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Original Article

Changes in the Features of Invasive Pneumococcal Disease after Introduction of the Seven-valent Pneumococcal Conjugate Vaccine in a Regional Core Hospital of Kochi, Japan

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Since the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) in 2007, invasive pneumococcal disease has declined, but the incidence of *Streptococcus pneumoniae* serotype 19A has risen worldwide. The present study examined changes in the features of invasive pneumococcal disease since the introduction of the PCV7 in Kochi, Japan. Pediatric cases of invasive pneumococcal disease were investigated before and after vaccine introduction (January 2008 to December 2013). Cases of invasive pneumococcal disease tended to decrease after PCV7 introduction. In addition, before introduction of the vaccine, most serotypes causing invasive pneumococcal disease were those included in the vaccine. However, after the introduction, we found cases infected by serotypes not covered by vaccine. Penicillin-resistant *S. pneumoniae* was the predominant serotype causing invasive pneumococcal disease before introduction of the PCV7, and the susceptibility of this serotype to antibiotics improved after vaccine introduction. Serotype isolates identified after vaccine introduction were also relatively susceptible to antibiotic therapy, but decreased susceptibility is expected.

Key words: seven-valent pneumococcal conjugate vaccine (PCV7), invasive pneumococcal disease (IPD)

In 2007, a seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States (US), resulting in a dramatic reduction in cases of invasive pneumococcal disease (IPD) [1]. Since then, the PCV7 has been used in other countries and similar outcomes have been reported [2, 3]. Soon after the introduction of the PCV7, isolates of non-PCV7 serotypes began to increase [4, 5]. Specifically, IPD caused by serotype 19A, a non-PCV7 serotype, became a problem in the US [6], apparently as a direct result of the vaccine introduction. In South Korea, however, IPD caused by serotype 19A was observed before the introduction of the PCV7 [7]. Thus, the increased prevalence of serotype 19A could not be attributed solely to the introduction of the PCV7. After the introduction of the PCV7, isolates of non-PCV7 serotypes were initially very susceptible to antibiotic therapy, but gained rapid resistance to antibiotics in the US [8].

In Japan, the PCV7 was made available on a voluntary basis beginning in February 2010. In the initial

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months after its availability, however, the estimated vaccination rate remained under 10% [9]. Therefore, beginning in November 2010, PCV7 vaccination of children younger than 5 years old was more aggressively promoted under a program called the Provisional Special Fund for the Urgent Promotion of Vaccination. In April 2013, the PCV7 was officially added to the schedule of routine vaccination for children. Introduction of the PCV7 may have both decreased the occurrence of IPD and changed the epidemic serotypes in Japan. The aim of this study was to examine changes in the features of IPD after the introduction of PCV7 in Kochi, Japan from January 2008 to December 2013.

Materials and Methods

Patients and definition of IPD. All subjects were patients under 18 years old who had been diagnosed with IPD at the Kochi Health Sciences Center, a tertiary hospital in Kochi prefecture. Surveillance was performed from January 2008 to December 2013. According to the Active Bacterial Core surveillance (ABCs) initiative of the The Centers for Disease Control and Prevention (CDC), IPD is defined as an illness in which pneumococcus is isolated from normally sterile bodily fluids, such as blood, cerebrospinal fluid, or pleural fluid. For the purposes of this study, sepsis was defined as identification of *Streptococcus pneumoniae* in the blood but not in the cerebrospinal fluid. If *S. pneumoniae* was detected in cerebrospinal fluid, the patient was diagnosed with meningitis. This study also investigated age, sex, sequelae, and how many times patients received PCV7 vaccines.

Serotype determination of S. pneumoniae. The Department of Bacteriology I of the National Institute of Infectious Diseases, Japan (NIID) identified the serotypes of *S. pneumoniae* isolated from study participants. Serotypes of all isolates were determined using the capsular Quellung reaction, with antiserum produced by the Statens Serum Institute (Copenhagen, Denmark) and serum produced at the Department of Bacteriology I of NIID. Sequence typing was performed according to the multilocus sequence typing (MLST) website (http://spneumoniae. mlst. net) (accessed March, 2015).

Antibiotic susceptibility testing. Susceptibility testing of isolates was performed via the broth microdilution method, and interpreted according to Clinical and Laboratory Standards Institute (CLSI) breakpoints [10]. This study was approved by the Ethics Committee of the Kochi Health Sciences Center.

Results

Clinical features of IPD cases. Fifteen cases of IPD were diagnosed in 14 patients (1 patient experienced recurrence) between April 2008 and May 2013. Among the 15 cases of IPD, 10 were diagnosed as cases of sepsis and 5 as cases of meningitis. None of the participating patients were diagnosed with pleuritis. Of the 14 patients, 7 were male and 7 were female (Table 1). The median age was 30 months, with a minimum age of 8 months and a maximum age of 10 years and 3 months. Descriptions of the sequelae identified in study participants are as follows. We experienced 3 cases with paralysis (Cases 1, 2, and 8). Case 1 was a female patient who experienced trivial right hemiplegia and mental retardation, both of which disabilities remained at the time of publication. Case 2 was a male patient who had 2 separate occurrences of meningitis; he experienced paralysis of his right hand following the first occurrence of IPD, but regained full function thereafter. At the second occurrence of IPD, a nasopharyngeal culture performed prior to antibiotic administration revealed *S. pneumoniae* (the serotype was not examined). But a negative result was found in a sample of ear discharge that was cultured 3 h after antibiotic administration. All immunological data, including the C3, C4, CH50, IgA, IgG, IgM and ratio of CD4/8, were within normal limits. The subclass of IgG was not examined. Both occurrences stemmed from the same serotype of *S. pneumonia* (6B). It is doubtful that the bronchitis or right otitis media were responsible for the patient's first occurrence of meningitis. During the patient's second occurrence of meningitis, left otitis media was also found, and was considered to be potentially causative. Nasopharyngeal culturing was performed prior to antibiotic administration. *S. pneumoniae* was found in the nasal culture, but not in a sample of ear discharge that was cultured 3 h after antibiotic administration. Case 8 contracted IPD after a traffic accident that resulted in a frontal bone fracture and subdural

Table 1 Clinical features and information for each case

	Sex	Age	Onset	Diagnosis	Serotype	ST	AS	PCV7	Sequelae	Past history
1	F	1 y	Mar. 2008	Meningitis	14*	NA	PISP	—	Right hemiplegia, mental retardation	
2	M	1 y	Jul. 2008	Meningitis	6B*	NA	PRSP	—	Right hand paralysis	Pneumonia, otitis media
		2 y	Nov. 2008	Meningitis	6B*	ST902	PRSP	—	—	
3	F	5 y	Jun. 2009	Sepsis	19F*	ST236	PRSP	—	—	Total anomalous pulmonary venous return, pulmonary atresia, dextrocardia, asplenia
4	F	8 m	Dec. 2009	Sepsis	19F*	ST236	PRSP	—	—	—
5	F	2 y	Jan. 2010	Sepsis	4*	NA	PSSP	—	—	Extremely low birth weight infant
6	M	1 y	Jan. 2010	Sepsis	6B*	NA	PRSP	—	—	—
7	M	1 y	Jan. 2010	Meningitis	6A	NA	PRSP	—	—	Upper respiratory inflammation (2 weeks before admission)
8	F	1 y	Mar. 2010	Meningitis	15A	NA	PRSP	—	Verbal disability, movement disability	Subarachnoid hemorrhage, frontal bone fracture, subdural hemorrhage (due to traffic accident)
9	M	10 y	Mar. 2010	Sepsis	23F*	ST1437	PISP	NA	—	Fanconi anemia, polydactyly, reflex nephropathy, solitary kidney
10	F	1 y	May. 2010	Sepsis	23F*	ST313	PRSP	NA	—	—
11	M	10 m	Jun. 2010	Sepsis	14*	ST343	PISP	NA	—	Pneumonia (3 weeks before admission to hospital)
12	F	8 m	Nov. 2011	Sepsis	15B	NA	PSSP	2 times	—	Persistent foramen ovale
13	M	1 y	Mar. 2012	Sepsis	19A	NA	PISP	3 times	—	Extremely low birth weight infant
14	M	3 y	Apr. 2013	Sepsis	19A	ST3111	PISP	1 time	—	Autism, pneumonia

*Indicates serotypes that are covered by the PCV7.

AS, antibiotic susceptibility; NA, not applicable; PISP, penicillin-intermediate *S. pneumonia*; PRSP, penicillin-resistant *S. pneumonia*; PSSP, penicillin-susceptible *S. pneumonia*; ST, strain type.

and subarachnoid hemorrhages. This patient initially experienced verbal and movement disabilities, but these symptoms were alleviated during her hospitalization. Serotype 15A, a non-PCV7 serotype, was identified in this patient. Case 3 was a female patient with congenital heart defects (total anomalous pulmonary venous return, pulmonary atresia, dextrocardia) and asplenia, who was diagnosed as meningitis complicated with infective endocarditis. This case was first treated for meningitis and then with a 23-valent pneumococcal polysaccharides vaccine for asplenia.

Serotypes of S. pneumoniae. Before 2010, most cases of IPD were caused by *S. pneumoniae* serotypes contained in the PCV7 (Table 1, Fig. 1). Since 2011, however, all identified IPD cases have been caused by non-PCV7 serotypes. Serotypes 6A and 15A were identified in 2010, and serotype 15B was identified in 2011. Serotype 19A was detected twice, in both 2012 and 2013. The sequence type (ST) of the specimen isolated in 2013 was ST3111, but data were not available about the ST of the specimen detected in 2012.

Antibiotic susceptibility. From 2008 to 2010, most serotypes identified were penicillin-resistant *S. pneumoniae* (PRSP), including serotype 6B (2008); serotype 19F (2009); and serotypes 6A, 6B, 15A, and 23F (2010) (Table 1, Fig. 2). Serotypes 14 and 23 (2010) were penicillin-intermediate *S. pneumoniae* (PISP), and serotype 4 (2010) was penicillin-susceptible *S. pneumoniae* (PSSP). Since 2011, 3 IPD cases caused by non-PCV7 serotypes have been identified; 2 of these cases were caused by PISP serotypes, and 1 case was caused by a PSSP serotype.

Discussion

Introduction of the PCV7 has reduced the inci-

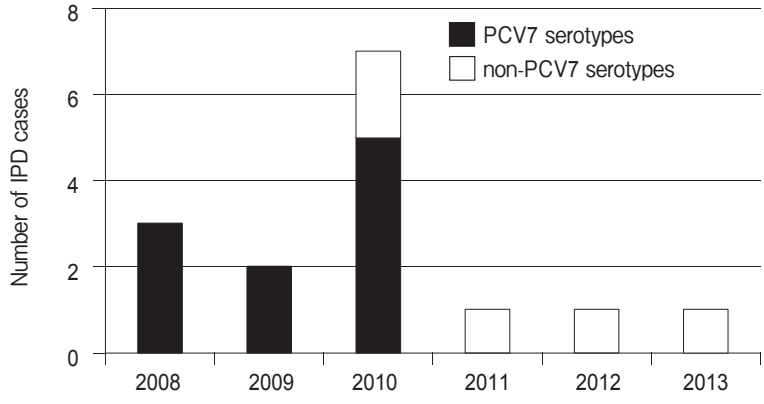

Fig. 1 The graph shows serotypes of *S. pneumoniae* which caused IPD from January 2008 to December 2013: black bars shows serotypes covered by PCV7 and white bars shows non-PCV7 serotypes. After 2011, serotypes covered by PCV7 were not found.

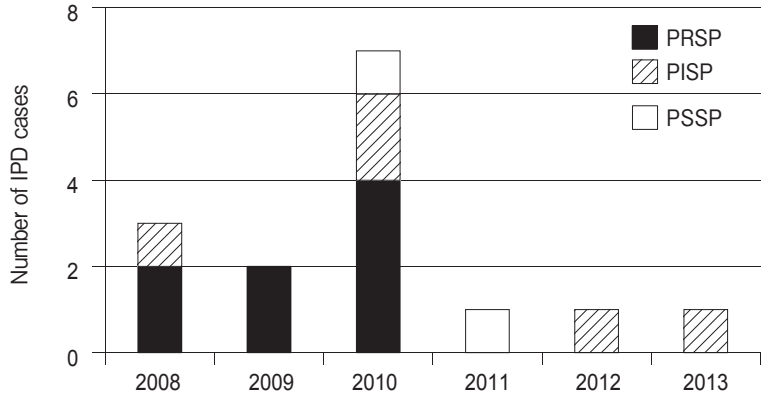

Fig. 2 The graph shows the antibiotic susceptibility of *S. pneumoniae*, which caused all of the cases IPD detected from January 2008 to December 2013: black, striped, and white bars show PRSP, PISP, PSSP, respectively. Before 2010, PRSP was dominant, but the susceptibility of these strains to antibiotics has been improved since 2011.

dence of IPD [11]. Furthermore, it has resulted in IPD-causing serotypes that are less harmful, and has improved the antibiotic susceptibility of these serotypes [12]. This study provides further evidence of these trends. A problematic increase in the occurrence of serotype 19A has also been identified [13]. This study found antibiotic susceptibility of serotype 19A to be relatively high, as compared with reports in other settings [6, 14, 15]. PISP clones were identified in 2012 and 2013 (Table 1), and *S. pneumoniae* serotype 19A may soon become antibiotic resistant. In addition to serotype 19A, other non-PCV7 serotypes have also been reported to increase [5], and these serotypes were also found in our hospital (Table 1). Research must continue to investigate the characteristics of new IPD-causing serotypes, as well as the continued progression of IPD after the introduction of the PCV7.

Our results indicate that the number of IPD cases in Kochi has decreased since the introduction of PCV7. Ishiwada *et al.* reported a decrease in IPD cases in Chiba prefecture, Japan (per 100,000 people under age 5) of from 21.3 in 2008 to 9.3 in 2013 [16]. This trend was also observed internationally [1–3].

The present study showed changes in the *S. pneumoniae* serotypes that caused IPD after 2010. Between 2008 and 2010, IPD was frequently caused by PCV7 serotypes. Some cases during this period had unusual features. Case 2 was diagnosed with IPD twice in 4 months, with the same serotype (6B) causing both occurrences of IPD (Table 1). It was suspected that, in addition to serotype 6B *S. pneumoniae*, this patient's bronchitis and otitis media may have been related to nasopharyngeal colonization of *S. pneumoniae*. Recurrence of bacterial meningitis was seen in about 1% of IPD cases [17]. King *et al.* reported that in 133 patients who experienced recurrence of IPD, serotype 6B was the most detected serotype, being associated with 12.8% of cases, and 62.4% of

all IPD recurrence was caused by PCV7 serotypes [18]. Other reports showed that PCV7 serotypes, particularly serotype 6B, were frequently associated with nasopharyngeal colonization serotypes before the introduction of the PCV7 [19–21]. Thus, a reduction of recurrent IPD can be expected after the introduction of the PCV7. Case 3 had asplenia and thus was at an increased risk for infection [22, 23]. Uchida *et al.* reported a case of asplenia in which the patient's anti-6B antibody was below the protective level both after she had received the PCV7 and after she was naturally infected with *S. pneumoniae* serotype 6B [23]. The possibility remains that patients with asplenia have difficulty developing vaccine-induced immunity to serotype 6B, and must therefore be very conscientious about potential pathogen exposure. After 2010, only non-PCV7 serotypes were observed, so the suppression of PCV7 serotype infection might increase the infection of non-PCV7 serotypes. In the study hospital, all cases of IPD since 2011 have been caused by non-PCV7 serotypes, with serotype 19A being detected in all IPD patients diagnosed in 2012 and 2013 (Table 1). This may reflect the fact that infection with serotype 19A is increasing in Japan. Increased infection with serotype 19A was expected, as reports have shown a rising rate of IPD caused by serotype 19A [6, 13]. In this study, the single serotype 19A detected in 2013 was identified as ST3111, the main type that has been detected in Japan [9, 24]. Interestingly, the most prevalent ST reported in other Asian countries (Korea, Malaysia, Taiwan, Saudi Arabia, Hong Kong, and India) was ST320 [25]. The reason that serotype 19A increased prior to the introduction of the PCV7 in Korea may be the emergence of the highly-resistant ST320 clone, in conjunction with overuse of antibiotics [26]. Antibiotic susceptibility is higher in ST3111 than in ST320 [9, 24], which may explain why serotype 19A did not increase in Japan before the introduction of the PCV7.

Our present data suggested that, after 2010, the antibiotic susceptibility of *S. pneumoniae* improved. This might have occurred as a result of serotype replacement. Chiba *et al.* showed overall increases in IPD susceptibility to antibiotics [27]. In the US, the incidence of IPD caused by serotype 19A increased after the introduction of the PCV7, and though initially susceptible, this serotype has become less susceptible to antibiotics in just a few years [12]. Some reports indicate that multidrug-resistant clones of serotype 19A have emerged [8, 28–31], but in the present study the serotype 19A cases in 2012 and 2013 were not resistant to antibiotics. No sequelae remained in either of the serotype 19A cases.

The 13-valent pneumococcal conjugate vaccine (PCV13), introduced in Japan in November 2013, is expected to lead to decreased incidence of IPD caused by PCV13 serotypes (such as serotype 19A). However, the possibility remains that the PCV13 will not provide adequate suppression of serotype 19A to prevent infection, and that multidrug-resistant clones will increase [8, 28–31]. Moreover, in the US, it has been reported that introduction of the PCV13 increased the occurrence of serotypes 11, 12, 15B, 15C, 22F, 23A, and 33F [32]. In this investigation, serotypes 15A and 15B, which are not covered by the PCV13, were also found, and thus, even after introduction of the PCV13, careful, continuous attention must be paid to the progression of IPD.

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