

Changes in the Pneumococcal Vaccine Serotypes in Adult Noninvasive Pneumonia after the Introduction of Pneumococcal Conjugate Vaccination for Children

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Abstract

Context: Although the incidence of invasive pneumococcal infections in children has decreased since the introduction of pneumococcal conjugate vaccines (PCVs), the appearance of serotype replacements has continued to increase. **Aims:** We examined the frequency of serotype replacements in adult cases of pneumococcal pneumonia. Furthermore, the transition in the coverage of vaccine serotypes (VTs) to non-VTs (NVTs) was also examined. **Settings and Design:** We investigated all confirmed cases of pneumococcal pneumonia in 303 adult patients admitted to Yamagata Saisei Hospital between April 2006 and March 2015. **Materials and Methods:** Pneumococcal serotypes were determined by testing for a specific type of antiserum using the capsular swelling method. **Statistical Analysis Used:** Chi-square tests were used to compare patient characteristics. **Results:** Annually, the number of admitted patients ranged from 24 to 43, with most of them being men (64.7% of the total patient cohort). Although many cases involved some underlying conditions, the rate of pneumococcal vaccination remained low. The average rate of multigeneration housing was high (37.6%). The rates of pneumococcal vaccine coverage declined since 2013 (7-valent PCV (PCV7), 18.5%; PCV13, 59.3%; and 23-pneumococcal polysaccharide vaccine (PPSV23), 66.7%) and were <50% for each vaccine (PCV7, 4.7%; PCV13, 32.6%; and PPSV23, 48.8%) in 2015. In addition, the VTs were replaced with NVTs in 2015 (48.8% vs. 51.2%). **Conclusions:** The frequency of NVTs in adult pneumococcal pneumonia increased in 2013, with the frequency exceeding that of the vaccine forms in 2015. Regular PCV vaccination of children and multigeneration housing seem to be associated with this reversed trend.

Keywords: Adult, generation housing, pneumococcal pneumonia, replacement, serotype, vaccines

INTRODUCTION

Pneumococcus (*Streptococcus pneumoniae*) is the most frequently occurring bacteria that cause respiratory infections worldwide. The pathological condition associated with infection is either invasive or noninvasive, and approximately 25% of the causes of severe infections with bacteremia leading to poor prognosis are common bacteria.^[1] Furthermore, the frequency of severe infections is higher in elderly patients and the clinical burden of severe infections continues to increase in countries like Japan, which has a rapidly growing elderly population.^[2-4] Therefore, finding an efficient way to control this disease is an urgent challenge.

One way to control infection is through pneumococcal vaccination. Although the 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been used for adult

vaccination in Japan since 1988, its vaccination rates remained low (approximately 25%) in 2013.^[5] However, the introduction of a publicly funded vaccination program for the elderly residents in the areas affected by the Great East Japan Earthquake in 2011 and the implementation of regular vaccination of adults aged 65 years or older since October 2014 has improved the vaccination rates. In addition, a 13-valent pneumococcal conjugate vaccine (PCV13) was made available for adults aged 65 or older from June 2014. In 2010, a 7-valent

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PCV (PCV7) program was launched on a voluntary basis for child vaccination. Public subsidies were also introduced in November of the same year. In 2013, regular vaccinations of children under the age of five were started in April; moreover, PCV7 was replaced with PCV13 in November 2013.

This study was conducted to understand the changes in pneumococcal serotype in adult pneumococcal pneumonia after vaccination strategies were changed in children.

MATERIALS AND METHODS

Patients

This study included adult patients with noninvasive pneumococcal pneumonia admitted to Yamagata Saisei Hospital primarily due to the development of respiratory symptoms between April 2006 and March 2015. We retrospectively examined the transition of the pneumococcal serotypes isolated and identified based on sputum tests and the characteristics of patients without respiratory infections 1 month before hospitalization. The diagnosis was confirmed symptomatically through coughing and purulent sputum, fever, leukocytosis, and elevated C-reactive protein. Cases where chest X-ray scans confirmed the presence of new infiltrative shadows were regarded as confirmed cases of pneumonia.

The following data were collected from medical records: Age, sex, smoking rate, the presence or absence of underlying conditions, history of PPSV23 vaccination, family living conditions, and death resulting from pneumonia within 30 days.

The bacterial cause was confirmed in cases in which Gram-stained sputum specimens demonstrated a large number of leukocytes (groups 3–5 based on Geckler classification) indicating bacterial phagocytosis. For cases in which bacterial phagocytosis was absent, a finding of at least 2+ ($\geq 10^5$ colony-forming units/mL) of isolated pneumococcal bacteria and the absence of other pathogenic bacteria apart from the former in the sputum cultures were considered as positive confirmation.^[6] Pneumococcal urinary antigen tests were also performed for all cases to aid in the diagnosis of pneumococcal pneumonia. A positive result in the optochin susceptibility test using a pure culture and the presence of the autolytic enzyme gene (*lytA*) in the polymerase chain reaction test further confirmed the presence of the pneumococcus bacteria.^[7] All the isolated bacteria were stored at -80°C in a microbank until use.

Examination of annual transitions in the coverage rates of PCV7, PCV13, and PPSV23 and determination of pneumococcal serotypes

The pneumococcal serotypes were determined by testing for a specific type of antiserum (Statens Serum Institute, Copenhagen, Denmark) using the capsular swelling method. As this method does not distinguish between serotypes 11E and 11A, this serotype was then described as “11A/E.” The same method was used to determine the serotype coverage for each pneumococcal vaccine.^[8] Furthermore, to evaluate serotype

replacement, serotypes including the PCV13 and PPSV23 vaccines were classified as vaccine serotypes (VTs) and the remaining as non-VTs (NVTs). Next, the isolated pneumococci were evaluated based on the 14 pneumonia-related deaths.

Statistical analysis

Chi-square tests were used to compare patient characteristics, including sex, smoking status, presence of underlying diseases, types of vaccinations, and multigeneration family housing condition. $P < 0.05$ was considered statistically significant.

Ethics

This study was approved by the Ethics Review Committee of Yamagata Saisei Hospital. In addition, Since the study was conducted retrospectively, consent forms were not requested.

RESULTS

Patient characteristics

A total of 303 confirmed cases of pneumococcal pneumonia were included in the study [Table 1]. During the study period, a minimum of 24 cases occurred in 2011 and 2012 and a maximum of 43 cases in 2015. The median age of the patients was 70 and 67 years in 2010 and 2014, respectively. For the remaining years, the median age was approximately 75 years, with no variation. Male patients constituted a larger proportion of the total cohort each year, with an overall total of 196 (64.7%) individuals. The proportion of patients with underlying conditions varied from 84.8% in 2010 to 55.2% in 2014. The majority of these conditions comprised of respiratory infections (58 cases), followed by cerebrovascular disease (41 cases).

There were no cases with PPSV23 vaccination in 2008, and this percentage increased by only 2.8% in 2009, whereas the observed rates for most other years ranged between 10% and 20% and increased to 27.3% in 2015.

With regard to family living conditions, the proportion of patients living in multigeneration housing (i.e., involving cohabitation by at least three generations) was the lowest in 2006 at 19.4% and highest in 2011 at 50%, with an overall average of 37.3%.

As a prognostic process following the onset of pneumonia, we also identified cases of pneumonia-related deaths that occurred within a 30-day period. Of the 303 patients analyzed, 14 died (4.6%) due to pneumonia-related causes. This number was the highest in 2010 and 2015, involving three cases each, and lowest in 2014 when no such deaths occurred.

Distribution of pneumococcal capsular serotypes and vaccine coverage rates

Over the 10-year period, various pneumococcal strains were classified and tabulated based on their serotypes: Serotype 3 was frequently isolated in 56 strains (18.5%), 6B in 26 strains (8.6%), and 35B in 25 strains (8.3%). Other serotypes isolated in at least ten strains were 6A, 6C, 10A, 11A/E, 15C, 19A, 19F, 23A, and 23F [Figure 1].

Table 1: Background of patients with noninvasive pneumococcal pneumonia between April 2006 and March 2015

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	P
Patients (n)	31	26	30	36	33	24	24	27	29	43	303	
Median age (distribution)	75 (22-96)	73 (30-91)	73 (37-90)	73 (29-97)	70 (56-94)	75 (39-93)	74 (50-100)	76 (29-95)	67 (27-91)	76 (37-90)	74 (22-100)	0.999
Male/female	22/9	18/8	18/12	22/14	25/8	15/9	18/6	14/13	17/12	27/16	196/107	<0.001
Smoking rate (%)	6.5	7.7	13.3	13.9	15.2	25	16.7	11.1	17.2	16.3	14.9	0.613
Presence of an underlying condition (%)	58.1	57.7	53.3	77.8	84.8	75	66.7	66.7	55.2	67.4	66.7	0.130
PPSV23 inoculation (%)	9.7	15.4	0	2.8	18.2	8.3	16.7	11.1	17.2	27.3	12.2	0.083
Percentage of patients in multi-generation housing (3+ generations)	19.4	30.8	43.3	47.2	39.4	50.0	29.2	48.1	38.5	34.9	37.6	0.301
Number of pneumonia-related deaths within 30 days	1	2	1	1	3	1	1	1	0	3	14	

PPSV23: 23-valent pneumococcal polysaccharide vaccine

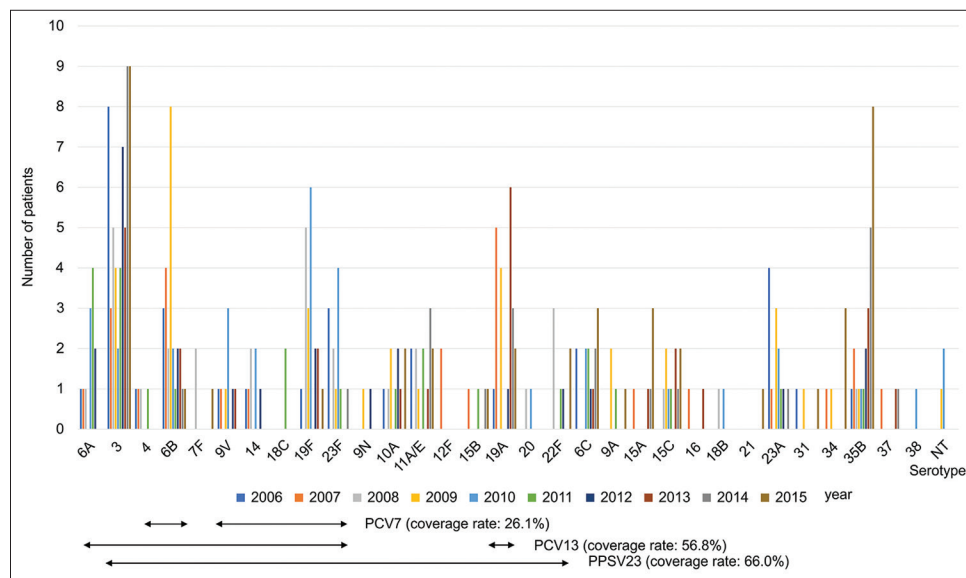


Figure 1: Serotype distribution and vaccine coverage rates for pneumococci derived from noninvasive pneumococcal pneumonia. Serotype 3 is most commonly isolated, followed by 6B and 35B. The coverage rates of 7-valent pneumococcal conjugate vaccines are low, while those of 23-valent pneumococcal polysaccharide vaccine are comparatively stable, with 13-valent pneumococcal conjugate vaccines falling between the two. The arrow shows a range of the serotypes included in each vaccine

Pneumococcal vaccine coverage rates and annual transitions

We calculated the coverage rate of PCV7, PCV13, and PPSV23 vaccines. Of the 303 cases, the coverage rate of the PCV7 serotype was 26.1% (79), while that of PCV13 and PPSV23 serotypes were 56.8% (172) and 66% (200), respectively [Figure 1]. The coverage rates of these vaccines were examined further. A marked decline was observed for PCV7 in 2011, and although it slightly recovered the following year, it declined again thereafter, reaching extremely low

coverage rates of 3% to 4% in 2014 and 2015. Furthermore, the coverage rate of PCV13 remained between 50% and 60%; however, it declined to below 50% in 2013 and further declined to 48.3% in 2014 and 32.6% in 2015. The coverage rates observed for PPSV23 were largely similar to those for PCV13, reaching 48.8% in 2015 [Figure 2].

The VT coverage, except for a high rate of 90% in 2008, remained at 70%, but it began to decline in 2013. In 2015, serotype substitution was prominently indicated when the coverage of VT was higher (51.2%) than that of NVT [Figure 3].

The 14 pneumonia-related deaths included two cases of serotypes 6B and 35B and one each of serotypes 6A, 6C, 9A, 9V, 15C, 19A, 19F, 23F, 37, and 38. Among these cases, six involved the VT serotypes and eight involved the NVT serotypes.

DISCUSSION

Studies reporting on pneumococcal serotype fluctuations among the Japanese population are relatively few and have been conducted over short periods.^[9,10] Long-term comparative studies must have desirable results to ascertain the longitudinal trends in serotype change, and an examination incorporating the health-care developments

within the study period is also necessary. Considering that the manufacturing method of PPSV23 was changed in 2006, we chose this year as the initial year of our study. Thus, this present study involved cases of pneumococcal pneumonia reported at our hospital over a 10-year period, including those that occurred before and after the PCV vaccines for children were introduced in Japan.

In the 303 pneumococcus isolates from sputum of patients with pneumococcal pneumonia, serotype 3 was most frequently isolated in 56 strains (18.5%), followed by 6B in 26 strains (8.6%) and 35B in 25 strains (8.3%). The coverage rates of serotypes PCV7, PCV13, and PPSV23 were 26.1%, 56.8%, and 66%, respectively. Although the PCV7 coverage was low, the PPSV coverage remained relatively consistent. However, the difference between these factors must be further examined.

In Japan, the voluntary vaccination of children with PCV7 was launched in February 2010, with public subsidies introduced in November of that year. Moreover, the regular vaccination of children under the age of five was introduced in April 2013, with a switch to PCV13 in November of that year. With the introduction of this medical policy, the PCV vaccination rate among children increased from 50% to 60% in 2011^[9] and to nearly all children in 2015.^[11]

In this study, the coverage of VT including PCV7 declined from 51.5% in 2010–16.7% in 2011. The introduction of public subsidies for childhood vaccination during this period was a major change in the medical policies associated with pneumococcal infection. Moreover, as the coverage further declined to 3.4% in 2014, the year after the regular vaccination for children was launched, the most pronounced outcomes included an increase in the childhood vaccination rate and changes in the regular PCV vaccination within an extremely short period.

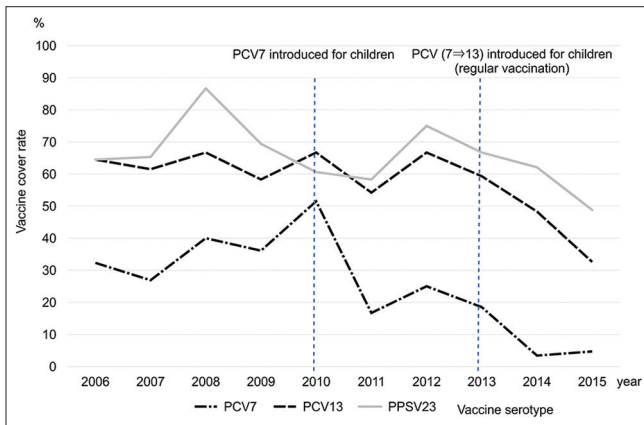


Figure 2: Annual transitions in the vaccine coverage rates. The coverage rates for 7-valent pneumococcal conjugate vaccines declined in 2011 and 2014. The coverage rates for 13-valent pneumococcal conjugate vaccines declined from 2014. The decline in coverage rates for 23-valent pneumococcal polysaccharide vaccine shows a similar trend to that for 13-valent pneumococcal conjugate vaccines, although it is more gradual than that for pneumococcal conjugate vaccines

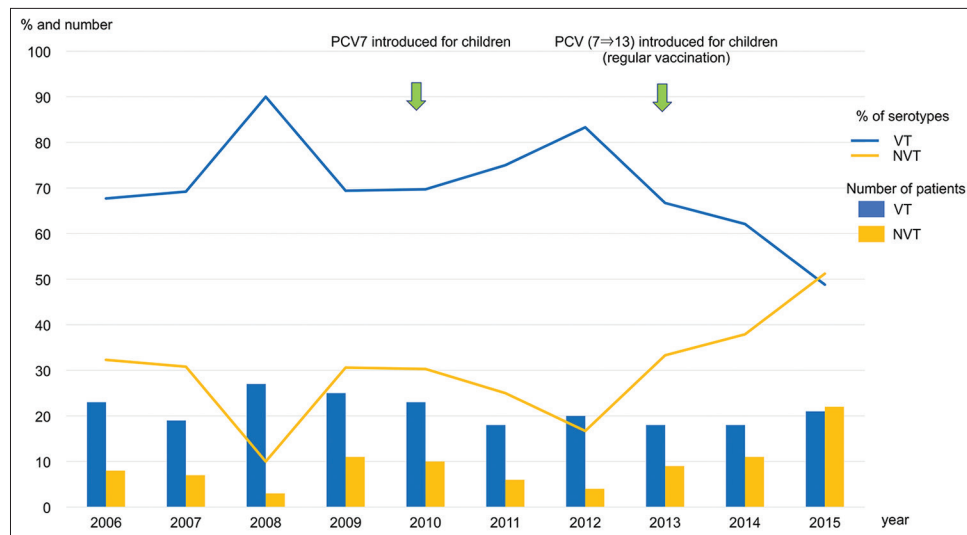


Figure 3: Annual transitions in the vaccine serotypes versus nonvaccine serotypes. The coverage rates for serotypes including 13-valent pneumococcal conjugate vaccines and 23-valent pneumococcal polysaccharide vaccine remain at 70% before declining slightly in 2013. This downward trend gets stronger until the coverage rates for the nonvaccine serotype surpass those for vaccine serotype

In addition, the PCV13 coverage decreased to below 50% from 2014, an extremely low rate as compared with that reported when PCV13 was first introduced.^[12] This decreasing trend of the coverage rates reflects the collective and protective effect of childhood vaccination.

Meanwhile, the decrease in PPSV coverage is clear when compared to that reported by Fukumi *et al.*^[13] (approximately 80%), a pioneering study in the Japanese context. Although this downward trend seems to have been influenced by PCV, it was not possible to determine the extent of the impact of PPSV vaccination in the present study owing to the low vaccination rates. Nevertheless, vaccination rates increased moderately after regular vaccinations for adults aged 65 and older were started in 2014. Hence, additional data must be collected to further clarify this point.

The most interesting point in our study was the reversal in the rates of coverage for VT and NVT. In this study, VT coverage remained between 70% and 80% from 2006 to 2012, with the exception of 2008. However, the introduction of regular PCV vaccination for children in 2013 signaled a noticeable decline in VT, with the relative proportion of NVT exceeding that of VT in 2015. We believe that this is the first study reporting the reversal of VT and NVT. The reversal of vaccine coverage might be a collective effect of the regular PCV vaccination in children that started in 2013, and the impact of PCV introduced for children on vaccine coverage has been confirmed by previous reports.^[14,15]

The onset of adult pneumococcal pneumonia has been related to contact with children with known pneumococcal infections.^[16] That is, pneumococcal bacteria are routinely transmitted from children to adults.^[17] Accordingly, the reversal phenomenon might be partially understandable if patients have had previous contact with an infected child. Therefore, we examined the family living situations of the patients as listed in their medical records. When assessment of the presence or absence of multigenerational cohabitation including children were included in the analysis, among other factors, in 90% of the cases the ages of other individuals living in the same household were unknown. However, a report from the Ministry of Internal Affairs and Communications Statistics Bureau revealed that the Yamagata Prefecture had the highest prevalence of multigeneration housing in Japan (a prefectural average of 17.8% compared to the national average of 5.7%)^[18] and cohabitation with young people was common. Therefore, we believe that the improvement in the rates of PCV vaccination in children could partially explain the reversal of VT and NVT coverage rates as reported in this study. The replacement of serotypes could also be due to an increase in adult vaccination rates. Therefore, continuous surveillance is important to ascertain the impacts of improved adult vaccination rates.

From a clinical point of view, it is important that the vaccine helps reduce the load of the associated diseases.

Our study involved a total of 14 deaths (4.6%). While some differences in pathogenicity were apparent among the serotypes,^[19] the predominance of any specific serotype cannot be ascertained. Among the 14 deaths, six involved VT, while eight involved NVT. In addition, since the history of PPSV vaccination was unknown for those who died, it was difficult to examine the effects of PPSV vaccination. While the effects of PPSV23 on invasive pneumococcal infections are well known, the effect of this vaccine against pneumonia is not clearly understood.^[20] However, PPSV vaccination was recently reported to be effective against pneumococcal pneumonia, which is a noteworthy result.^[21]

Our study had several limitations. It was a single-center retrospective study, and thus, we cannot conclude that our findings represent a broad-based phenomenon. However, considering that it was conducted in a medical system over a 10-year period, we believe that our findings demonstrate a real and steady trend.

Adult pneumococcal pneumonia is of increasing importance today given the rising number of cases in the elderly and patients with underlying diseases. While pneumococcal vaccination is certainly one measure to counter this, the question of how to use this more efficiently is a pressing concern among medical workers and patients worldwide. The same is true in clinical practice in Japan. We undertook this study because we felt it was extremely important to understand the vaccination status quo and to consider the problems apparent therein and from the data obtained.

CONCLUSIONS

The considerable replacement of serotypes as a result of the improvement in PCV vaccination rates among children has a significant impact on the cases of pneumonia in adults. It has also resulted in a reversal in the coverage rates of VT and NVT. Continued surveillance of the distribution of pneumococcal serotype is needed for better clinical outcomes.

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Conflicts of interest

There are no conflicts of interest.

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