Local outbreak of *Streptococcus pneumoniae* serotype 12F caused high morbidity and mortality among children and adults

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**Abstract**

Pneumococcal serotype replacement is an important issue after the introduction of pneumococcal conjugate vaccine (PCV) in children. After the introduction of 13-valent PCV, the incidence of invasive pneumococcal diseases (IPD) caused by *Streptococcus pneumoniae* serotype 12F (Sp12F) have increased in some countries; however, an outbreak of Sp12F has not been reported in the post-13-valent PCV era. We experienced a local outbreak of Sp12F during March through May 2016 in Tsuruoka city, Japan after the introduction of 13-valent PCV in 2013. The IPD patients were two children and seven adults, three of whom died with a rapid disease progress. Although the clear transmission route was not determined, eight of the nine patients (89%) had close contact with children, which suggests that transmitted colonisation of Sp12F among children and adults might be the source of transmission. Continuous monitoring of IPDs, along with the determination of pneumococcal serotypes, is warranted in the post-13-valent PCV era. New IPD control strategies may be needed if this fatal outbreak continues to occur.

Invasive pneumococcal disease (IPD) is defined as an infection confirmed by isolation of *Streptococcus pneumoniae* (*S. pneumoniae*) from sterile sites (e.g. blood, cerebrospinal fluid) and can cause substantial morbidity and mortality. More than 90 *S. pneumoniae* serotypes have been reported and certain serotypes cause IPD. As compared with IPD caused by other serotypes, those attributed to *S. pneumoniae* serotype 12F (Sp12F) result in greater morbidity and mortality [1].

A 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in Japan in 2010 and a 13-valent PCV (PCV13) replaced the PCV7 in 2013. The interval from the start of PCV7 to the introduction of PCV13 was brief in Japan because PCV7 was introduced later than other countries. However, PCV13 is now widely used as a mandatory vaccine in the Japanese National Immunization Program (NIP) [2]. Importantly, Sp12F is not covered by PCV7 or PCV13 but is covered by the 23-valent pneumococcal polysaccharide vaccine (PPSV23), which has been included in the NIP since October 2014 for adults aged 65 years or older. After the introduction of PCV7 to the NIP, followed by that of PCV13, the IPD cases among children decreased down to about 40% [3]. However, the rate of IPD caused by non-PCV13 serotypes increased in both children [3] and adults [4], because of serotype replacement, i.e., the increase in the prevalence of non-PCV serotypes replacing PCV serotypes and consequent decrease in PCV effectiveness [3, 5].

Tsuruoka city has a population of approximately 130 000 and is located in northern Japan, in Yamagata prefecture, near the Japan Sea. Tsuruoka Municipal Shonai Hospital is the only tertiary hospital in the area and all patients with severe infections are admitted to this hospital. In this report, we describe an outbreak of IPD cases caused by Sp12F during a 3-month period. Importantly, a paediatric case of IPD caused by Sp12F has been reported in Japan [6] and elsewhere, there is no report of the outbreak spreading to both children and adults.

In this study, nine patients were admitted to the hospital under the diagnosis of a community-acquired IPD based on isolation of Sp12F from blood or cerebrospinal fluid from 1 March through 31 May 2016. Of note, no community outbreak caused by influenza, respiratory syncytial virus, or other respiratory viruses was observed during the period. All adult patients were evaluated for pneumonia and spleen presence by chest and abdominal computed tomography (CT), respectively. Spleen volume was calculated retrospectively by...
the following standard formula: spleen volume (cm\(^3\)) = 30 + 0.58 (maximal width \(\times\) height \(\times\) thickness at hilum) [7].

IPD was defined as isolation of \textit{S. pneumoniae} from blood or cerebrospinal fluid cultures. Occult bacteremia was defined as a positive blood culture without an obvious source of infection. Child contact was defined as living with children younger than 15 years or spending more than 8 hours per 4 weeks with children, as in previous studies [8] among adult patients and visiting a day-care center daily among paediatric patients. The hypoplastic spleen was defined as a spleen volume less than 100 cm\(^3\) (normal range, 100–250 cm\(^3\)) [7].

The patient clinical data were collected from the medical records and subsequent questionnaires distributed to patients and patients’ families. The questionnaires were sent to patients or their family members by the Shonai Public Health Department in October and November 2016. The clinical information collected included age, sex, past medical history, focus of IPD, Charlson Comorbidity Index (for adults), Pitt Bacteremia Score (for adults), outcome, pneumococcal vaccine history and history of child contact. The Charlson Comorbidity Index predicts mortality by comorbid conditions among adults and is useful in objectively evaluating patient background [9]. The Pitt Bacteremia Score predicts mortality in the intensive care unit among patients with bacteremia (cutoff, >4 points) [10].

To investigate the source of infection, the locations of places where patients and their family members worked or visited were mapped by using the addresses of their workplace, school, group nursing home, friends’ homes and family home.

After the isolation of \textit{S. pneumoniae}, serotyping was performed with pneumococcal typing antisera (Statens Serum Institut, Copenhagen, Denmark) at the National Institute of Infectious Diseases, Japan. Additionally, multilocus sequence typing (MLST) of each isolate was performed by a previously described method [11]. Sequence types (STs) were determined by comparing sequences obtained from the current outbreak with those in the pneumococcal MLST database (https://pubmlst.org/spneumoniae/, accessed 4 June 2018).

Whole-genome sequencing and phylogenetic analysis were performed according to our previous study with modification to the removal of single-nucleotide variations (SNVs) on recombinogenic region [12]. To exclude SNVs on recombinogenic regions, SNV clusters (>2 single-nucleotide polymorphisms within 100 bp) were removed. The nucleotide sequence data obtained in this study were submitted to the DNA Data Bank of Japan Sequenced Read Archive under the accession numbers DRX114436–114444.

We identified nine cases of IPD caused by Sp12F during the period from 1 March through 31 May 2016 (Table 1), including two children (22%) and seven adults (78%). Among the nine patients, four (44%) had pneumonia and three (33%) had meningitis. Both children completed PCV13; however, no adults had received PCV13 or PPSV23, although three had the opportunity to receive PPSV23 as part of the NIP. Eight of the nine patients had child contacts. In addition, six of the seven adults (86%) had a smoking history.

Every adult patient had a low Charlson Comorbidity Index score, which indicates that they did not have underlying diseases that increase sepsis risk. The three patients who died had a Pitt Bacteremia Score greater than 4 and were in critical condition on admission. These patients responded poorly to treatment and died on the day, or within a few days, of admission. Interestingly, although patients 2 and 8 did not have underlying diseases, abdominal CT revealed splenic hypoplasia (spleen

### Table 1. Summary of 9 cases of invasive pneumococcal disease caused by serotype 12F

<table>
<thead>
<tr>
<th>No.</th>
<th>Date of onset</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Outcome</th>
<th>Pneumococcal vaccination</th>
<th>Smoking</th>
<th>Child contact</th>
<th>Known immunodeficiency</th>
<th>Splenic volume (cm(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/28</td>
<td>89 years</td>
<td>F</td>
<td>Meningitis, Septic arthritis</td>
<td>Cure</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>−</td>
<td>117</td>
</tr>
<tr>
<td>2</td>
<td>4/1</td>
<td>50 years</td>
<td>M</td>
<td>Pneumonia</td>
<td>Death</td>
<td>0</td>
<td>5</td>
<td>None</td>
<td>+</td>
<td>69a</td>
</tr>
<tr>
<td>3</td>
<td>4/2</td>
<td>73 years</td>
<td>M</td>
<td>Pneumonia</td>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>−</td>
<td>137</td>
</tr>
<tr>
<td>4</td>
<td>4/13</td>
<td>83 years</td>
<td>F</td>
<td>Pneumonia</td>
<td>Death</td>
<td>2</td>
<td>2</td>
<td>None</td>
<td>+</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>4/22</td>
<td>1 year 4 month</td>
<td>M</td>
<td>Occult bacteremia</td>
<td>Cure</td>
<td>0</td>
<td>NA</td>
<td>PCV13 × 4</td>
<td>+</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>4/27</td>
<td>56 years</td>
<td>F</td>
<td>Meningitis</td>
<td>Cure</td>
<td>0</td>
<td>NA</td>
<td>PCV13 × 4</td>
<td>+</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>5/8</td>
<td>59 years</td>
<td>M</td>
<td>Pneumonia</td>
<td>Death</td>
<td>0</td>
<td>7</td>
<td>None</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>5/9</td>
<td>67 years</td>
<td>F</td>
<td>Meningitis</td>
<td>Cure</td>
<td>59</td>
<td>NA</td>
<td>PCV13 × 4</td>
<td>+</td>
<td>180</td>
</tr>
<tr>
<td>9</td>
<td>5/20</td>
<td>1 year 5 month</td>
<td>M</td>
<td>Meningitis</td>
<td>Cure</td>
<td>NA</td>
<td>NA</td>
<td>PCV13 × 4</td>
<td>+</td>
<td>180</td>
</tr>
</tbody>
</table>

WGS, whole-genome sequencing; CCI, Charlson Comorbidity Index; PBS, Pitt Bacteremia Score; NA, not available; PCV13, 13-valent pneumococcal conjugate vaccine.
rent local outbreak of Sp12F is important, because it spread increasing since the introduction of PCV13. In addition, the cur-

Among the 9 isolates of Sp12F, 8 formed a cluster in the SNV-based phylogenetic tree, which varied by 0 or 1 SNV. However, I isolate dif-

To our knowledge, this is the first report of local outbreak caused by Sp12F after the introduction of PCV13. We identified nine cases of IPD (including three adult deaths) that were attrib-

Although Sp12F may be more likely to cause meningitis and can be more invasive than other serotypes, no previous study has reported a brief outbreak of Sp12F affecting both adults and children. Additionally, most past outbreaks were caused by ST218 [1], the present outbreak was caused by ST4846, which was not previously reported. Whole-genome sequencing analyses showed that 8 isolates, which varied by 0 and 1 SNV, were genet-

In Japan, the incidence of IPD decreased in children after the introduction of PCV7; however, IPD caused by non-PCV13 serotypes have been increasing because of serotype replacement [3]. Thus, the total number of IPD has not changed since the intro-

Continuous monitoring of IPD, along with the determination of pneumococcal serotype, is thus mandatory to improve under-

In conclusion, An IPD outbreak caused by genetically identical Sp12F resulted in high morbidity and mortality after the post-PCV era, in Tsuruoka city, Japan. Sp12F could become an important serotype associated with endemic severe IPD. Continuous monitoring of IPD, along with the determination of pneumococcal serotype, is thus mandatory to improve under-

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Conflict of interests. The authors declare that they have no conflicts of interest.

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