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Import-Associated Measles Outbreak Including Hospital- and Clinic-Based Transmission in the Non-Endemic Hokkaido District, Japan, 2014

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Measles, caused by the measles virus (MV), is an acute and highly contagious disease that is mainly characterized by high fever and cough followed by the appearance of a systemic maculopapular rash (1).

In Japan, mandatory reporting of measles was implemented into the surveillance system in January 2008. In 2012, the Japanese government revised the “Special Infectious Disease Prevention Guidelines on Measles” that were originally published in December 2007, and set a goal to achieve nationwide eradication of measles by fiscal year 2015, and to maintain a measles-free status thereafter (2,3). Suspected clinical cases of measles must be identified early in the course of the disease, whether the case is import-associated or indigenous. Import-associated measles cases can be divided into 3 categories: (i) imported cases, (ii) cases that are linked epidemiologically to imported ones, and (iii) cases for which an epidemiological link has not been identified but the viral genotype suggests recent importation (4). In recent years, the number of cases of measles has dramatically decreased in Hokkaido district, northern islands of Japan; however, a few sporadic cases are still reported (5–7). The purpose of this paper is to describe the status of measles and the surveillance activities in Hokkaido district in 2014.

Laboratory investigations for suspected cases of measles were performed for a total of 38 individuals in Hokkaido district in 2014 (Table 1). Of those, 12 cases had been vaccinated, 10 cases were unvaccinated, and 16 cases had an unknown vaccination history. Throat swabs ($n = 35$), urine samples ($n = 30$), and blood samples ($n = 32$) were examined at Sapporo City or the Hokkaido Institutes of Public Health to confirm MV infection.

In accordance with the laboratory diagnostic manual for MV infection established by Tashiro et al. (8), for each suspected case, the viral RNA of the nucleoprotein (*N*) and the hemagglutinin (*H*) genes are detected using reverse transcription polymerase chain reaction. When the *N* gene is detected, phylogenetic analysis of the strain is performed to identify the genotype using the nucleotide sequences recommended by the World Health Organization (WHO) (450 bases), as previously

described (7). Sera or plasma IgM index values are also measured using an enzyme immunoassay (EIA) kit, which has been recently improved and commercialized (Denka Seiken Co., Tokyo, Japan) (9). The laboratory investigations conducted for suspected measles cases in Hokkaido district in 2014 and the results are shown in Table 1.

This study was performed following approval by the Ethics Committee of Hokkaido Institute of Public Health.

The MV genome was detected in 12 of the 38 cases. The IgM index value was measured in 25 suspected cases. Of these cases, 11 tested positive for IgM antibodies. Of those showing positivity for IgM antibodies, 10 cases were officially reported as measles, and 1 case was excluded because the genome was negative despite appropriate timing for sample collection. In total, 13 cases were officially reported as measles (Tables 1 and 2). The *N* gene for MV was detected in 12 cases (GenBank accession numbers: LC040956, LC041247-9, and LC049565-72). Of these, 11 strains belonged to the genotype B3 and 1 strain was genotype D8. Cases 1 and 13 (case numbers correspond to those in Table 2) were considered to have been caused by imported viruses because the individuals had traveled to the Philippines and Indonesia, respectively, during the incubation period. All of the other cases were probably infected within Hokkaido district.

The chronological course for the occurrence of the cases that were positive for genotype B3 is shown in Fig. 1. All of the genotype B3 sequences were identical to each other. The genotype B3 cases were reported in cities I, II, and III located in the central area of Hokkaido within a 50-km radius. In these cities, many residents commute to work or school. The local Center for Public Health in city II released a detailed surveillance report for cases 2, 6–10, and 12 (10). Briefly, case 2 (the index case) began with fever on March 14, 2014. His condition deteriorated and he underwent medical inves-

Table 1. Laboratory diagnoses of suspected cases of measles performed in commercial laboratories and prefectural or municipal Public Health Institutes in Hokkaido district, Japan, 2014

Suspected case	No. of positive IgM antibodies ¹⁾ /cases tested	No. of positive MV genome/cases tested	Officially notified measles case
38	11/25	12/37	13

¹⁾ IgM index values in sera or plasma were measured using an EIA kit; positive (> 1.2), equivocal ($0.8–1.2$), negative (< 0.8).

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Table 2. Epidemiological information and laboratory diagnoses of measles cases performed in commercial laboratories and prefectural or municipal Public Health Institutes in Hokkaido district, Japan, 2014

Case No. ¹⁾	Age (yr)/ Sex	Date of onset of illness (mo/day)	Specimen	Day of collection after the onset	Symptom and sign other than fever, rash, or cough	IgM index value ²⁾	RT-PCR (genotype)	Vaccination status	Traveling history and the period of the stay (mo/day)
1	28/F	3/1	Sw, U, B	4	—	19.89	B3	Unknown	Philippines, 2/11–26
2	24/M	3/14 (rash: 3/19)	Sw, U	23	Koplik spots, rhinorrhea, conjunctival hyperemia	9.89	B3	Unknown	—
3	17/F	3/19 (rash: 3/24)	Se	6	—	8.64	n.i. ³⁾	Unknown	—
4	15/M	3/21 (rash: 3/23)	Sw, U, B	10	Conjunctival hyperemia, Koplik spots	19.89	B3	Unvaccinated	—
5	30/M	3/25 (rash: 3/26)	Sw, U, B	8	Koplik spots, rhinorrhea, conjunctival hyperemia	18.0	B3	Unknown	—
6	1/F	3/26 (rash: 3/30)	Sw, Se	6 (Se: 8)	Rhinorrhea	16.92	B3	Unvaccinated	—
7	24/F	3/27 (rash: 3/31)	Sw, U, B	5	Koplik spots, rhinorrhea, conjunctival hyperemia	12.40	B3	Unknown	—
8	8/M	3/30 (rash: 4/1)	Sw, Se	5	—	1.95	B3	Twice (in 1 and 6 years olds)	—
9	52/F	4/1	U	2	Koplik spots, rhinorrhea	Not tested	B3	Unvaccinated	—
10	1/F	4/3 (rash: 4/6)	Sw, U, B	4	Koplik spots, rhinorrhea, conjunctival hyperemia	19.89	B3	Once (2014/3/27)	—
11	28/M	4/9 (rash: 4/18)	Sw, U, B	9	Koplik spots, conjunctival hyperemia	Not tested	B3	Unknown	—
12	1/M	4/14 (rash: 4/16)	Sw, U, Se	3	Rhinorrhea	0.27	B3	Once (2014/4/10)	—
13	0/F	6/21 (rash: 6/24)	Sw, Se	6	Enteritis	14.76	D8	Unvaccinated	Indonesia, 6/7–13

¹⁾: Case 3 was reported from commercial laboratories to the surveillance system.

²⁾: Criterion of IgM index values correspond to those in Table 1.

³⁾: n.i., No information about the detection of MV genome.

M, male; F, female; Sw, swab; U, urine; Se, serum; B, blood.

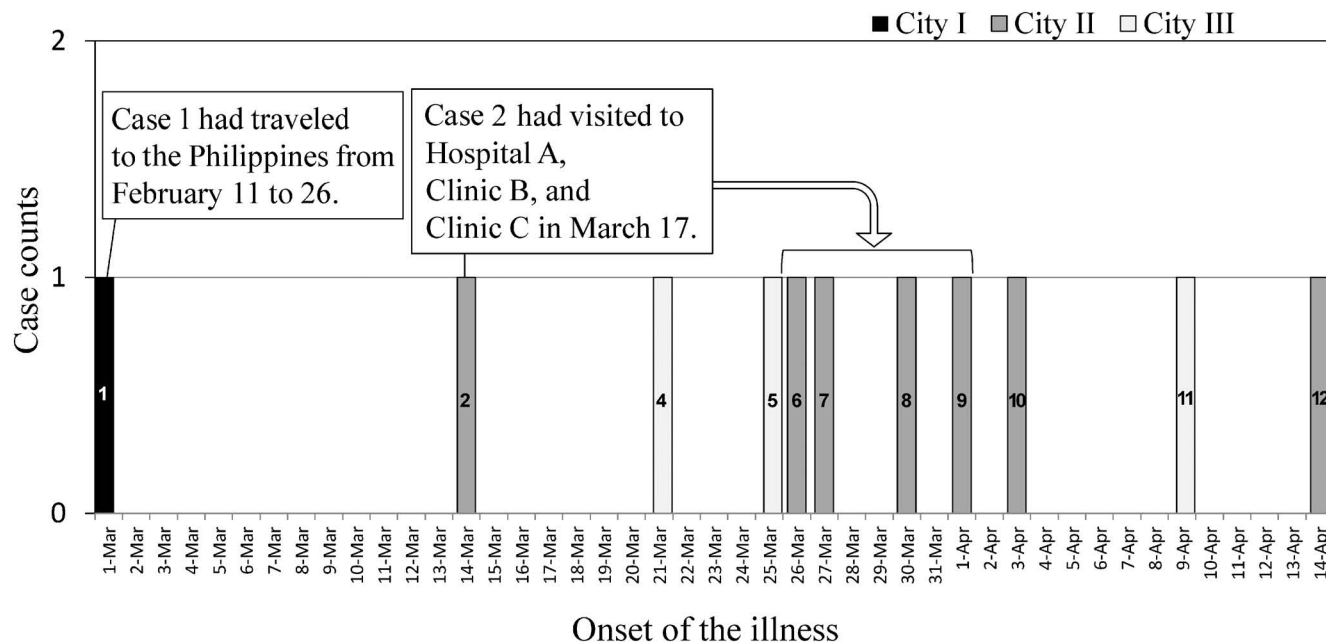


Fig. 1. Distribution of laboratory-confirmed measles cases by date, whose specimens were positive for the genotype B3, Hokkaido district, Japan, March 1–April 14, 2014. Case numbers correspond to those in Table 2.

tigations at hospital A. Subsequently, he visited ophthalmological clinic B, and nose, ears and throat clinic C. Finally, he was admitted to hospital A on March 19 until March 25 with suspected chickenpox. During this period, it is thought that the MV was transmitted to case 9 who engaged in cleaning work at hospi-

tal A, to case 7 who was an office worker in clinic B, and to cases 6 and 8 who visited clinic C during the same period. In addition, case 2 had visited a facility in city III to renew his car license. The epidemiological linkages between case 1 reported in city I, cases 10 and 12 reported in city II, and cases 3, 4, 5, and 11 reported in

city III are not clear. Case 10 developed clinical symptoms within 7 days of receiving the measles vaccination, and her IgM index value was extremely high. In contrast, case 12 developed symptoms within 4 days of vaccination and tested negative for IgM antibodies. The reason for the negative IgM result is unknown because the serum sample was collected on day 3 following the onset of illness.

Despite high immunization coverage, infections due to import-associated MV are difficult to prevent (11). Unvaccinated individuals, including those who refuse vaccination, increase the risk of MV transmission (11,12). Except for individuals who cannot be vaccinated because of medical reasons, everyone should receive at least 2 doses of the measles vaccine (3). Furthermore, vaccination prior to international travel should be highly recommended for susceptible individuals (4).

Increasing levels of international travel do mean that infection due to imported MV may occur (13,14). It is important to prevent viral transmission by these unexpected cases. All individuals with suspected measles are required to provide appropriate clinical samples for testing in order for a diagnosis of measles to be confirmed (3). Vaccination status, recent travel history, and contact evidence for individuals suspected of having measles should be clarified, at least. In addition to active surveillance and developing the molecular epidemiology, an adequate vaccination program for susceptible individuals should be continued even after eradication of the disease.

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Appendix In March 2015, Japan was nationally verified as having achieved measles elimination by WHO Regional Office for the Western Pacific (15).

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Conflict of interest None to declare.

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