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National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Pneumococcal infections as of March 2013

Streptococcus pneumoniae is a gram-positive diplococcus causing respiratory infections. The capsular polysaccharide (CPS) that encapsulates the microorganism is an important virulence factor and, at the same time, the antigenic determinant of the serotype. Ninety-three serotypes are known. The complement-dependent opsonization induced by the serotype-specific antibody is the major host defense mechanism.

Many children carry *S. pneumoniae* in the nasopharyngeal cavity (see p. 57 of this issue), which often causes otitis media and pneumonia (see p. 58 of this issue). Most of the adult cases of community-acquired pneumonia are not associated with bacteremia, and *S. pneumoniae* is responsible for 20-40% of such cases (see p. 59 of this issue). Once it invades the blood stream, *S. pneumoniae* causes invasive pneumococcal disease (IPD) (see pp. 61 & 62 of this issue). IPD is defined as any condition in which *S. pneumoniae* is present in blood, cerebrospinal fluid or another normally sterile body site. IPD consists of meningitis and "non-meningitis bacteremia" associated with pneumonia, sepsis, etc.

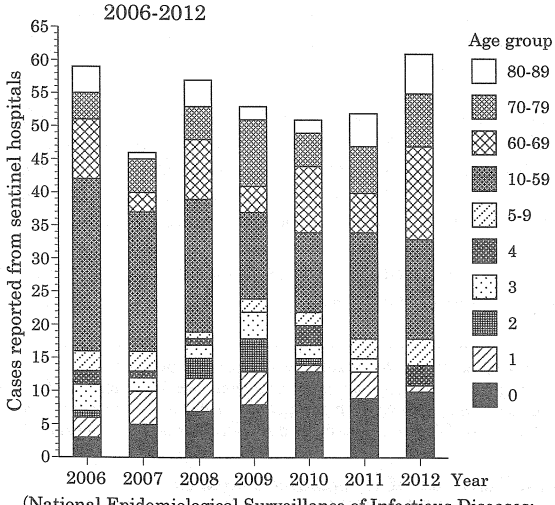
Vaccines and serotypes: Two types of pneumococcal vaccines have been approved in Japan, i.e., 23-valent CPS vaccine (PPV23) and 7-valent conjugate vaccine (PCV7). The antigen contained in PPV23 is CPS, a T-cell independent antigen, which cannot induce memory B cells and is devoid of booster effect upon the second shot. The antigen contained in PCV7 is CPS conjugated with diphtheria toxin mutant CRM_{197}. It induces serotype-specific (i.e., anti-CPS) IgG antibody even in young children, as it induces antibody production in T-cell dependent manner.

PPV23 obtained the pharmaceutical approval in Japan in 1988. Previous studies demonstrated that "PPV23 reduced the risk of IPD caused by vaccine serotypes in immunocompetent aged persons" (Jackson LA, *et al.*, Clin Infect Dis 47: 1328-1338, 2008). More recent studies in Japan demonstrated that PPV23 protected the aged persons from pneumococcal pneumonia and reduced their medical cost (Maruyama T, *et al.*, BMJ 340: c1004, 2010, Kawakami K, *et al.*, Vaccine 28: 7063-7069, 2010).

PCV7 obtained the pharmaceutical approval in Japan in October 2009. Since November 2010, when "vaccination promotion program of cervical cancer and other vaccine preventable diseases" started, immunization of PCV7 among children less than 5 years of age has been subsidized by public money.

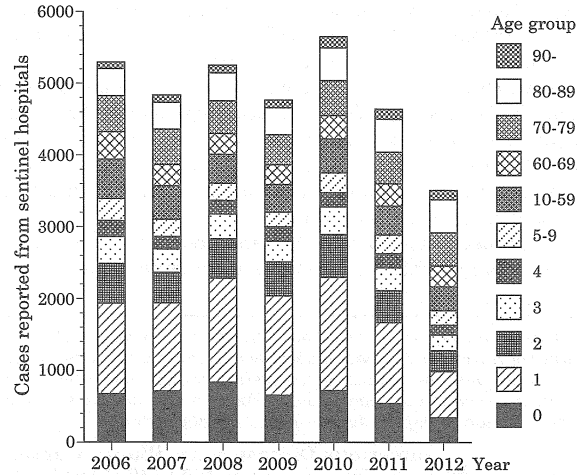
According to "Research report on evidence of and measures for improvement of usefulness of vaccination" (Ihara-Kamiya Research Project that started in 2007), incidence of IPD per 100,000 population under the age of five decreased significantly owing to the immunization program. Namely, meningitis decreased from 2.8 in 2008-2010 to 0.8 in 2012 (decrease by 71%), and non-meningitis IPD from 22.2 to 10.6 (decrease by 52%) (see p. 62 of this issue).

Figure 1. Pneumococcal meningitis cases by age group, 2006-2012



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 31, 2013)

Figure 2. Cases of penicillin-resistant *Streptococcus pneumoniae* infection by age group, 2006-2012



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 31, 2013)

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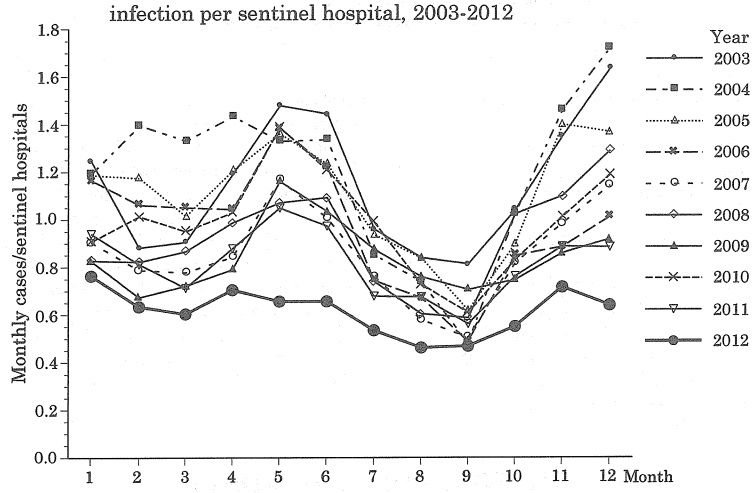
(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Monthly cases of penicillin-resistant *Streptococcus pneumoniae* infection per sentinel hospital, 2003-2012



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 31, 2013)

About 70% of the *S. pneumoniae* isolates from pediatric IPD cases have been determined for the serotype. Before the start of the public subsidy, predominant serotypes were 6B followed by 14, 23F and 19A. Later than April 2011 (about 5 months after the start of subsidy), the order was changed to 19A, followed by 6B, 14, and 23F. During the same period, serotypes 19A, 15A, 15B, 15C, 22F and 6C that were not included in the antigens of PCV7 increased in proportion and in number (see p. 64 of this issue), while PCV7 serotypes as a whole decreased in proportion (from 78.3% to 44.4%) and in number. These findings suggest that the serotype replacement occurred within 2 years after the introduction of PCV7.

National Epidemiological Surveillance of Infectious Diseases (NESID): Surveillance of *S. pneumoniae* infections has not been conducted as such. It has been done as surveillance of bacterial meningitis including *S. pneumoniae* infection (category V infectious disease that requires weekly report from sentinel hospitals*) and penicillin-resistant *S. pneumoniae* (PRSP) infections (category V infectious disease that requires monthly report from sentinel hospitals*). For criteria of notification, see http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01.html.

*There are about 500 sentinel hospitals in Japan, which are selected from those equipped with departments of pediatrics and internal medicine and with more 300 beds.

1) Bacterial meningitis caused by *S. pneumoniae*: From 2006 to 2012, the total number of reports from sentinel hospitals remained in the same level, 40-60 cases per year, though patients in 2-3 years of age decreased in 2012. The age of patients is distributed widely from 0 to ≥80 years (Fig. 1).

2) PRSP infections: From 2006 to 2011, annual report from sentinel hospitals was around 5,000. In 2012, it decreased to 3,500 owing particularly to the decrease of patients less than 5 years of age (Fig. 2). The age distribution was wide from 0 to ≥90 years. There were two seasonal peaks in May and December every year since NESID of PRSP infections started in 1999 (See Fig. 3, which shows the trend since 2003). In 2012, when the total annual incidence decreased dramatically, the two peaks disappeared.

Laboratory diagnosis: *S. pneumoniae* is identified by hemolytic pattern on the blood agar (α-hemolysis), bile solubility test, optochin test, etc. The serotyping is usually done by capsule quellung reaction, but serotyping using multiplex PCR is also useful as a screening method (see p. 67 of this issue). Quantification of serotype-specific IgG (μg/ml) using ELISA for assaying the humoral immunity and the multiplex opsonization assay (MOPA) for assaying the serotype-specific opsonization activity are available in some research institutes (see p. 66 of this issue).

Therapy: The first choice is penicillin antibiotics. However, the proportion of PRSP among *S. pneumoniae* isolates increased from 1985 and reached 63% in 2009. Eighty-eight percent of *S. pneumoniae* isolates are now resistant to macrolide antibiotics. However, a high dose of β-lactam antibiotic is effective to most cases of community-acquired pneumonia or of non-meningitis infections caused by PRSP. A high dose of β-lactam antibiotic in combination with vancomycin is recommended for treatment of meningitis cases caused by PRSP.

Future Challenges: In March 2013, the government submitted a bill to the Diet to modify the Preventive Vaccination Law to include PCV7, *Haemophilus influenzae* type b (Hib) and human papilloma virus (HPV) vaccines in the routine immunization. From April 1 of 2013, "invasive *S. pneumoniae* infection", together with "invasive *H. influenzae* infection", becomes a category V infectious disease that requires the notification of all the cases. At the same time, "meningococcal meningitis", a category V infectious disease that required notification of all the cases will be revised to "invasive meningococcal infection" including non-meningitis meningococcal bacteremia.

Medical institutions, health centers, prefectural and municipal public health institutes, and National Institute of Infectious Diseases should intensify the infectious agent surveillance of *S. pneumoniae* including serotyping.

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 Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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