Original Article

The Largest Measles Outbreak, Including 38 Modified Measles and 22 Typical Measles Cases in Its Elimination Era in Yamagata, Japan, 2017

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SUMMARY: The incidence of modified measles (M-Me), characterized by milder symptoms than those of typical measles (T-Me), has been increasing in Japan. However, the outbreak dominated by M-Me cases has not been thoroughly investigated worldwide. The largest importation-related outbreak of measles with genotype D8 occurred in Yamagata Prefecture, Japan, from March to April 2017. We confirmed 60 cases by detecting the genome of the measles virus (MeV). Among the cases, 38 were M-Me and 22 were T-Me. Thirty-nine (65.0%) patients were 20–39 years of age. Three out of 7 primary cases produced 50 transmissions, of which each patient caused 9–25 transmissions. These patients were 22–31 years old and were not vaccinated. Moreover, they developed T-Me and kept contact with the public during their symptomatic periods. Considering that M-Me is generally caused by vaccine failure, some individuals in Japan may have insufficient immunity for MeV. Accordingly, additional doses of measles vaccine may be necessary in preventing measles importation and endemicity among individuals aged 20–39 years. Furthermore, to accurately and promptly diagnose individuals with measles, particularly those who can be considered as primary cases, efforts must be exerted to detect all measles cases using epidemiological and genetic approaches in countries where measles elimination had been achieved.

INTRODUCTION

Measles is a highly contagious acute infection caused by the measles virus (MeV). In typical measles (T-Me), patients develop nonspecific prodromal symptoms (fever, coryza, cough, and conjunctivitis) 8–12 days post-infection, followed by a generalized maculopapular rash (1,2). Unvaccinated individuals are at high risk of measles and its complications, including death (3). Because of its contagiousity, MeV requires a > 95% vaccination rate with 2 doses of measles vaccine and catch-up vaccinations to maintain sufficient levels of herd immunity (2,4).

Japan achieved measles elimination in March 2015 by providing 2 doses of measles vaccine and by using the laboratory-based surveillance system according to the guideline for the prevention of specific infectious disease: measles established in 2007 (5–7). However, in Japan, the immunological statuses of individuals differ according to age because the vaccination program has been changed in a phased manner since routine vaccination started in 1978 (8,9). From 2012 to 2016, the annual number of imported and importation-related measles cases was between 35 and 462 (10).

Modified measles (M-Me) is characterized by mild illness and an atypical clinical course and is usually observed in a patient who has insufficient immunity because of primary or secondary vaccine failure (8,11). These patients could be sources of infection even though the risk is low (12–14). To prevent measles transmission and outbreaks, both M-Me and T-Me cases should be accurately diagnosed.

In the Yamagata Prefecture, Japan, no measles cases were not vaccinated. Moreover, they developed T-Me and kept contact with the public during their symptomatic periods. Considering that M-Me is generally caused by vaccine failure, some individuals in Japan may have insufficient immunity for MeV. Accordingly, additional doses of measles vaccine may be necessary in preventing measles importation and endemicity among individuals aged 20–39 years. Furthermore, to accurately and promptly diagnose individuals with measles, particularly those who can be considered as primary cases, efforts must be exerted to detect all measles cases using epidemiological and genetic approaches in countries where measles elimination had been achieved.

MATERIALS AND METHODS

Detection of the MeV gene: We tested the specimens of peripheral blood mononuclear cells, throat swabs, urine, and serum according to the section of measles in the laboratory manual for pathogen detection (15). Briefly, qualitative real-time reverse transcription polymerase chain reaction (RT-PCR) that targets the N gene was performed for all specimens; then, conventional RT-PCR that targets the N and H genes was conducted for specimens that yielded intermediate results in the
The genotypes of MeV were determined using the sequence of 450 base-pair fragments in the N gene with an ABI Prism 310 Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA), as previously described (16). All the PCR tests for the detection of the MeV genome in patients with suspected measles in Yamagata were performed at the Yamagata Prefectural Institute of Public Health. In addition, molecular amplification methods were used in laboratories outside Yamagata for other patients with suspected measles who moved from Yamagata before the onset.

**Epidemiological analysis:** We defined cases of T-Me and M-Me according to the guidelines of the notification criteria, which are defined in the Japanese law in the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Disease. T-Me cases were defined as the presence of fever, rash, and catarhal symptoms (one or more of the following symptoms: conjunctivitis, coryza, pharyngeal pain, and cough). On the other hand, M-Me cases were defined as the presence of one or 2 of the 3 clinical symptoms. A body temperature ≥37°C was considered as fever in this study. Several patients with measles were diagnosed with M-Me at the time of hospital visit, which is prior to the development of the 3 symptoms; these patients were considered to have T-Me. All patients with T-Me and M-Me were diagnosed based on laboratory tests for the MeV genome in this study. However, they were not clinically diagnosed.

The staff of the public health centers interviewed patients with measles and collected data on age, sex, day of onset, symptoms, highest body temperature during illness, and activity histories. We defined the day of infection as the earliest day in which the patient had potential contact with a source of infection and the day of onset as the earliest day in which the patient developed symptoms of measles. Furthermore, the incubation period was defined as the number of days between the day of infection and the day of symptom onset.

**Detection of IgM antibody:** After the end of the outbreak, we assayed serum MeV-specific IgM antibodies using the Measles IgM-EIA (Denka Seiken, Tokyo, Japan) according to the manufacturer’s instructions. The antibody tests were performed on serum specimens only with the approval of patients with measles.

**Statistical analysis:** To compare the differences between T-Me and M-Me, student’s t-test or chi-square test was performed. To evaluate the correlation between the proportions of disease type and the doses of measles vaccines, asymptotic linear-by-linear association test was used. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Ethical considerations:** This study was performed using data collected based on the Japanese law in the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. The study protocol was approved by the ethics committee of Yamagata Prefectural Institute of Public Health (approval no.: YPIPHEC 17-10).

**RESULTS**

**Detection of MeV gene:** From March to May 2017, approximately 3,700 individuals who had contact with patients who developed measles in the Yamagata Prefecture, Japan, were assessed by healthcare professionals from the public health centers. In total, 60 patients tested positive for the MeV genome. In Yamagata, the MeV genome was detected in 53 (38.7%) out of 137 patients with symptoms of measles. The MeV genotype was determined as D8 in 50 out of 53 cases (Genbank accession nos.: LC311245– LC311307). All sequences were completely identical to those of the N gene that was detected in an outbreak in Indonesia in 2014 (Genbank accession no.: KT964107) (17).

**Outbreak description:** During the outbreak, 60 measles cases were confirmed from March 3 to April 15, 2017 (Fig. 1). The index case involved a man in his twenties who had traveled to Bali Island, Indonesia, from February 20 to February 26, 2017. He came to Yamagata on March 2, 2017 via a bullet train (Shinkansen) to attend a driving school in Okitama district, which is located south of Yamagata. After developing fever on March 3, he continued attending the driving school and stayed in the hotel until he was admitted in a hospital on March 8, 2017. Clinical history and physical examination revealed a temperature >40°C, coryza, cough, pharyngeal pain, generalized rash, and diarrhea; MeV genomes were detected in his specimens on March 9, 2017. Thereafter, the prefectural health and welfare planning division made an official announcement to call the attention of the public due to measles outbreak on the same
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After the index case, 25 second-generation cases, 27 third-generation cases, 2 fourth-generation cases, and 5 cases of unknown origin were reported (Fig. 1). According to their addresses, 52 cases were inhabitants of the Yamagata Prefecture, and 8 cases, including the index case, which involved a patient who attended a driving school, were inhabitants of areas outside the Yamagata Prefecture (Fig. 2).

On May 17, 2017, measles epidemic had ended because no additional cases were observed for 4 weeks.

Characteristics of patients with measles: The baseline characteristics of the 22 (36.7%) patients with T-Me and 38 (63.3%) patients with M-Me are shown in Table 1. Approximately 65.0% of the patients were 20–39 years. Among the 36 vaccinated patients, 83.3% presented with M-Me. The mean body temperature of the patients with M-Me was significantly lower than that of patients with T-Me. Asymptotic linear-by-linear association test indicated a trend in which the proportion of M-Me cases increased with increasing vaccination doses. In addition, among the 38 patients with M-Me, 9 patients had been diagnosed with modified measles at the time of detection of MeV genome, and then progressed to typical measles. Seven people were examined and notified outside of Yamagata. Three patients inside the dotted circle developed symptoms at the facility.

Table 1. Baseline characteristics of typical measles and modified measles patients in an importation-related measles outbreak, Yamagata Prefecture, Japan, 2017

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical measles (n = 22)</th>
<th>Modified measles (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean ± SD)</td>
<td>31.0 ± 13.9</td>
<td>30.3 ± 9.0</td>
<td>0.84</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>4 (18.2)</td>
<td>5 (13.2)</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>6 (27.3)</td>
<td>13 (34.2)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>4 (18.2)</td>
<td>16 (42.1)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>5 (22.7)</td>
<td>3 (7.9)</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>2 (9.1)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>7 (31.8)</td>
<td>9 (23.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>No. of doses of measles vaccine*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (57.1)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>3 (21.4)</td>
<td>24 (70.6)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>3 (21.4)</td>
<td>6 (17.6)</td>
<td>0.049</td>
</tr>
<tr>
<td>Incubation period (days, mean ± SD)</td>
<td>13.8 ± 2.7</td>
<td>14.2 ± 2.9</td>
<td>0.55</td>
</tr>
<tr>
<td>Body temperature (°C, mean ± SD)</td>
<td>39.0 ± 1.1</td>
<td>37.9 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*: The number of cases with unknown vaccine history, 8 and 4 for typical and modified measles cases, respectively, was excluded for asymptotic linear-by-linear association test.

Fig. 2. The geographical distribution of patients according to their addresses. Black-filled circles in the map of Japan indicate the index case and patients outside of Yamagata. Numbers of cases in each district in Yamagata prefecture are shown under the name of districts.

Fig. 3. Transmission chains of measles patients in an importation-related measles outbreak, Yamagata Prefecture, Japan, March–April 2017. The nodes represent individuals that were infected, and their color represents a disease type. A line between 2 nodes represents MeV transmission. Nodes are assembled according to the place of infection and divided into 3 districts by broken lines. PrC: Primary case. *: Nine patients had been diagnosed with modified measles at the time of detection of MeV genome, and then progressed to typical measles. †: Seven people were examined and notified outside of Yamagata. ‡: Three patients inside the dotted circle developed symptoms at the facility.
19, 11, and 8 presented with fever only, fever and rash, and fever and catarrhal symptoms, respectively.

**Transmission pathways:** We confirmed that 54 of 59 cases had a direct or indirect epidemiological association with the index case (Fig. 3). MeV transmissions primarily occurred in the Okitama district. Then, MeV was transmitted to neighboring districts. We defined the patient who was the source of MeV infection as the primary case (PrC) (18). Seven PrCs were identified, and their characteristics are shown in Table 2. PrCs A–C were 22–31 years of age and were not vaccinated. They developed T-Me and produced 9–25 transmissions. PrCs A and B had contact with the public during their symptomatic periods from March 3–8 and March 15–22, respectively. Although the symptomatic period of PrC C was shorter than that of PrCs A and B, PrC C had contacted several individuals in the facility. All measles transmissions, except for the household transmission of PrC B, occurred in public areas, including hospitals and related institutions. It was confirmed that all PrCs did not receive 2 doses of measles vaccine. In addition, PrC G who presented with fever and catarrhal symptoms was the only patient with M-Me who transmitted MeV to others.

**Detection of IgM antibodies:** In total, 8 (25.8%) of 31 patients with measles tested positive for serum MeV-specific IgM antibodies (Fig. 4). IgM-negative cases were identified between 0 and 4 days after the onset of symptoms. Furthermore, only 3 (15.8%) of 19 patients with M-Me tested positive for the antibody.

**DISCUSSION**

In this study, we aimed to elucidate the features of measles outbreak that occurred in Japan, where measles had been eliminated by establishing high levels of population immunity. In particular, our study provides information to better understand the characteristics of patients with M-Me. Imported and importation-related measles cases, particularly PrCs, could result in 60-patient outbreaks in countries in which measles epidemic has been eliminated but is in the transitional stage in terms of the development of immunological protection for measles.

Outbreaks dominated by M-Me cases have not been thoroughly investigated compared with those dominated by T-Me cases (19–22). To eradicate measles worldwide, efforts must be exerted in detecting all patients with measles, even if they have mild symptoms. In Japan, where epidemic measles has been eliminated but is in the transitional stage in terms of the development of immunological protection for measles, the proportion of M-Me cases among the notified cases increased by 32% in 2016 (10). There is an obvious need to understand M-Me cases, and a more effective way of diagnosing the condition must be established.

In outbreaks dominated by M-Me cases, the symptoms of patients with M-Me after diagnosis should be cautiously monitored. Our results showed that patients with M-Me had mild symptoms, and only one patient with M-Me transmitted measles to others (Tables 1 and 2). Accordingly, the contagiosity of patients with M-Me

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### Table 2. Characteristics of 7 primary cases of measles, and the number and places of transmissions they produced

<table>
<thead>
<tr>
<th>PrC(1)</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Measles type</th>
<th>Vaccination status</th>
<th>Symptomatic period(2)</th>
<th>No. of transmissions</th>
<th>Places of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>M</td>
<td>Typical</td>
<td>None</td>
<td>5</td>
<td>25</td>
<td>Driving school, hotel, hospital</td>
</tr>
<tr>
<td>B</td>
<td>31</td>
<td>M</td>
<td>Typical</td>
<td>None</td>
<td>7</td>
<td>9</td>
<td>Household, clinic and related institution, company and related office</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>M</td>
<td>Typical</td>
<td>None</td>
<td>3</td>
<td>16</td>
<td>Facility</td>
</tr>
<tr>
<td>D</td>
<td>22</td>
<td>F</td>
<td>Typical</td>
<td>Unknown</td>
<td>1</td>
<td>2</td>
<td>Store, restaurant</td>
</tr>
<tr>
<td>E</td>
<td>63</td>
<td>M</td>
<td>Typical</td>
<td>None</td>
<td>1</td>
<td>1</td>
<td>Facility</td>
</tr>
<tr>
<td>F</td>
<td>51</td>
<td>F</td>
<td>Typical</td>
<td>None</td>
<td>6</td>
<td>1</td>
<td>Clinic</td>
</tr>
<tr>
<td>G</td>
<td>34</td>
<td>M</td>
<td>Modified</td>
<td>One dose</td>
<td>1</td>
<td>1</td>
<td>Store</td>
</tr>
</tbody>
</table>

1) Primary case.
2) Duration between the day of symptom onset and the day of specimen collection.

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**Fig. 4.** The results of serum measles virus-specific IgM assay by days after symptom onset. Samples derived from 31 laboratory-confirmed measles patients were assayed.
may be lower than those with T-Me. By contrast, patients with M-Me at the time of hospital visit could develop T-Me and become PrCs (Fig. 3). Awareness-raising activities are effective for early medical examinations of contacts with measles patients; however, the clinical course of measles when diagnosed in the early stage should be assessed by public health officials to prevent unexpected measles transmissions.

Precise and prompt identification of T-Me cases in outbreaks dominated by M-Me cases is the most important way to eliminate epidemics in their early stages. In this study, 3 unvaccinated patients with T-Me caused almost all measles transmissions (Table 2). Considering that the increase in the number of persons who had contact with patients with T-Me caused the geographical and prolonged spread of MeV (Figs. 1, 3), measles control must focus on patients with T-Me, and the identification of individuals who had contact with patients with T-Me may be efficient in saving public health costs.

Two doses of measles vaccine are essential in preventing transmissions (2,4). With regard to this outbreak, a Japanese study has shown that majority of measles cases involved individuals aged 20–39 years who received one dose and 2 doses of measles vaccines (8). To prevent measles outbreaks, additional doses might be needed, particularly for individuals aged 20–39 years who did not receive 2 doses in Japan. Considering that this outbreak originated from an imported case of measles, 2 doses must be administered, particularly for travelers who visit regions with measles endemic, and this was recently recommended by the Japanese Ministry of Health, Labour and Welfare (23).

The public should be informed about the length of stay and the place where an individual with measles, particularly an individual with T-Me, stayed. In general, when places where patients with serious infectious diseases stayed are announced to the public, economic losses occur. Conversely, public health officials must exert efforts and allocate a budget when infectious diseases spread when the places are not announced. Unfortunately, almost all measles transmissions occurred in public places in this study (Table 2). However, it is challenging to confirm whether appropriate announcements of those places were performed. We proposed that guidelines for the decision-making process of nationally or municipally unified disclosure standards for announcements should be considered. The criteria will lead to the control of measles outbreaks.

For promptly detecting patients with measles, molecular amplification methods for the MeV genome may be useful during measles outbreaks that are dominated by M-Me cases. We identified 38 patients with M-Me who presented with mild symptoms or fever using molecular amplification methods. By contrast, the low IgM positivity of patients with measles suggests that antibody tests are not effective in accurately detecting patients with measles, particularly those with M-Me who only had mild symptoms (Fig. 4). Previous studies have shown that the use of assay techniques in identifying the presence of IgM in patients early in the clinical course would not be effective in diagnosing the infection (24,25). The importance of molecular amplification methods for MeV may increase with the increase in M-Me cases via the progression of measles control worldwide.

Our study had several limitations. First, misdiagnosed measles cases might exist because individuals with mild symptoms and those without idea that they had contact with a patient who developed measles would not suspect the infection. Second, the day of symptom onset was adjusted to the day of fever onset in some cases even if they developed catarrhal symptoms prior to fever because some patients forgot the day of catarrhal onset. Third, vaccination histories might not be accurate because some information, such as the time they received the vaccination and the contents of the vaccination, was not clear. Thus, IgG and IgG avidity must be further investigated to validate the immunological status of patients at the time of diagnosis (26). Lastly, we considered PrC C as the infection source in the facility according to the activity histories of PrC C and 2 associates (Fig. 3). Moreover, we considered that the case of the 2 associates who developed M-Me was not associated with measles transmission because preceding studies have indicated that the transmissibility of M-Me was low (12,13).

In conclusion, the measles outbreak in Yamagata Prefecture, Japan, in 2017 was caused by importation and was transmitted primarily by 3 unvaccinated patients, who were considered as PrCs, including the index case. In Japan, individuals with insufficient immunity for MeV, particularly those aged 20–39 years, should receive additional doses of measles vaccine to prevent epidemics and importations of measles. Furthermore, to accurately and rapidly diagnose patients with measles, public health officials and healthcare providers should exert efforts in detecting all measles cases using epidemiological and genetic approaches.

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Conflict of interest None to declare.

REFERENCES