -values were calculated by Fisher's exact test. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; and VT, vaccine type.

of adult CAP incidence caused by serotypes of PCV13-PCV7 following infant PCV13 vaccination (8). Therefore, it is a reasonable assumption that the serotype distribution of adult pneumococcal pneumonia in Japan will change during the post-PCV13 period (9,10). Sustaining a nationwide surveillance system and periodic reporting is therefore crucial for investigating the effect of routine PCV13 vaccinations for children on pneumococcal serotype distribution in Japan.

In our systematic review, we identified a prospective surveillance study of IPD cases, including those of bacteremic pneumococcal pneumonia from April 2010 to March 2013, as reported by Ubukata (20). In comparison with bacteremic pneumococcal pneumonia, the total proportion of PCV7-covered serotypes was significantly lower and the total proportion of non-VTs was significantly higher in pneumococcal pneumonia cases from September 2011 to January 2013 (1,17) ($P = 0.001$ by Fisher's exact test). Considering the low prevalence of bacteremia among pneumococcal pneumonia cases in Japan ($< 5\%$) (1), this difference may be attributable to the difference in the patient population between bacteremic and non-bacteremic pneumococcal pneumonia cases and the difference in the pathogenicity of each serotype. In future studies, the concurrent surveillance of serotype distribution among bacteremic and non-bacteremic pneumococcal pneumonia cases may be used to elucidate the difference.

The adult pneumococcal vaccination strategy has not been decided on the basis of an international consensus. The Advisory Committee on Immunization Practices in the United States recommends combination strategies using PCV13 and PPV23 for adults aged 65 or older (37), whereas the Japanese Ministry of Health, Labour and Welfare recommends using only PPV23 as a routine vaccination for the elderly. According to recent meta-analyses, the effectiveness of PPV23 against IPD was 50–54% (38), but there is still controversy about its preventive effects against pneumococcal pneumonia (39). In our study, there was a significant increase in the total proportion of serotypes of PPV23-PCV13, which may have the same trend even after the replacement of PCV7 by PCV13 for children. Therefore, routine vaccination by PPV23 is probably important to prevent adult pneumococcal pneumonia caused by serotypes of PPV23-PCV13. However, the total proportion of PCV13-covered serotypes, including 6A/6C, was as high as 63.4% in the post-PCV7 period in our study, which leads to a concern that PCV13-covered strains may possess a large proportion of the serotypes among adult pneumococcal pneumonia even after the replacement of PCV7 by PCV13 for children. Recently, it was reported by the CAPITA trial that PCV13 vaccination for adults older than 65 years decreased the incidence of pneumonia caused by PCV13-covered serotypes by 45% (40). Owing to lack of evidence on studies on serotype-specific vaccine effectiveness of PPV23 for adult pneumococcal pneumonia, PCV13 vaccination adding to the routine PPV23 is possibly an effective option. However, we cannot yet make a conclusion about the best pneumococcal vaccination strategy, and we must observe the serotype distribution and disease burden of pneumococcal infections for several more years.

This study has the following limitations. First, de-

spite the pooled data analysis, the analyzed sample size was small. The number of studies that were relevant to our objective was limited. Second, there was some heterogeneity between each study in the pooled analysis regarding the diagnostic criteria, differentiation of 6A/6C, and target disease (i.e., including CAP, health care-associated pneumonia, or all LRTI). Particularly, 100 non-pneumonia LRTI cases included in the study by Shoji et al. (17) might have influenced our results. We therefore conducted a sensitivity analysis excluding the study by Shoji et al. and found that the pooled estimates were almost identical to the primary analysis. All their isolates were cultured from samples collected from the lower respiratory tract. The impact of inclusion of non-pneumonia LRTI cases on our findings must have been at minimum. Although we collected data from studies that reported reasonable diagnostic criteria and methods for serotyping, there is a possibility of information bias because of the limited diagnostic sensitivity of the culture. Because all of the studies reported serotype distributions based on cultured isolates, there must have been undiagnosed pneumococcal infection cases in each study. To overcome these matters, standardized diagnostic criteria and a combination of diagnostic tests, such as culturing, serotype-specific urinary antigen detection, and PCR for secretions from the lower respiratory tract may be useful in future surveillance. Nevertheless, we comprehensively surveyed published articles and assembled the frequencies of a wide range of serotypes, which can provide additional insight.

In conclusion, serotype replacement has occurred for adult pneumococcal pneumonia in Japan after child vaccination with PCV7. Further observations based on nationwide surveillance are crucial for investigating serotype replacement in the post-PCV13 phase.

Conflict of interest The Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University received financial support for a prospective pneumonia surveillance study from Pfizer. We do not have any other competing interest to disclose.

REFERENCES

- Morimoto K, Suzuki M, Ishifuji T, et al. The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. *PLoS One*. 2015;10:e0122247.
- Pletz MW, Von Baum H, Van Der Linden M, et al. The burden of pneumococcal pneumonia - Experience of the German competence network CAPNETZ. *Pneumologie*. 2012;66:470-5.
- Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One*. 2013;8:e0060273.
- Holter JC, Muller F, Bjorang O, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis*. 2015;15:64.
- Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010;201:32-41.
- Miller E, Andrews NJ, Waight PA, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis*. 2011;11:760-8.
- Lee S, Bae S, Lee KJ, et al. Changes in serotype prevalence and antimicrobial resistance among invasive *Streptococcus pneumoniae* isolates in Korea, 1996–2008. *J Med Microbiol*. 2013;62(Pt 8):1204-10.
- Rodrigo C, Bewick T, Sheppard C, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia.

- Eur Respir J. 2015;45:1632-41.
9. Payaras A, Villoslada A, Garau M, et al. Evolution of pneumococcal infections in adult patients during a four-year period after vaccination of a pediatric population with 13-valent pneumococcal conjugate vaccine. *Int J Infect Dis*. 2015;33:22-7.
10. Horacio AN, Lopes JP, Ramirez M, et al. Non-invasive pneumococcal pneumonia in Portugal--serotype distribution and antimicrobial resistance. *PLoS One*. 2014;9:e103092.
11. Chiba N, Morozumi M, Shouji M, et al. Changes in capsule and drug resistance of pneumococci after introduction of PCV7, Japan, 2010–2013. *Emerg Infect Dis*. 2014;20:1132-9.
12. Naito T, Matsuda N, Tanei M, et al. Relationship between public subsidies and vaccination rates with the 23-valent pneumococcal vaccine in elderly persons, including the influence of the free vaccination campaign after the Great East Japan Earthquake. *J Infect Chemother*. 2014;20:450-3.
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336-41.
14. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-9.
15. Watanabe H, Sato S, Kawakami K, et al. A comparative clinical study of pneumonia by penicillin-resistant and -sensitive *Streptococcus pneumoniae* in a community hospital. *Respirology*. 2000;5:59-64.
16. Akata K, Chang B, Yatera K, et al. Distribution and annual changes in *Streptococcus pneumoniae* serotypes in adult Japanese patients with pneumonia. *J Infect Chemother*. 2015;21:723-8.
17. Shoji H, Maeda M, Shirakura T, et al. Changes in the distribution of capsular serotypes of *Streptococcus pneumoniae* isolated from adult respiratory specimens in Japan. *Intern Med*. 2015;54:1337-41.
18. Isozumi R, Ito Y, Ishida T, et al. Genotypes and related factors reflecting macrolide resistance in pneumococcal pneumonia infections in Japan. *J Clin Microbiol*. 2007;45:1440-6.
19. Qin L, Watanabe H, Yoshimine H, et al. Antimicrobial susceptibility and serotype distribution of *Streptococcus pneumoniae* isolated from patients with community-acquired pneumonia and molecular analysis of multidrug-resistant serotype 19F and 23F strains in Japan. *Epidemiol Infect*. 2006;134:1188-94.
20. Ubukata K, Chiba N, Hanada S, et al. Serotype changes and drug resistance in invasive pneumococcal diseases in adults after vaccinations in children, Japan, 2010–2013. *Emerg Infect Dis*. 2015;21:1956-65.
21. Kawaguchiya M, Urushibara N, Ghosh S, et al. Serotype distribution and susceptibility to penicillin and erythromycin among noninvasive or colonization isolates of *Streptococcus pneumoniae* in northern Japan: a cross-sectional study in the pre-PCV7 routine immunization period. *Microb Drug Resist*. 2014;20:456-65.
22. Furuya Y, Fukuda Y, Nomura N, et al. Sensitivity surveillance of *Streptococcus pneumoniae* isolates for several antibacterial agents in Gifu and Aichi prefecture (2008–2009). *Jpn J Antibiot*. 2012;65:1-14. Japanese.
23. Suzuki K, Nishimaki K, Okuyama K, et al. Trends in antimicrobial susceptibility of *Streptococcus pneumoniae* in the Tohoku district of Japan : a longitudinal analysis from 1998 to 2007. *Tohoku J Exp Med*. 2010;220:47-57.
24. Mitsuyama J, Yamaoka K, Asano Y, et al. Sensitivity surveillance of *Streptococcus pneumoniae* isolates for several antibiotics in Gifu prefecture (2004). *Jpn J Antibiot*. 2006;59:137-51. Japanese.
25. Shiojima T, Fujiki Y, Sagai H, et al. Prevalence of *Streptococcus pneumoniae* isolates bearing macrolide resistance genes in association with integrase genes of conjugative transposons in Japan. *Clin Microbiol Infect*. 2005;11:808-13.
26. Kasahara K, Maeda K, Mikasa K, et al. Clonal dissemination of macrolide-resistant and penicillin-susceptible serotype 3 and penicillin-resistant Taiwan 19F-14 and 23F-15 *Streptococcus pneumoniae* isolates in Japan: a pilot surveillance study. *J Clin Microbiol*. 2005;43:1640-5.
27. Akashi T, Kono M, Hoshina S, et al. Epidemiological study of *Streptococcus pneumoniae* isolated from small hospitals. *Tokyo Jikeikai Med J*. 2005;120:19-33. Japanese.
28. Ubukata K, Kobayashi R, Chiba N, et al. Surveillance based on molecular epidemiology for *Streptococcus pneumoniae* isolates between 1998 and 2000 in Japan. *Jpn J Chemother*. 2003;51:60-70. Japanese.
29. Ubukata K, Asahi Y, Okuzumi K, et al. Incidence of Penicillin-Resistant *Streptococcus pneumoniae* in Japan, 1993–1995. *J Infect Chemother*. 1996;1:177-84.
30. Oguri T. Epidemiological markers of common bacterial pathogens: serotype - *Streptococcus pneumoniae*. *Clin Med Microbiol*. 1996;23:685-91. Japanese.
31. Fukumi H, Kaneko Y, Agata T, et al. Studies on the clinical application of pneumococcal vaccine. Distribution of *Streptococcus pneumoniae* in Japan. *Kansenshogaku Zasshi*. 1984;58:39-53. Japanese.
32. Eto M, Mizunaga S, Fukuda Y, et al. Sensitivity surveillance of *Streptococcus pneumoniae* isolates for several antibacterial agents in Gifu and Aichi prefecture (2010–2011). *Jpn J Antibiot*. 2013;66:265-82. Japanese.
33. Funatsu T, Mizunaga S, Fukuda Y, et al. Sensitivity surveillance of *Streptococcus pneumoniae* isolates for several antibacterial agents in Gifu and Aichi prefectures (2011–2012). *Jpn J Antibiot*. 2015;68:225-42. Japanese.
34. Qin L, Masaki H, Watanabe K, et al. Antimicrobial susceptibility and genetic characteristics of *Streptococcus pneumoniae* isolates indicating possible nosocomial transmission routes in a community hospital in Japan. *J Clin Microbiol*. 2007;45:3701-6.
35. Rikitomi N, Sow PS, Watanabe K, et al. Rapid increase of pneumococcal resistance to β -lactam and other antibiotics in isolates from the respiratory tract (Nagasaki, Japan: 1975–1994). *Microbiol Immunol*. 1996;40:899-905.
36. The Japanese Respiratory Society. The committee for The Japanese Respiratory Society guidelines for management of respiratory infections. CHAPTER 4: Diagnosis of community-acquired pneumonia. *Respirology*. 2006;11:S83.
37. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822-5.
38. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: a systematic review and meta-analysis. *Vaccine*. 2016;34:1540-50.
39. Schiffner-Rohe J, Witt A, Hemmerling J, et al. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk – a systematic review and meta-analysis. *PLoS One*. 2016;11:e0146338.
40. Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Eng J Med*. 2015;372:1114-25.