Three Cases of Invasive Pneumococcal Disease with Multiple Serotype Replacement in Vaccinated Children

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Despite having undergone mandatory PCV7 vaccinations, three young children were hospitalized with invasive pneumococcal infections. Among them, two cases were diagnosed as having meningitis and one had bacteremia. Serotype ‘15A’ in one meningitis case was outside the range covered by PCV7 and PCV13 vaccinations, and that case was fatal. Voluntary PCV13 vaccination has been in place in Japan since autumn 2013; however, serotype replacement with uncovered serotypes is a possibility that physicians should consider.

Key words: invasive pneumococcal disease (IPD), PCV7, PCV13, serotype replacement, meningitis

Case Report

In 2012, a 16-month-old girl presented with cough, rhinorrhea, and pyrexia of at least 1 week’s duration. She had no particular past history, and had received three PCV7 vaccinations. The day before hospitalization, she had a sudden convulsion but recovered after treatment with a diazepam suppository from her family doctor. The following day, she had a second tonic clonic convulsion and was admitted to her local hospital. Central spinal fluid examination revealed the following: cell count, 1,328/μl; protein level, 380 mg/dl; glucose level, 0 mg/dl. Blood examination showed a white blood cell count of 27,390/μl and C-reactive protein at 13.4 mg/dl. She was diagnosed with bacterial meningitis, and the pathogen responsible, Streptococcus pneumoniae, was rapidly detected by an immunochromatographic assay. Meropenem, cefotaxime and dexamethasone were commenced promptly. However, her general condition worsened, resulting in cardiopulmonary arrest. She was transferred to the emergency department of Nihon University Itabashi Hospital for intensive care. However, on her way to hospital, a second cardiopulmonary arrest occurred in the ambulance. As her electrocardiogram showed pulseless electrical activity when she arrived, we started cardiopulmonary resuscitation immediately, but she did not respond to analeptics and died.

Within 6 months of the above case, two other cases of S. pneumoniae (meningitis and bacteremia) were treated at our hospital. Streptococcus pneumoniae was detected from cerebrospinal fluid cultures in both first and the second cases. In the first case, specimen was obtained at prior hospital and its serotype was PISP 15A, a non-PCV7 serotype. Confirmation of elevated antibodies against PCV7 serotypes was obtained. In case 2, although the causative serotype was not specified, antibodies for all serotypes contained in PCV7 were examined and excluded. In the third case, S. pneumoniae was detected from...
blood culture and its serotype was detected as PISP 19A, also a non-PCV7 serotype. Three cases are summarized in the Table.

**Discussion**

In 2006, the Japanese IPD Surveillance Study Group investigated the relationship between the age distribution and convalescence profile of IPD, and registered 193 children under 17 years old in the study. Among those pediatric IPD patients, 92% were 4 years old or younger; 59.1% of them had septicemia, 22.8% had pneumonia, and 15.5% had meningitis. In this survey, 14.5% of the children whose data were available had underlying diseases, including cancer, diabetes, and cardiovascular disease, for example. These data signaled that children who lack obvious underlying diseases also need to be protected from IPD.

At the time of this Japanese report (2010) there were 93 *S. pneumoniae* serotypes and PCV7 comprised seven serotypes (i.e., 4, 6B, 9V, 14, 18C, 19F, and 23F). In their newer publication in 2013, the Japanese IPD Surveillance Study Group reported that PCV7 covered 71.8% of the IPD serotypes in 2006 and these serotypes decreased to 51.6% in 2011 before and after PCV7 was introduced in Japan. Ishiwa et al. reported that in the Chiba Prefecture of Japan, the incidence of IPD under 5 years of age decreased from 26.1 cases per 100,000 in 2009 to 9.3 per 100,000 in 2013, and the average number of IPD cases among children younger than 5 years of age in 2011–2013 decreased by 51% (*p* < 0.0001) compared with cases occurring in 2008–2010. In the United States, PCV7 was introduced in 2000 and PCV7 serotype IPD in children was reduced by 94% until 2007.

However, the Japanese IPD Surveillance Study Group reported that the serotypes detected from IPD patients had changed since introducing PCV7, and the serotype coverage range of PCV7 in 2007 was 76.8% of that in 2010, and 37% of that in 2011 to 2012. After introduction of PCV7, non-PCV7 serotypes started spreading and the PCV7 serotype declined, a phenomenon called serotype replacement. The non-PCV7 serotypes 6C, 15A, 15B, 19A, and 22F have gradually increased, and 19A is the most common in Japan and the United States. After PCV7 was introduced, the prevalence of serotype 19A increased from 6.2% to 21.8% for IPD overall. The newer PCV13 vaccine includes the following six additional serotypes: 1, 3, 5, 6A, 7F, and 19A. PCV13 cannot prevent all possible serotype replacements; however, the Ministry of Health, Labour and Welfare (Japan) states that PCV13 will provide at least 30% better protection of children from IPD than it does at present. Similar findings for serotype replacement have been reported in several countries, including France, Norway and the Netherlands.

Indeed, Kaplan et al. reported that IPD caused by the additional six serotypes reduced in eight major pediatric hospitals in the United States and IPD from serotype 19A reduced by 58% after PCV13 was introduced. In the United States, addition of the six new serotypes resulted in a 63% reduction in IPD among children less than 5 years of age from 2006 to 2007. Hicks et al. reported that serotypes 3, 15, 19A, 22F, and 33F increased after PCV13 was introduced. Similar findings for PCV13 against IPD in elderly people were found; indeed, non-PCV7 serotypes increased in this age group. In the present report, in addition to the serotype 19A case of fatal meningitis, we experienced a serotype 15A case of bacteremia; this serotype is not included in PCV7 or PCV13.

Contracting IPD is still possible, even in children vaccinated with PCV13. A very recent report from the Israeli Bacteremia and Meningitis Active Surveillance Group warns that serotype 12F in non-PCV13 serotypes has become most common along with a decrease in 19A after introducing PCV13. Various non-PCV7 and non-PCV13 serotypes have possibly become dominant in different areas of the world. Whenever a new effective vaccine against *S. pneumoniae* is produced in the future, global IPD surveillance will still be needed, and information about serotype replacement will remain important.

**Table** Summery of three cases of invasive pneumococcal disease despite of PCV7 vaccination

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Sex</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>meningitis</td>
<td>meningitis</td>
</tr>
<tr>
<td>Vaccination</td>
<td>PCV7 × 3 times</td>
<td>PCV7 × 4 times</td>
</tr>
<tr>
<td>Serotype</td>
<td>PISP 15A</td>
<td>All PCV7 type were excluded, but not detected.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>MEPM + CTX</td>
<td>VCM + CTX</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Died</td>
<td>Discharged after 25 days</td>
</tr>
</tbody>
</table>

MEPM, meropenem; CTX, cefotaxime; VCM, vancomycin chloride

**References**


