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National Institute of Infectious Diseases and
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## <THE TOPIC OF THIS MONTH>
## Pneumococcal infections in 2017, Japan

*Streptococcus pneumoniae* is a gram-positive diplococcus and one of the major respiratory pathogens. *S. pneumoniae* colonizes the nasopharynx of 40 to 60% of infants, and nasopharyngeal carriage plays a pivotal role in horizontal transmission of this pathogen in the community. The capsular polysaccharide (CPS) on the bacterial surface is the most important virulence factor and is also the antigenic determinant of serotypes. Currently, 97 serotypes are known, and the complement-dependent opsonization induced by the serotype-specific antibody is the major host defense mechanism against pneumococcal infections.

*S. pneumoniae* causes non-invasive infectious diseases such as pneumonia, otitis media, and sinusitis in children and adults. Most community-onset pneumonia cases in adults (community-acquired and hospital-acquired pneumonia) are pneumonia not associated with bacteremia, and approximately 20% of the causative bacteria in these cases are *S. pneumoniae*. In addition, *S. pneumoniae* causes invasive pneumococcal disease (IPD) that may be accompanied by meningitis or bacteremic pneumonia. IPD refers to illness with detection of *S. pneumoniae* from normally sterile sites.

**Vaccine and serotype**: Pneumococcal vaccines approved for marketing in Japan include the 23-valent pneumococcal polysaccharide vaccine (PPSV23), the 13-valent pneumococcal conjugate vaccine (PCV13), and the 10 valent pneumococcal conjugate vaccine (PCV10).

With the initiation of a vaccination promotion program for cervical cancer and other vaccine-preventable diseases in November 2010, immunization of children <5 years of age with PCV7 became possible through governmental funding (jointly funded by federal and local jurisdiction levels). PCV7 was included in the routine immunization program in April 2013. In November 2013, PCV13 replaced PCV7 as a routine immunization for children. PCV10 was not added to the routine immunization program. PPSV23 was licensed in Japan in March 1988, and in August 1992, its use became covered by health insurance for the prevention of pneumococcal infections in patients who have undergone splenectomy. PPSV23 was included in the routine immunization program starting in October 2014 for individuals aged 65 years and those aged 60-64 years who have heart, kidney, or respiratory disorders or immunity-related disorders caused by human immunodeficiency virus. Currently, an interim routine immunization program is in place for five years until March 2019, for select age groups among adults ≥65 years of age. In addition, PCV13 was licensed for adults ≥65 years of age in June 2014, available on a voluntary basis.

**Laboratory diagnosis**: *S. pneumoniae* is identified by methods such as alpha-hemolysis using blood agar, a bile solubility test, or an optochin test. While determination of serotype is carried out by capsule-quelling reaction, serotyping based on multiplex PCR targeting serotype-specific genes is also useful as a screening method (see pp. 110&111 of this issue).

**National Epidemiological Surveillance of Infectious Diseases (NESID)**: IPD was included in the list of category V infectious diseases in April 2013. A total of 11,170 (male to female ratio of 1.49: 1) cases were reported from April 2013 to December 2017. The reported number of cases increased annually (Table, Figure 1 in p. 108). The number of cases tended to increase from winter to spring. The reported number of cases per 100,000 population also increased annually, and in 2017, there were 2.53 cases for the total population, 9.47 for children <5 years of age, and 5.38 for adults ≥65 years of age (Table). A bimodal peak of IPD cases was observed in children and the elderly; the proportions of cases <5 years of age was 17% and those ≥65 years of age was 56% (Figure 2).

Table. Reported cases of invasive pneumococcal disease, April 2013-December 2017

| Year of diagnosis | No. of cases | | | No. of cases per 100,000 | | | No. of fatal cases at the time of notification (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Age group (year) | | Total | Age group (year) | | Total | Age group (year) | |
| | | <5 | ≧65 | | <5 | ≧65 | | <5 | ≧65 |
| 2013 | 1,006 | 261 | 478 | 0.79 | 4.98 | 1.50 | 67(6.7%) | 1(0.4%) | 46(9.6%) |
| 2014 | 1,841 | 362 | 977 | 1.45 | 6.94 | 2.96 | 114(6.2%) | 5(1.4%) | 85(8.7%) |
| 2015 | 2,365 | 392 | 1,309 | 1.86 | 7.54 | 3.86 | 147(6.2%) | 2(0.5%) | 109(8.3%) |
| 2016 | 2,747 | 403 | 1,589 | 2.16 | 8.12 | 4.59 | 186(6.8%) | 3(0.7%) | 147(9.3%) |
| 2017 | 3,211 | 466 | 1,891 | 2.53 | 9.47 | 5.38 | 196(6.1%) | 3(0.6%) | 156(8.3%) |

*%=fatal cases/total cases (National Epidemiological Surveillance of Infectious Diseases: as of June 1, 2018)

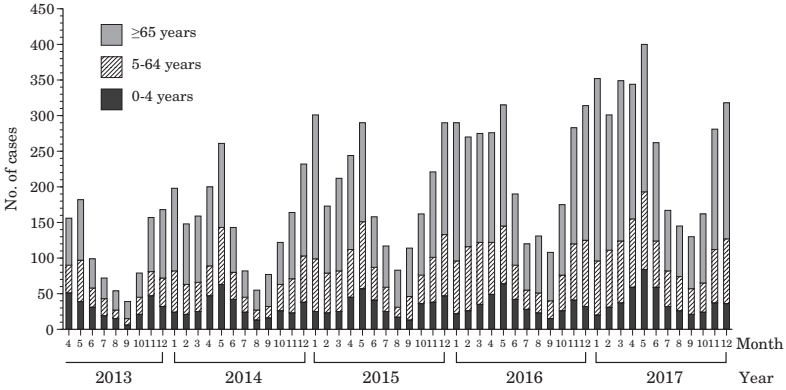
(Continued on page 108′)

(THE TOPIC OF THIS MONTH-Continued)

As for clinical presentations among cases <5 years of age, 9% were meningitis, 17% bacteremic pneumonia (pneumonia), and 57% bacteremia without any focal sign (bacteremia). Among cases ≥65 years of age, the respective proportions were 10%, 51%, and 29%. The proportion of fatal cases among all reported cases at the time of report was 6.1% in 2017; this was 0.6% in cases <5 years of age and 8.3% in cases ≥65 years of age (Table in p.107).

Approximately 5,000 cases of penicillin-resistant *S. pneumoniae* (PRSP) infections were reported annually from designated sentinel hospitals between 2008 and 2011. In contrast, the annual number of cases declined to around 2,000 after 2015. In addition, the reported number of IPD cases due to PRSP similarly decreased (see p.109 of this issue).

Figure 1. Monthly number of reported invasive pneumococcal disease cases, April 2013-December 2017 (n=11,170)

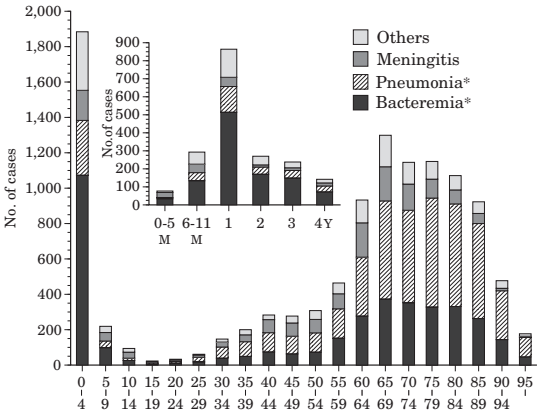



(National Epidemiological Surveillance of Infectious Diseases: as of June 1, 2018)

**IPD surveillance**: According to the report on pediatric IPD surveillance (Suga study group, supported by a grant from the Japan Agency for Medical Research and Development), the incidence of IPD in children in 2013 decreased by 57% compared with that in the period from 2008 to 2010, before the introduction of PCV. Following replacement with PCV13 in November 2013, the incidence of IPD caused by PCV13 types decreased by 97% in 2017. However, the incidence of IPD for non-PCV13 types increased by 304%, indicating serotype replacement (see p. 112 of this issue).

According to the report on adult IPD surveillance (Oishi study group, supported by a grant from the Ministry of Health, Labour and Welfare of Japan), the median age of 897 patients was 71 years, 61% were male, 75% had comorbidities, and 31% had an immunocompromised condition. Clinically, 60% presented as pneumonia, 16% as bacteremia, 15% as meningitis, and 8% as other. The proportion of cases with fatal outcomes at the time of report was 19%. Serotype distribution of the causative bacteria suggested an indirect effect of PCV introduction in children (see p. 114 of this issue). For adult IPD cases in the 2017 fiscal year, the distribution of causative bacteria were 7.3% PCV7 serotype, 31% PCV13 serotype, and 64% PPSV23 serotype. In addition, as part of the National Epidemiological Surveillance of Vaccine-Preventable Diseases program, the serotype of the causative bacteria among IPD cases is being investigated (see p. 110 of this issue).

Figure 2. Age distribution of invasive pneumococcal disease cases, April 2013-December 2017 (n=11,170)




*Pneumonia denotes bacteremic pneumonia, and bacteremia denotes bacteremia without any focal sign

(National Epidemiological Surveillance of Infectious Diseases: as of June 1, 2018)

**Pneumococcal pneumonia surveillance**: According to pneumococcal pneumonia surveillance in adults, the respective proportions of the PCV13 serotype and PPSV23 serotype were 54% and 67% for the causative bacteria in 2012, but the respective proportions declined to 32% and 49% in 2016. This was also thought to be an indirect effect of PCV in children (see p. 117 of this issue). Since the recombination of genes occurs frequently in *S. pneumoniae*, changes in the serotype due to such recombination, so-called capsule switching, is known to occur. Therefore, whole genome sequence analysis is required when investigating a cluster of pneumococcal infection cases involving different serotypes (see p. 118 of this issue).

**Vaccine effectiveness of PPSV23**: The vaccine effectiveness (VE) of PPSV23 for preventing IPD was analyzed based on the adult IPD surveillance data. The estimated VE was 45% for PPSV23 type IPD, and 87% for 12F type IPD. The estimated VE of PPSV23 vaccination for adults ≥65 years of age was 39% (see p. 115 of this issue). VE of PPSV23 in preventing pneumococcal pneumonia in adults ≥65 years of age was also analyzed, employing the test-negative design. The estimated VE was 27.4% for all pneumococcal pneumonia, and 33.5% for PPSV23 type pneumococcal pneumonia (see p. 117 of this issue).

**Preventive measures**: The national vaccination program for pneumococcal vaccine targeting children <5 years and adults ≥65 years of age who are at increased risk of pneumococcal infections, including IPD, is currently in place. The immunogenicity of PPSV23 in allogenic hematopoetic stem cell transplantation recipients, who are at high-risk of IPD, has also been reported (see p. 119 of this issue). While the cumulative vaccination coverage of PCV13 in children was high (97% for the first dose and 94% for the additional dose) (https://www.niid.go.jp/niid/images/vaccine/cum-vaccine-coverage/cum-vaccine-coverage_28.pdf), the vaccination coverage of PPSV23 for adults ≥65 years has remained at around or under 40% (see p. 121 of this issue). Increasing the vaccination coverage of PPSV23 for adults ≥65 years is warranted from the perspective of individual-level protection. Serotype distribution of pneumococcal isolates should be monitored continuously as the possibility of serotype replacement in children and adults in the future remains.

*The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.*

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