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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>
Invasive *Haemophilus influenzae* infections in Japan

Haemophilus influenzae is a small Gram-negative bacillus. It is carried by many infants in their nasopharyngeal cavities (see p. 193 of this issue). There are two clinical types; the one is systemic invasive type and the other is localized non-invasive type. The systemic invasive type is generally severe and the bacteria can be found in otherwise aseptic sites, such as, blood, cerebrospinal fluid, etc. *Haemophilus influenzae* is classified into the encapsulated strains and the non-typable strains. *Haemophilus influenzae* with capsular type b (Hib) is the major cause of the infantile invasive *H. influenzae* infections (see p. 187 of this issue). Non-typable *H. influenzae* (NTHi) is a major cause of non-invasive bacterial infections among infants and adults (e.g. otitis media and exacerbation of chronic obstructive pulmonary diseases, etc.).

Capsular type and Hib vaccine: Encapsulated strains are classified into 6 capsular types from a to f. Capsular type is determined by bacterial agglutination test using capsular antigen-specific antibodies or by capsular type-specific gene amplification using polymerase chain reaction (PCR) (see p. 192 of this issue) (see Laboratory Manual for Bacterial Meningitis in Pathogen Detection Manual, http://www.nih.go.jp/niid/images/lab-manual/hib-meningitis.pdf).

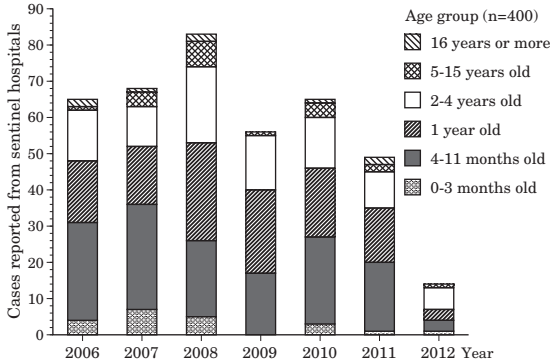
In Japan, a tetanus toxoid conjugated Hib vaccine (Hib vaccine in short) has been used since December 2008. Since November 2010, the Hib vaccine to children of less than 5 years of age has been paid by the public under the "Program of accelerated vaccination with cervical cancer and other vaccines". In April 2013, the immunization act was revised to include Hib vaccine in the routine immunization. The routine vaccination consists of three shots to children aged two months to less than seven months, which is followed by the fourth booster shot one year after the third shot (see p.199 of this issue).

The antigen determinants are capsular polysaccharides (polyribosylribitol phosphate: PRP) present on the bacterial surface. Protection from infection is mediated by antibodies against serotype-specific PRP. The immunogenicity of Hib vaccine is evaluated by ELISA titration of serum anti-PRP IgG or by serum bactericidal assay (SBA), which measures bactericidal activity of serum by using Hib as a target (see p.190 of this issue).

Epidemiological situation: Until April 2013 when the Enforcement Regulations for the Infectious Diseases Control Law were revised, meningitis caused by *H. influenzae* had been reported as "bacterial meningitis" together with other bacterial meningitis. They were reported from about 500 sentinel hospitals in Japan. Total 347-477 bacterial meningitis cases were reported annually from 2006 to 2010, among which 56-83 were due to *H. influenzae* (Table 1). Among the total 400 *H. influenzae* meningitis cases reported in 2006-2012, 372 cases (93%) were patients younger than 5 years. Thanks to the public payment of Hib vaccine, the frequency of *H. influenzae* meningitis decreased to 49 cases in 2011 and to 14 cases in 2012. The reduction was found mainly among patients younger than 2 years of age (Fig. 1).

After the revision of the Enforcement Regulations for the Infectious Diseases Control Law, invasive infections by *H. influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* became category V infectious diseases, which require reporting of all the cases. Accordingly, these infections are now excluded from the category of “bacterial

Figure 1. Number of annually reported *Haemophilus influenzae* meningitis cases by age, 2006-2012



(National Epidemiological Surveillance of Infectious Diseases: As of May 15, 2013)

Tabel 1. Number of annually reported bacterial meningitis cases that were caused by different pathogens, 2006-2012

Pathogen	2006	2007	2008	2009	2010	2011	2012	Total
Haemophilus influenzae	65	68	83	56	65	49	14	400
Streptococcus pneumoniae	59	46	57	53	51	52	61	379
Streptococcus agalactiae (GBS)	7	10	10	9	23	24	23	106
Other bacteria	53	59	69	80	90	89	126	566
Not detected	27	15	8	11	26	24	42	153
Not specified	136	181	179	252	222	272	200	1,442
Total	347	379	406	461	477	510	466	3,046

(National Epidemiological Surveillance of Infectious Diseases: As of May 15, 2013)

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(THE TOPIC OF THIS MONTH-Continued)

Table 2. Number of invasive *Haemophilus influenzae* infections reported from week 14 (April 1-7) to week 23 (June 3-9) of 2013 (n=31)

Week of diagnosis	Prefecture	Gender	Age	Meningitis	Bacteremia	Hib vaccination history*	Remark
18	Tokyo	Male	0 month	No	Yes	No	
19	Fukuoka	Female	2 month	Yes	Yes	Unknown	
23	Chiba	Female	9 month	No	Yes	Unknown	
22	Ibaraki	Female	1	No	Yes	Unknown	
18	Tokyo	Male	1	No	Yes	Yes, 4 times	Pneumonia
14	Tokyo	Female	5	No	Yes	Yes, once	
19	Hyogo	Female	14	No	Yes		
20	Kanagawa	Male	19	No	Yes		Pneumonia
21	Hokkaido	Male	24	No	Yes		Pneumonia
23	Tokyo	Female	59	No	Yes		Pneumonia
21	Shiga	Male	65	No	Yes		Pneumonia
23	Ibaraki	Male	68	No	Yes		Pneumonia
18	Aichi	Male	69	No	Yes		Death
16	Kanagawa	Male	71	No	Yes		Pneumonia
17	Kanagawa	Male	71	No	Yes		
17	Okinawa	Female	74	No	Yes		Pneumonia
20	Okinawa	Male	77	No	Yes		Pneumonia
19	Fukuoka	Male	80	No	Yes		Pneumonia
18	Gunma	Female	81	No	Yes		Pneumonia
23	Aichi	Male	81	No	Yes		Pneumonia
22	Osaka	Female	82	No	Yes		Pneumonia, death
14	Okayama	Male	82	No	Yes		Pneumonia
18	Ibaraki	Male	83	No	Yes		
20	Shiga	Male	87	No	Yes		Pneumonia
18	Hyogo	Male	89	No	Yes		
14	Tokyo	Female	89	No	Yes		Pneumonia, type b
19	Yamagata	Female	90	No	Yes		
23	Kanagawa	Male	91	No	Yes		
21	Aichi	Female	92	No	Yes		Pneumonia
18	Wakayama	Male	92	No	Yes		
15	Fukuoka	Female	95	No	Yes		Death

* From November 2010 to March 2013, Hib vaccine for children aged from 2 months to 4 years was covered by public fund and in April 2013 it was incorporated in the routine immunization.

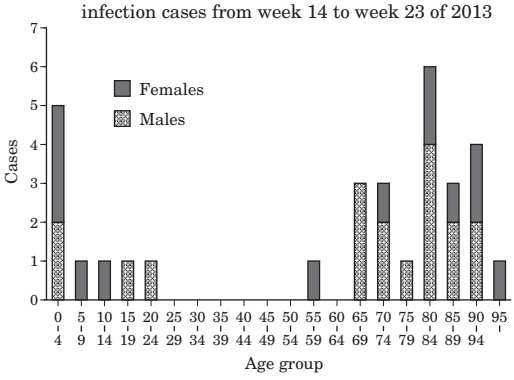
(National Epidemiological Surveillance of Infectious Diseases: As of June 12, 2013)

meningitis".

The notification criterion for "invasive *H. influenzae* infection" (including Hib meningitis) is the case, from whose cerebrospinal fluid or blood *H. influenzae* is detected by isolation of bacteria or by detection of bacterial DNA (http://www.nih.go.jp/niid/images/iasr/34/401/de4011.pdf).

Table 2 lists 31 invasive *H. influenzae* infection cases notified under the National Epidemiological Surveillance of Infectious Diseases (NESID) since April 2013 (14th to 23rd week). In Fig. 2 that shows the age distribution, there are two peaks, the one in young children and the other in adults above 60 years of age. Most cases in the aged group were *H. influenzae* pneumonia associated with bacteremia. Three among them died. Capsular type was determined only in one case, which was capsular type b.

Figure 2. Age distribution of invasive *Haemophilus influenzae* infection cases from week 14 to week 23 of 2013



(National Epidemiological Surveillance of Infectious Diseases: As of June 12, 2013)

According to the data from 10 prefectures in Japan (Ihara-Kamiya Research Group: "Research on evidence and recommended policies on better use of vaccinations" started in 2007), the frequency of invasive *H. influenzae* infection per 100,000 population under 5 years of age was 7.7 for meningitis type and 5.1 for non-meningitis type in 2008-2010. In 2012 the frequency went down to 0.6 for meningitis type (reduction by 92%) and to 0.9 (reduction by 82%) for non-meningitis type (see p. 194 & 195 of this issue). The similar tendency was noted in the nation-wide surveillance data obtained by Japan Nosocomial Infections Surveillance: JANIS (see p. 197 of this issue).

Emergence of drug-resistant strain: There are two types of drug resistant *H. influenzae* strains known, β-lactamase producers and β-lactamase non-producers. The frequency of the β-lactamase-non-producing ampicillin-resistant (BLNAR) isolate is increasing in recent years (see p. 192 & 195 of this issue), which should be further monitored (see IASR 31: 92-93, 2010; http://idsc.nih.go.jp/iasr/31/362/tpc362.html & IASR 23: 31-32, 2002; http://idsc.nih.go.jp/iasr/23/264/tpc264.html).

Measures to be taken: Increase of invasive *H. influenzae* infection caused by non-b type *H. influenzae* (including NTHi) after introduction of Hib vaccine has been reported in abroad. In Japan, a meningitis case of *H. influenzae* capsular type f was reported among those who had received three Hib vaccine shots (see p. 195 of this issue). Invasive NTHi infections have been reported among infants and adults (see p. 188 & 189 of this issue). Accordingly, surveillance of invasive *H. influenzae* infections after introduction of routine immunization of Hib vaccine should be directed not only to Hib itself but also to *H. influenzae* of other capsular types and NTHi. Pathogen surveillance of *H. influenzae*, including capsular type analysis, is planned as an activity of the National Epidemiological Surveillance of Vaccine Preventable Diseases infection source investigation from 2013FY.

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, and quarantine stations, have provided the above data.

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