Original Article

Difference between Japanese Secondary and Tertiary Medical Facilities Regarding Changes in the Hospitalization of Children for Pneumonia after the Introduction of the Pneumococcal Conjugate Vaccine

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SUMMARY: This study aimed to compare hospitalization of children for pneumonia between secondary and tertiary medical facilities, which hospitalize many children without and with underlying diseases, respectively, after the introduction of the pneumococcal conjugate vaccine (PCV). Our retrospective study included children admitted to the Department of Pediatrics at Kitakyushu General Hospital, a secondary medical facility, and the Hospital of the University of Occupational and Environment Health, Japan, a tertiary medical facility, from 2009 to 2013 for pneumonia. We compared the change in the rate of hospitalization for pneumonia after the introduction of the 7-valent PCV between the secondary and tertiary medical facilities. Hospitalization of patients with pneumonia declined by 28.8% in our secondary medical facility. In particular, hospitalization for pneumonia other than confirmed mycoplasmal or viral pneumonia was significantly reduced by 49.2%. In contrast, hospitalization of patients with pneumonia did not decline in our tertiary medical facility. After the introduction of PCV, hospitalization of children for pneumonia was not reduced at the tertiary medical facility. Various other pathogens besides pneumococcus may be associated with the development of pneumonia in children with underlying diseases.

INTRODUCTION

Pneumonia is one of the most common diseases in childhood. *Streptococcus pneumoniae* is the most common causative pathogen of pneumonia and accounts for an estimated 17% to 44% of hospitalizations for pneumonia in children (1–3). The 7-valent pneumococcal conjugate vaccine (PCV7), which was introduced into the U.S. Infant Immunization Program in 2000, reduced the rate of hospitalization for pneumonia in children aged < 2 years (4). The same tendencies were also shown in other clinical trials in developing countries (5,6). In Japan, the incidence of pneumococcal meningitis and bacteremia in children was markedly decreased after the introduction of PCV7 in 2010 (7). In addition, the reduction of community-acquired pneumonia and pneumococcal pneumonia in children aged < 5 years was also observed in Japan (8).

Most subjects of previous studies did not have any underlying diseases. Unlike the reduction in hospitalization

for pneumonia in children without underlying diseases after the introduction of PCV7, the change in the rate of hospitalization of children with underlying diseases has been uncertain.

To estimate the effectiveness of PCV7 in the children with underlying diseases, we compared the change in the rate of hospitalization for pneumonia after the introduction of PCV7 in the Japanese National Immunization Programs between a secondary and a tertiary medical facility, which hospitalize many children without and with underlying diseases, respectively.

MATERIALS AND METHODS

Study population: Kitakyushu General Hospital is a secondary medical facility, and the Hospital of the University of Occupational and Environmental Health, Japan, is a tertiary medical hospital, with pediatric wards that can hospitalize up to 43 and 27 patients, respectively. Both of these hospitals are located in Kitakyushu City, with a population of approximately 1 million. The patients with severe diseases are hospitalized in the intensive care unit of each hospital. From January 1, 2009, to December 31, 2013, 6,629 and 1,770 patients were admitted to the Department of Pediatrics at Kitakyushu General Hospital and the Hospital of the University of Occupational and Environment Health, Japan, respectively.

PCV7 was introduced in Japan on February 1, 2010, and official financial support for PCV7 vaccination for

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children < 5 years started in Kitakyushu City on January 1, 2011. Finally, this vaccine was incorporated into the Japanese National Vaccine Program on April 1, 2013. With the assistance of the official financial support, immunization coverage of PCV7 increased from 35% in 2010 to 58% in 2012 (9). We compared the hospitalization rates of pneumonia before (2009 and 2010) and after (2012 and 2013) the beginning of official financial support for PCV. Children hospitalized in 2011 were excluded because it was considered a transition year.

The backgrounds and diagnoses of the patients were retrospectively investigated based on the medical records and laboratory and microbiological data. We diagnosed pneumonia if it was described in the list of discharge diagnosis. Patients who did not develop pneumonia on admission were excluded.

Types of pneumonia: Rapid antigen detection tests for adenovirus (Mizuho Medy, Saga, Japan; Alfresa Pharma, Osaka, Japan), influenza virus (Mizuho Medy; Becton & Dickinson, Franklin Lakes, NJ, USA), and respiratory syncytial virus (Mizuho Medy; Alfresa Pharma), and the detection of *Mycoplasma pneumoniae* DNA by loop-mediated isothermal amplification using throat swabs or serologic tests for *M. pneumoniae* (particle agglutination antibody; FUJIREBIO, Tokyo, Japan; considered positive for ≥ 4 -fold rise of antibody titer in paired sera) were performed to identify the causative pathogens of pneumonia when clinically indicated. Cultures of blood or sputum (if possible) were performed on admission. Based on the results of these microbiological analyses, the patients were classified into groups according their types of pneumonia; viral pneumonia, mycoplasmal pneumonia, pneumonia with bacteremia, and pneumonia other than confirmed viral or mycoplas-

mal pathogen. Bacterial pneumonia except pneumonia with bacteremia, was included in pneumonia other than confirmed viral or mycoplasmal pneumonia because there were no specific clinical data to distinguish between bacterial pneumonia and pneumonia of unknown etiology. Although the causative bacteria cannot be confirmed completely by isolating bacterial pathogens from nasal swabs mainly reflect the colonization of the nasopharynx, we investigated bacterial pathogens using this method in the patients classified as having pneumonia other than confirmed viral or mycoplasmal pneumonia.

Statistical analysis: Comparisons of the proportions were analyzed using the chi-squared test. The Mann-Whitney *U*-test was used to compare differences between quantitative variables. Quantitative data are presented as medians, depending on the distribution of the data. In all cases, *p* values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using Dr. SPSS II software, ver. 11.0J for Windows (Chicago, IL, USA).

RESULTS

A total of 2,953 and 2,350 patients were hospitalized at our secondary medical facility before (2009 and 2010) and after (2012 and 2013) the beginning of official financial support, respectively. Of all hospitalizations, 816 (27.6%) and 581 (24.7%) patients had a diagnosis of pneumonia before and after the beginning of official financial support, respectively. Thirty-five (5.0%) of 695 and 64 (8.8%) of 730 patients hospitalized at our tertiary medical facility had a diagnosis of pneumonia during before and after the official financial support period, respectively. The patients' clinical characteristics

Table 1. Comparison of demographic characteristics of the patients hospitalized for pneumonia between the 2 facilities

Characteristic	2009–2010 ²⁾		2012–2013 ²⁾	
	Secondary medical facility (n = 816)	Tertiary medical facility (n = 35)	Secondary medical facility (n = 581)	Tertiary medical facility (n = 64)
Age, median; months (range)	24 (1–168)	28 (1–148)	21 (1–164)	57 (2–175)*
Sex, man (%)	428 (52.5)	20 (57.1)	305 (52.5)	33 (51.6)
With underlying diseases ¹⁾	7 (0.9)	22 (62.9)*	3 (0.5)	34 (53.1)*
Chromosomal abnormality	0 (0)	6 (17.1)*	1 (0.2)	9 (14.1)*
CNS malformation	0 (0)	0 (0)	0 (0)	1 (1.6)
Cerebral palsy	0 (0)	4 (11.4)*	0 (0)	8 (12.5)*
Epilepsy	4 (0.5)	4 (11.4)*	0 (0)	6 (9.4)*
Squela of hypoxic encephalopathy	0 (0)	2 (5.7)*	0 (0)	2 (3.1)*
Neuromuscular disease	0 (0)	3 (8.6)*	0 (0)	2 (3.1)*
Inborn error of metabolism	1 (0.1)	0 (0)	0 (0)	1 (1.6)*
Hematological cancer	0 (0)	0 (0)	0 (0)	1 (1.6)*
Non-hematological cancer	0 (0)	1 (2.9)*	1 (0.2)	0 (0)
Hematologic disease	0 (0)	0 (0)	0 (0)	1 (1.6)*
Prematurity	2 (0.2)	1 (2.9)*	1 (0.2)	1 (1.6)
Bronchopulmonary dysplasia	0 (0)	1 (2.9)*	0 (0)	1 (1.6)*
Interstitial pneumonia	0 (0)	0 (0)	0 (0)	1 (1.6)*

* *p* < 0.05 when compared with the secondary medical facility.

¹⁾: No. (%), not otherwise specified.

²⁾: 2009–2010: before the beginning of official financial support; 2012–2013: after the beginning of official financial support. CNS, central nervous system.

are shown in Table 1. The median age of the patients hospitalized for pneumonia at our tertiary medical facility were significantly older than those at our secondary medical facility (before, $p = 0.004$; after, $p < 0.001$). The rates of the patients with some underlying diseases of the hospitalized patients for pneumonia at our tertiary medical facility, aged < 2 and ≥ 2 years were 23.5% and 79.0%, respectively (data not shown).

The proportion of patients hospitalized for pneumonia was significantly higher in our secondary medical facility than in our tertiary medical facility (before, $p < 0.001$; after, $p < 0.001$). In our secondary medical facility, the hospitalizations for all-cause pneumonia declined by 28.8% after the beginning of official financial support of PCV vaccination ($p = 0.02$), whereas those in our tertiary medical facility increased by 82.9% ($p = 0.01$) (Table 2). These tendencies were noted among all age groups (Fig. 1A and B). The number of the patients with pneumonia other than confirmed mycoplasmal or viral pneumonia was significantly reduced by 49.2% in our secondary medical facility ($p < 0.001$), whereas there was no significant change in our tertiary medical facility (Table 2). The number of patients hospitalized

for pneumonia with bacteremia was also reduced in our secondary medical facility after the beginning of official financial support for PCV vaccination, but the difference was not statistically significant. *S. pneumoniae* was isolated from blood cultures of all 6 patients hospitalized for pneumonia with bacteremia before the beginning of official financial support. After the beginning of official financial support, *Haemophilus influenzae* was isolated from the blood cultures of 1 patient. No patient with a diagnosis of pneumonia with bacteremia was hospitalized at our tertiary medical facility during either study period. In our secondary medical facility, the number of patients with pneumonia other than confirmed viral or mycoplasmal pneumonia decreased among all age groups (Fig. 2A). In our tertiary medical facility, the number of patients hospitalized for these kinds of pneumonia also decreased among the patients aged < 2 years but not those aged ≥ 2 years (Fig. 2B).

The bacterial pathogens isolated from nasal swabs from patients with pneumonia other than confirmed viral or mycoplasmal pneumonia are shown in Table 3. The proportion of patients from whom *S. pneumoniae* was isolated in our secondary medical facility was signifi-

Table 2. Comparison of the changes of the hospitalization for pneumonia in the 2 medical facilities between 2009–2010 and 2012–2013

	Secondary medical facility				Tertiary medical facility			
	No. (%)		Change rate, %	<i>p</i> -value	No. (%)		Change rate, %	<i>p</i> -value
	2009–2010 ¹⁾	2012–2013 ¹⁾			2009–2010	2012–2013		
All-cause hospitalization	2,953	2,350	–20.4		695	730	5.0	
All-cause pneumonia hospitalization	816 (27.6)	581 (24.7)	–28.8	0.02	35 (5.0)	64 (8.8)	82.9	0.01
Subgroups								
viral	110 (13.5)	169 (29.1)	53.6	< 0.001	2 (5.7)	11 (17.2)	450	< 0.01
mycoplasmal	9 (1.1)	60 (10.3)	566.7	< 0.001	0 (0.0)	3 (4.7)	NA	0.19
other than confirmed viral/mycoplasmal	691 (84.7)	351 (60.4)	–49.2	< 0.001	33 (94.3)	50 (78.1)	51.5	0.09
pneumonia with bacteremia	6 (0.7)	1 (0.2)	–83.3	0.14	0 (0.0)	0 (0.0)		

¹⁾: 2009–2010: before the beginning of official financial support; 2012–2013: after the beginning of official financial support. NA, not applicable.

Fig. 1. Changes of the number of patients hospitalized for all types of pneumonia according to age in a secondary medical facility (A) and a tertiary medical facility (B). a: before the beginning of official financial support (2009 and 2010); b: after the beginning of financial support (2012 and 2013).

Fig. 2. Changes of the number of patients hospitalized for pneumonia other than confirmed mycoplasmal or viral pneumonia according to age in a secondary medical facility (A) and a tertiary medical facility (B). a: before the beginning of official financial support (2009 and 2010); b: after the beginning of official financial support (2012 and 2013).

Table 3. The proportion of bacterial pathogens that commonly cause pneumonia in children isolated from nasal swab in the patients hospitalized for pneumonia except for confirmed mycoplasmal or viral pneumonia in the 2 facilities

Pathogen	2009–2010 ¹⁾		2012–2013 ¹⁾	
	Secondary medical facility (n = 682) No. (%)	Tertiary medical facility (n = 31) No. (%)	Secondary medical facility (n = 350) No. (%)	Tertiary medical facility (n = 38) No. (%)
<i>Streptococcus pneumoniae</i>	378 (55.4)	6 (19.4)*	179 (51.1)	6 (15.8)*
<i>Haemophilus influenzae</i>	299 (43.8)	10 (32.3)	209 (59.7)	8 (21.1)*
<i>Moraxella catarrhalis</i>	218 (32.0)	7 (22.6)	180 (51.4)	7 (18.4)*

* $p < 0.05$ when compared with the secondary medical facility.

¹⁾: 2009–2010: before the beginning of official financial support; 2012–2013: after the beginning of official financial support.

cantly higher than that in our tertiary medical facility ($p < 0.05$).

DISCUSSION

As in previous studies (4,8,10,11), in the present study, the number of patients hospitalized for pneumonia in the secondary medical facility declined after the beginning of official financial support of PCV vaccination. In particular, the number of patients with pneumonia other than confirmed viral or mycoplasmal pneumonia was markedly reduced. Interestingly, the number of hospitalizations of patients aged ≥ 5 years was also reduced even though only children aged < 5 years could receive official financial support for PCV vaccination. The number of elderly adults hospitalized for pneumonia declined after the introduction of PCV for children aged < 5 years (12). Although further long term study is needed because of the short study period of the present study, an indirect effect of PCV vaccination may contribute to the reduction in hospitalizations for pneumonia in children aged > 5 years.

Unlike our results in the secondary medical facility, the number of pediatric patients hospitalized for pneumonia in our tertiary medical facility did not decline after the introduction of PCV. The change in the rate of the hospitalization of children with underlying diseases after the introduction of PCV has been uncertain. In our tertiary medical facility, many patients with severely impaired mobility, such as those with a chromosomal abnormality, cerebral palsy, sequela of hypoxic encephalopathy, and neuromuscular diseases, were hospitalized for pneumonia (Table 1). These patients generally have obstructive and restrictive respiratory disorders, making it difficult to clear out sputum from airways (13,14), and are prone to develop lower respiratory tract infection due to oral bacteria (15). In the patients hospitalized at our tertiary medical facility for pneumonia, the proportion of patients without underlying diseases was higher in children aged < 2 years, and the number of the hospitalizations for pneumonia other than confirmed viral or mycoplasmal pneumonia in this age group decreased after the implementation of official financial support for PCV vaccination. In contrast, most patients aged ≥ 2 years had some underlying diseases, and the number of patients hospitalized for these kinds of pneumonia was

not reduced. Based on these findings, it can be presumed that *S. pneumoniae* may be associated with a smaller population of the patients hospitalized for pneumonia, especially those aged ≥ 2 years, at the tertiary medical facility compared with the patients hospitalized at the secondary medical facility. Furthermore, in the present study, *S. pneumoniae* was more frequently isolated from nasal swabs in the patients hospitalized in the secondary medical facility (Table 3). Although the causative bacteria could not be confirmed completely, these results also suggested that the proportion of the patients with acute pneumonia caused by *S. pneumoniae* might be higher in the secondary medical facility than in the tertiary medical facility.

The present retrospective study has some limitations. First, the present ecological analysis could not definitively identify the causative pathogens of pneumonia. Second, comparison of just 2 facilities may have introduced a bias with respect to the underlying diseases of patients hospitalized at a single tertiary medical facility. The present study suggested that PCV had limited effectiveness for preventing hospitalization for pneumonia, at least in pediatric patients with severe impaired mobility. Finally, the study period of the present study was too short to precisely determine the difference in the efficacy of PCV with respect to hospitalization for pneumonia between patients with and without underlying diseases. Further long-term multicenter observational studies are warranted to confirm these findings.

In conclusion, we showed a difference in the change of the hospitalization for pneumonia between 2 facilities after the introduction of PCV. This result suggested that PCV might not be as effective in preventing hospitalization for pneumonia among children with underlying diseases as it may be among children without underlying diseases. PCV vaccination has been recommended for children at high risk of invasive pneumococcal disease (16). In addition to PCV vaccination, other actions may be needed to prevent the development of pneumonia in pediatric patients with underlying diseases.

Conflict of interest None to declare.

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