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National surveillance for meningococcal disease in Japan, 1999–2014

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ABSTRACT

We summarize the epidemiology of Japanese meningococcal disease with serogroup distribution. One hundred seventy-eight meningococcal meningitis cases were reported from April 1999 to March 2013 to the national surveillance system. From April 2013, bacteremia was added to the condition of reporting invasive meningococcal disease (IMD). Since then, 59 IMD cases were reported by the end of 2014. Approximately two thirds of the cases were male and the median age was 56 years (range: 0–93 years). Only 3% of the cases were <5 years old. One third of reported cases were meningitis and the others were bacteremia. The annual incidence (2014) for IMD was 0.028 per 100,000 and case fatality rate (CFR) was 19%. Serogroup Y (42%) was the most dominant serogroup, followed by C (12%), B (7%) and W (3%). Even though the number of reported cases has increased after the amendment of reporting requirements, the incidence of IMD is still low in Japan. Underreporting may play a role in this low incidence. Improving on the limitations of the surveillance system is necessary to capture the true epidemiology and accurate serogroup distribution of IMD cases in Japan, which is essential for making effective recommendations on newly licensed vaccine.

1. Introduction

Neisseria meningitidis causes invasive infections, such as meningitis, bacteremia, and pneumonia. There are at least 12 serogroups, but the majority of invasive meningococcal infections are caused by serogroups A, B, C, X, Y, or W [1].

The annual number of meningococcal infections worldwide is estimated to be at least 1.2 million, with 135,000 deaths [2].

Although *N. meningitidis* is isolated worldwide, the estimated incidence and predominant serogroups of invasive meningococcal disease (IMD) is quite different by countries. In western pacific regions, published data for population based incidence and serogroup distribution of IMD were very limited. China, Korea, Philippines, Singapore and Taiwan were reported to be low incidence level of IMD, less than 0.2 cases per 100,000 per year [3,4].

In Japan, more than 4000 cases of meningitis were reported during the first half of the 1900s in an epidemic that peaked around 1945. Cases subsided sharply after the war, and less than 100 cases were reported in 1969. Subsequently, decreased to less than 30 cases per year in 1978 and to a single digits in the 1990s. These declines were seen in the absence of active control measures for meningococcal diseases such as vaccination.

Since then, 7–21 cases have been reported annually [5]. All reported cases have been sporadic except for one outbreak [6].

Recently, while not included as a routine vaccination, meningococcal ACWY conjugate vaccine (MCV4) has been approved for licensure in July 2014 and on market since May 2015 in Japan. To make a good use of available vaccine, understanding the current epidemiology and serogroup distribution of IMD cases is necessary. Thus, we summarize the epidemiology of IMD including serogroup distribution in Japan.

2. Materials and methods

2.1. Surveillance for meningococcal diseases in Japan

In 1999, meningococcal meningitis was designated as a notifiable disease regulated by the Infectious Disease Control Law in Japan. Since April 2013, bacteremia has been added to a reportable condition with meningococcal meningitis and categorized as IMD [5]. Physicians in all clinics and hospitals ought to notify for all cases to local public health authorities within 7 days after diagnosis. Physicians are required to report demographic information,

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syndrome, exposure history and evidence for diagnosis about every patient meeting the case definition. All of the case data were condensed to the National Epidemiological Surveillance of Infectious Diseases (NESID) system.

2.2. Case definition

Case definition for meningococcal meningitis and invasive meningococcal disease (IMD) are as following:

Meningococcal meningitis: isolation of *N. meningitidis* from blood or cerebrospinal fluid with symptoms of meningitis.

Invasive meningococcal disease (IMD): isolation of *N. meningitidis* or detection of *N. meningitidis* specific gene from blood or cerebrospinal fluid with symptoms of meningitis or bacteremia.

2.3. Data and isolates collection for cases

Information on meningococcal meningitis cases and IMD cases were retrospectively collected. Serogrouping of causative isolates was conducted by either Department of Bacteriology I, National Institute of Infectious Diseases (NIID) Japan or prefectural and municipal public health laboratories. Serogroups of causative isolates are not mandatory to be reported to NESID system. Thus, if the serogroup information was missing, we actively contacted local health department and/or municipal public health laboratories whether laboratory testing for serogroups has been conducted. If not, we made efforts to collect meningococcal isolates for further testing. In some cases, serogroups were determined by using commercial based latex agglutination kit in hospital laboratories. Serogroups between Y and W were indistinguishable using this test kit.

2.4. Meningococcal isolates growth and serogroup typing conditions at NIID

The isolates were stored in gelatin disks at −80 °C [7]. *N. meningitidis* strains (serogroup A, NCTC 10025 serogroup B, ATCC 13090; serogroup C, ATCC 13102) were used as standard reference strains for serogrouping. Strains were routinely grown on GC agar plates at 37 °C in 5% CO_2. The serogroup was determined by slide agglutination with polyclonal antisera against serogroups A, B, C, D, X, Y, Z, E and W (Difco) or non-culture PCR-based methodologies [8].

2.5. Data analysis

Collected data on cases were descriptively summarized. Also we calculated case fatality rate (CFR) and annual incidence of IMD for Japan (2014). We used national population estimates data, as of October 1st, 2014 [9] for denominator. Annual incidence was only calculated for 2014, because surveillance system was transitioned in April 2013.

3. Results

One hundred seventy-eight meningococcal meningitis cases were reported from April 1999 to March 2013. Among those, 111 (62%) were male and the median age was 27 years old (range: 0–89). Yearly incidences from 2000 to 2012 were between 0.005 and 0.017 per 100,000. The fatal cases were evenly distributed from young to elderly and the overall CFR was 8%.

After the amendment of surveillance system on April 1, 2013, 59 IMD cases have been reported by end of 2014. The number of yearly reported cases increased since 2013; one third of reported cases were meningitis and the others were bacteremia (Fig. 1). Cases were reported from all around the country and no imported case has been reported. Five cases were reported to live in dormitory or nursing home (eight cases reported unknown). No outbreak has been notified. Thirty-seven (63%) were male case and the median age was 56 years (range: 0–93). Twelve percent of the cases were <20 years old and only 3% of the cases were <5 years old (Fig. 2). The annual incidence (2014) for IMD was 0.028 per 100,000 and CFR was 19%.

Among 59 reported IMD cases, *N. meningitidis* was isolated from blood in 42 cases (71%), from cerebrospinal fluid in 10 cases (17%), from both blood and cerebrospinal fluid in 6 cases (10%), and from brain tissue in one case. Serogroup Y (42%; 25/59) was the most common, followed by C (12%; 7/59), B (7%; 4/59) and W (3%; 2/59). Five percent of tested isolates (3/59) were reported as Y or W due to the characteristics of rapid diagnostic test. Finally, 31% (18/59) of the reported cases of serogroup were unknown because isolates were not collected (Fig. 3).

4. Discussion

We summarize current epidemiology of IMD in Japan by analyzing the national case based surveillance data. Since bacteremia has been added to reportable condition in 2013, reported cases of IMD doubled. Although the incidence was quite low, CFR was high and majority of patients were elderly. Dominant serogroup was Y.

Since bacteremia has been added to the reportable condition, it enable us to compare the incidence with other countries. The annual incidence (per 100,000 population) of IMD in Japan (0.028 (2014)) was lower than that of other developed western countries, such as U.S. (0.14 (2013)), Europe (0.92 (2009)) and Australia (1.2 (2009)) [3,10]. The reason for low incidence of IMD in Japan than western developed countries is unclear. Nevertheless, Asian countries do report similar low incidence of IMD such as 0.1–0.2 cases per 100,000 population (2000–2001) in Taiwan [11] and 0.06–0.08 per 100,000 population in Korea [12].

Multiple reasons may contribute to the low incidence. For instance, due to the universal insurance system, doctor and patient's behavior may differ from other countries; result in frequent antibiotic use and doctors testing practices. On the other hand, considering common low incidence reported from Asia, climate and cultural behavior is truly associated with low incidence of IMD. However, the reasonable explanation of low IMD incidence in Japan might be due to underreporting. Since those data we used are from passive surveillance, there is always a possibility of underreporting. As a matter of fact, the incidence of cases in infants and young children is low, which does not correlate with what is reported from other countries with strong surveillance systems in place to detect meningococcal disease, such as the U.S. and Europe [13,14]. Furthermore, when *N. meningitidis* is isolated from sterile fluid such as joint fluid and pericardial fluid, cases are not currently accepted by NESID. Thus, those cases are not included in our results. CFR could be also underestimated, since the status of the case is at the time of the case being reported to NESID. Although with underreporting issues, Japan still has high CFR as other developed countries.

There are many challenges to knowing the true burden of IMD in Japan. Nevertheless, the risk of acquiring IMD does exist. An IMD outbreak occurred among students and staff in a high school dormitory in 2011 with diagnosis of two bacteremia out of five IMD cases. On August, 2015, participants of the World Scout Jamboree (WSJ) held in Japan were involved in serogroup W meningococcal disease outbreak [15]. These indicate the potential risk of Japanese developing IMD. Japanese travelers to endemic countries and students attending US colleges are increasing and fairly number of persons who have persistent complement component deficiencies (0.1% of the Japanese population), anatomic/functional asplenia, and patients under the treatment of the using Eculizmab [16] exists.