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

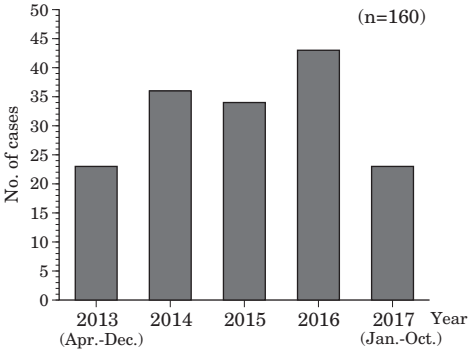
<THE TOPIC OF THIS MONTH>
Invasive meningococcal infection, April 2013-October 2017, Japan

Neisseria meningitidis is a gram-negative diplococcus. It can be isolated from the nasopharynx of healthy persons, albeit infrequently, and is transmitted by droplet aerosol or secretions from colonized persons. There are four classifications of invasive infection, namely, bacteremia without sepsis, sepsis unassociated with meningitis, meningitis and meningoencephalitis. Development of sepsis has poor prognosis. Waterhouse-Friderichsen syndrome is an acute fulminant form, manifesting as adrenal bleeding and/or systemic shock. Noninvasive presentation includes various manifestations, such as pneumonia and urethritis. Incubation period ranges from 2-10 days (average of 4 days) and the disease onset is sudden.

Changes over time in the notification conditions associated with meningococcal infections: In Japan, since the time prior to the Second World War, diseases associated with meningococcal infection had been notified as "epidemic cerebrospinal meningitis" under the Communicable Diseases Prevention Law; circa 1945, approximately 4,000 cases were reported annually. Since then, notifications of case patients decreased substantially, declining to <100 since 1969 and to <30 since 1978. Under the Infectious Diseases Control Law, enforced in April 1999, meningococcal meningitis became classified as a category IV notifiable infectious disease (In November 2003, it was changed to a category V infectious disease). From 1999 to March 2013, 7-21 cases were reported annually (IASR 34: 361-362, 2013). In addition, following the serogroup B meningococcal outbreak experience in a high school dormitory in Miyazaki Prefecture in May 2011, where multiple cases of meningitis and non-meningitis (e.g., sepsis) cases occurred (IASR 32: 298-299, 2011; IASR 34 367-368, 2013), meningococcal meningitis became newly designated as a category II school infectious disease under the School Health and Safety Act in April 2012.

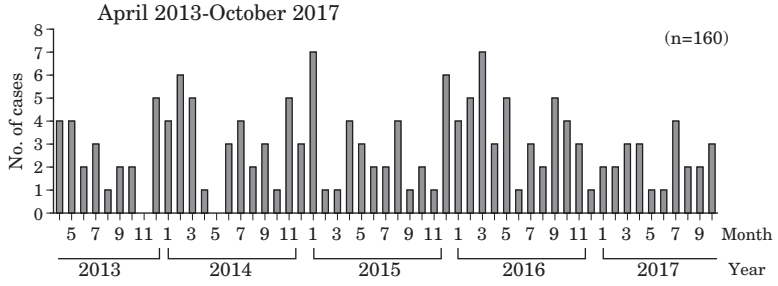
Amendment to the notification conditions regarding invasive meningococcal infection in 2013 and epidemiological trends since April 2013: Given the above situation, in April 2013, meningitis and sepsis caused by *N. meningitidis* became notifiable as "invasive meningococcal infection", classified as a category V infectious disease (notification criteria in http://www.niid.go.jp/niid/images/iasr/34/406/de4061.pdf). Since then, through October 2017, a total of 160 cases were notified (Fig. 1). Though a clear seasonality cannot be discerned, notifications tended to increase from November to March (Fig. 2).

Figure 1. Reported number of invasive meningococcal infection cases in Japan, April 2013-October 2017



(National Epidemiological Surveillance of Infectious Diseases: as of November 29, 2017)

Figure 2. Monthly number of reported invasive meningococcal infection cases, April 2013-October 2017



(National Epidemiological Surveillance of Infectious Diseases: as of November 29, 2017)

In addition, since 21 May 2015, there was a change in the notification requirement from "within 7 days of diagnosis" to "immediate" notification. And, since 21 November 2016, detection of the pathogen was no longer limited to those from blood or cerebrospinal fluid, and case patients with detection of the pathogen from other sterile sites also became notifiable.

Gender and age distribution (Fig. 3): Among the cases reported from April 2013 to October 2017, the male-to-female ratio was about 3:2, and many cases were those aged 0-4 years, 15-19 years, and those in their 40s to early 70s. Based on the information at the time of notification, two thirds of the reported deaths were among those aged in their 10s to 50s. Among invasive meningococcal infection cases, reported as such since 2013, the case-fatality rate at the time of notification was 15.0% (24/160).

Serogroup distribution: *N. meningitidis* species are classified into 12 serogroups based on the difference in their capsular polysaccharides, and such serogroup information from clinical isolates is imperative for vaccine selection. The majority of invasive infections are caused by serogroups A, B, C, Y and W. From April 2013 to October 2017, there were 160 reported cases of

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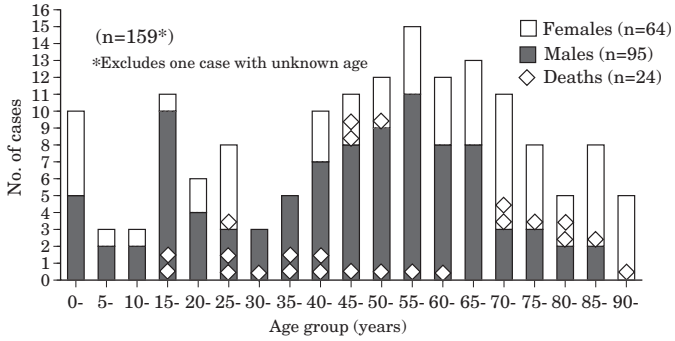
(THE TOPIC OF THIS MONTH-Continued)

invasive meningococcal infection, and among them, serogroup information was obtained from 116 (72.5%) cases (Fig. 4). Serogroup Y was the most frequent serogroup (75 cases), followed by serogroup B (15 cases), serogroup C (13 cases) and serogroup W (5 cases). In addition, there were 4 cases that could not be distinguished between serogroup Y and W and 4 non-typable strain cases (Fig. 4). In the past, serogroup B was considered to be predominant but recently serogroup Y is dominant in Japan (see p. 3 of this issue).

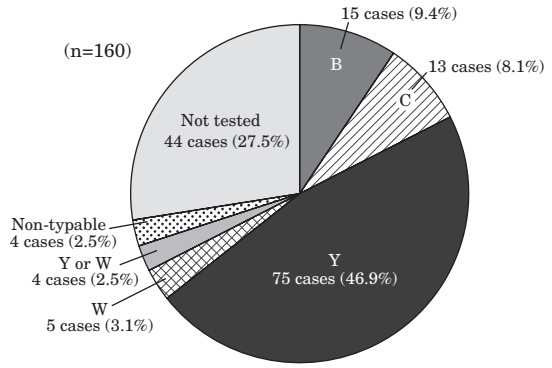
The Department of Bacteriology I of the National Institute of Infectious Diseases (NIID) conducts high precision molecular epidemiologic analyses, using multilocus sequence typing (MLST) and referencing the results to the international database. From April 2013 to October 2017, 77 isolates were collected. While the majority of the domestic isolates belonged to known genotypes such as ST-23 complex and ST-41/44 complex, some isolates could not be genotyped, indicating the emergence of meningococci different from preexisting ones, and signifying the necessity for molecular epidemiologic analysis of *N. meningitidis* (see p. 3 of this issue).

Figure 3. Age distribution of invasive meningococcal infection cases by gender, April 2013-October 2017



(National Epidemiological Surveillance of Infectious Diseases: as of November 29, 2017)

Figure 4. Serogroups of *Neisseria meningitidis* isolates from invasive meningococcal infection cases, April 2013-October 2017



(Based on results of tests performed at NIID and data from the National Epidemiological Surveillance of Infectious Diseases, as of November 29, 2017)

Treatment and vaccines: For treatment, intravenous administration of penicillin G, ampicillin or third generation cephem antibiotics is used. In the case of an occurrence of a patient with invasive meningococcal infection, for preventing further transmission, it is recommended that notification be made immediately to the public health center, with rapid contact investigation and post-exposure prophylaxis of close contacts as soon as possible (IASR 34: 366-367, 2013). For post-exposure chemoprophylaxis, ciprofloxacin, rifampicin or ceftriaxone have been frequently used, as the domestic isolates have been known to be generally sensitive to most antibiotics; however, as the quinolone-resistant strain has been detected from recent domestic isolates, caution is needed in the selection of antibiotics (IASR 38: 83-84, 2017).

The quadrivalent meningococcal conjugate vaccine that protects against four (A, C, Y and W) of the 12 serogroups received approval for domestic production in July 2014, and the products were placed on the market in May 18, 2015. Thus, while limited to certain serogroups, the prevention of invasive meningococcal infection and vaccination of close contacts have become possible in Japan. Since this vaccine available domestically is ineffective against serogroup B, serogroup information from invasive meningococcal infection patients is becoming increasingly important from the standpoint of response.

Outbreaks abroad and risk factors: In the "meningitis belt" region in sub-Saharan Africa, serogroup A was predominant, but after the vaccination campaign, other meningococcus serogroups are being detected. In Europe, the United States and Australia, B, C and Y serogroups make up the majority of the serogroups (see p. 8 of this issue). While cyclical epidemics continue to occur in the meningitis belt, sporadic cases and outbreaks at student dormitories are reported in developed countries. Since meningococcal disease has the ability to cause serious public health impact and to spread rapidly internationally, the International Health Regulations list meningococcal infection as a disease of "special national or regional concern" in Annex 2 (http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf).

Risk factors for invasive meningococcal infection include those such as the Hajj, mass gatherings such as international events where there is a large number of participants, and settings such as student dormitories where there is communal living. (see p. 4 of this issue). Many of the cases reported domestically have often lacked overseas travel history (see p. 7 of this issue), indicating a need to recognize that infection can also occur domestically. In the situation of case occurrence, rapid notification and implementation of epidemiological investigation are necessary as infection prevention measures (see p. 5 of this issue). For the development of interventions, the analysis of the bacterial isolates is important, allowing for the importation route of meningococci to be traced and potential domestic transmissions to be detected. Therefore, close collaboration and strengthening the network among the clinical setting, local governments, prefectural and municipal public health institutes and NIID is necessary.

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 Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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