Advance Publication by J-STAGE

Japanese Journal of Infectious Diseases

The largest measles outbreak, including 38 modified measles and 22 typical measles cases, Yamagata, Japan, 2017 in its elimination era

Kenichi Komabayashi, Junji Seto, Shizuka Tanaka, Yu Suzuki, Tatsuya Ikeda, Noriko Onuki, Keiko Yamada, Tadayuki Ahiko, Hitoshi Ishikawa, and Katsumi Mizuta

Received: February 22, 2018. Accepted: June 5, 2018
Published online: June 29, 2018
DOI:10.7883/yoken.JJID.2018.083

Advance Publication articles have been accepted by JJID but have not been copyedited or formatted for publication.
Title: The largest measles outbreak, including 38 modified measles and 22 typical measles cases, Yamagata, Japan, 2017 in its elimination era

Running head: Measles outbreak in Yamagata, 2017

Keywords: Vaccination, Imported measles, Elimination era, Primary case

Authors: Kenichi Komabayashi¹, Junji Seto¹, Shizuka Tanaka¹, Yu Suzuki¹, Tatsuya Ikeda¹, Noriko Onuki², Keiko Yamada³, Tadayuki Ahiko¹,¹, Hitoshi Ishikawa⁵, Katsumi Mizuta¹

¹Department of Microbiology, Yamagata Prefectural Institute of Public Health, Yamagata 990-0031, Japan; ²Yamagata Prefecture Division of Health and Welfare Planning, Yamagata 990-8570, Japan; ³Okitama Public Health Center, Yamagata 992-0012, Japan; ⁴Murayama Public Health Center, Yamagata 990-0031, Japan;

⁵Shonai Public Health Center, Yamagata 997-1392, Japan

*Corresponding author: Kenichi Komabayashi, DVM

Department of Microbiology, Yamagata Prefectural Institute of Public Health, 1-6-6 Tokamachi, Yamagata, Yamagata 990-0031, Japan

Tel: +81-23-627-1373; Fax: +81-23-641-7486

E-mail: komabayashike@pref.yamagata.jp
駒林賢一 1), 瀬戸順次 1), 田中静佳 1), 鈴木裕 1), 池田辰也 1), 大貫典子 2), 山田敬子 3), 阿彦忠之 1,4), 石川仁 5), 水田克巳 1)

1) 山形県衛生研究所, 微生物部, 990-0031 山形市十日町 1-6-6
2) 山形県健康福祉部健康福祉企画課
3) 山形県置賜保健所
4) 山形県村山保健所
5) 山形県庄内保健所
SUMMARY

Modified measles (M-Me), characterized by milder symptoms than typical measles (T-Me), has been increasing in Japan, but M-Me dominated outbreak has not been investigated sufficiently worldwide. During March–April 2017, there was the largest importation-related outbreak of measles with genotype D8 in Yamagata, Japan, after Japan had achieved measles elimination in 2015. We confirmed 60 cases by detecting measles virus (MeV) genome, among whom 38 M-Me and 22 T-Me cases were identified. Thirty-nine cases (65.0%) were between 20–39 years of age. Three out of seven primary cases produced 50 transmissions, in which each patient caused 9–25 transmissions. They were aged 22–31 years with no vaccination, 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 with insufficient immunity for MeV might exist in Japan. Accordingly, additional doses of measles vaccine may be needed especially for people aged 20–39 years to prevent measles importation and endemicity. Furthermore, to correctly and rapidly diagnose measles, especially to identify patients who could become primary cases, efforts to detect all measles cases using epidemiological and genetic approaches should be made in countries where measles elimination had been achieved.
INTRODUCTION

Measles is a highly contagious acute infectious disease caused by the measles virus (MeV). In typical measles (T-Me) patients, non-specific prodromal symptoms (fever, coryza, cough, and conjunctivitis) develop 8 to 12 days post-infection, followed by a generalized maculopapular rash (1, 2). Unvaccinated people are at high risk of measles and its complications, including death (3). Because of its contagiosity, MeV requires a >95% vaccination rate of two 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 the enforcement of two doses of measles vaccine and the laboratory-based surveillance system based on the guideline for the prevention of specific infectious diseases: measles established in 2007 (5–7). In Japan, however, the immunological statuses of people differ according to age because the vaccination program has been changed in a phased manner since routine vaccination for measles was started in 1978 (8, 9). During 2012–2016, 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 case who has insufficient immunity.
because of primary or secondary vaccine failure (8, 11). These patients could be sources of transmission even though the risk is low (12–14). In order to prevent measles transmission and outbreaks, cases of M-Me should be adequately diagnosed, as should cases of T-Me.

In the Yamagata Prefecture, Japan, no measles cases had been observed since 2011; however, we experienced an importation-related outbreak of measles predominantly involving M-Me during March–April 2017. That was the largest outbreak after measles elimination was achieved in Japan (10). We aimed to elucidate the features of the outbreak and to evaluate why the outbreak occurred on such a large scale in the measles elimination era in Japan.

MATERIALS AND METHODS

Detection of the MeV gene

We tested 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) targeting the N gene was performed for all specimens; then conventional RT-PCR targeting the N and H genes were performed for the specimens
which yielded intermediate results in the real-time RT-PCR. The genotypes of MeV were determined by the sequence of 450 base-pair fragments in the \( N \) gene using an ABI Prism 310 Genetic Analyzer (Thermo Fisher Scientific) as previously described (16). All the PCR tests for MeV genome detection in patients with suspected measles in Yamagata were performed at the Yamagata Prefectural Institute of Public Health. In addition, molecular amplification methods for the other patients with suspected measles, who moved from Yamagata before onset, were performed in laboratories outside Yamagata.

**Epidemiological analysis**

We defined cases of T-Me and M-Me according to the guidelines of notification criteria which are defined by Japanese law in the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Disease. T-Me cases fulfilled the symptoms of fever, rash, and catarrhal symptoms (one or more of conjunctivitis, coryza, pharyngeal pain, and cough). On the other hand, M-Me cases were defined as having one or two of the three clinical symptoms. A body temperature of \( \geq 37°C \) was considered as fever in this study. Several measles patients were diagnosed with M-Me at the time of hospital visit, prior to the development of the three symptoms; we classified those patients as T-Me. All cases of T-Me and M-Me were diagnosed
based on laboratory tests for the MeV genome in this study, and not clinically diagnosed.

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

**Detection of IgM antibody**

After the end of the outbreak, we assayed serum MeV-specific IgM antibodies using 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 measles patients.

**Statistical analysis**

To compare the differences between T-Me and M-Me, Student’s t test or chi-squared test was performed. To evaluate the correlation between proportions of disease type and the received doses of measles vaccines, asymptotic linear-by-linear
association test was applied. We regarded P< 0.05 as 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 under Japanese law, under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. This 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

During March–May 2017, approximately 3,700 people who had contacted measles patients in the Yamagata Prefecture, Japan were surveyed by the public health centers. In all, 60 cases yielded positive results for the MeV genome in their specimens. In Yamagata, the MeV genome was detected from 53 (38.7%) out of 137 patients with symptoms of measles. The genotype of MeV was determined as D8 in 50 of the 53 cases (Genbank accession nos. LC311245–LC311307). All of those sequences were completely identical to that of the N gene detected in an outbreak in Indonesia in 2014
Outbreak description

During the outbreak, 60 measles cases were confirmed from 3 March to 15 April 2017 (Fig. 1). The index case was a male 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 on a bullet train (Shinkansen) to attend a driving school in Okitama district, which is located to the south of Yamagata. After developing a fever on March 3, he kept attending the driving school and staying in the hotel until he was admitted to a hospital on March 8 2017. Clinical history and physical examination revealed a temperature of over 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 attention to an outbreak of measles on the same day.

Following 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 Yamagata Prefecture, and 8 cases, including the index case, who had attended the driving school, were inhabitants of areas outside Yamagata Prefecture (Fig. 2).
It was considered on May 17 2017 that the epidemic of measles had ended because no additional cases had been notified for four weeks.

**Characteristics of measles cases**

The baseline characteristics of 22 cases (36.7%) of T-Me and 38 (63.3%) cases of M-Me are shown in Table 1. Cases aged 20–39 years comprised 65.0%. The proportion of M-Me cases among 36 vaccinated cases was 83.3%. The mean body temperature among cases with M-Me was significantly lower than those with T-Me. Asymptotic linear-by-linear association test indicated a trend in which the proportion of M-Me cases were increased as the doses of vaccination increased. In addition, among the 38 M-Me cases, symptoms of 19, 11, and 8 patients were a 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 link with the index case (Fig. 3). MeV transmissions occurred mainly in the Okitama district, after which MeV was transmitted to neighboring districts. We defined the patient, who was the source of MeV infection among a group of people, as the primary case (PrC) (18). Seven PrCs were identified, and their characteristics are shown in Table 2. PrC A–C who were 22–31 years of age with no vaccination developed T-Me and produced 9–
25 transmissions. PrCs A and B came into contact with the public during their symptomatic periods, March 3 to 8 and March 15 to 22, respectively. Although the symptomatic period of PrC C was shorter than that of PrCs A and B, PrC C had contacted many people in the facility. All measles transmissions, except for the household transmission of PrC B, occurred in public areas, including hospitals and related institutions. No PrC with two doses of measles vaccine was confirmed. In addition, PrC G with a fever and symptoms of catarrh was the only M-Me patient who transmitted MeV to others.

Detection of IgM antibodies

Serum MeV-specific IgM antibody tests were positive in 8 (25.8%) of 31 measles cases (Fig. 4). IgM negative cases were identified between 0 and 4 days after the onset of symptoms. Furthermore, only 3 (14.3%) of 19 M-Me cases showed positive results for the antibody test.

DISCUSSION

In this study, we aimed to elucidate the features of a measles outbreak that occurred in Japan, where measles had been eliminated by establishing high levels of population immunity. In particular, our report would be helpful to understand the characteristics of M-Me patients. We demonstrated that imported and
importation-related measles cases, especially PrCs could cause sixty-patient outbreaks in countries in which epidemic measles has been eliminated but are in the transitional stage in terms of the development of immunological protection for measles.

M-Me dominated outbreaks have not been investigated sufficiently in comparison with T-Me dominated outbreaks (19–22). To eradicate measles from the world, efforts for detecting all measles patients, even if they have mild symptoms, are important. In Japan, where epidemic measles has been eliminated but is in the transitional stage regarding 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 better way of diagnosis.

In M-Me dominated outbreaks, symptoms of M-Me patients after diagnosis should be monitored carefully. Our results showed that M-Me patients had mild symptoms, and only one M-Me patient transmitted measles to others (Table 1, 2). Accordingly, the contagiosity of M-Me patients may be lower than T-Me patients. On the other hand, M-Me patients at the time of hospital visit could progress to 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 diagnosed in the early stage should be surveyed by public health officials to prevent
unexpected measles transmissions.

Precise and prompt identification of T-Me cases in M-Me dominated outbreaks is the most important way to end epidemics in their early stages. In this study, three unvaccinated T-Me patients caused almost all measles transmissions (Table 2). Given that the increase of contacted persons with T-Me patients caused the geographical and prolonged spread of MeV (Fig. 1, 3), measles control focused on T-Me patients and its contacts may be efficient in saving public health costs.

Two doses of measles vaccine are essential to prevent measles transmissions (2, 4). This outbreak and a Japanese study concordantly showed the result that persons aged 20-39 years, who include both the generation of one-dose and two-dose measles vaccinations, were the majority of measles cases (8). To prevent measles outbreaks, additional doses might be needed, especially for people aged 20–39 years without two doses in Japan. Given that this outbreak originated from an imported case of measles, two doses should be necessary especially for travelers who visit measles endemic regions, as recently recommended by the Japanese Ministry of Health, Labour and Welfare (23).

The places and periods where measles patients, especially T-Me patients, stayed should be appropriately announced to the public as much as possible. In general,
announcements of the places where patients with serious infectious diseases stayed incur economic losses. Conversely, public health officials must spend great effort and cost when infectious diseases spread when the places are not announced. Unfortunately, almost all measles transmissions occurred in public places in this study (Table 2), but it is difficult to say whether appropriate announcements of those places were performed. We propose that the guideline for a decision-making process of nationally or municipally unified disclosure standards for announcements should be considered. Those criteria will lead to the control of measles outbreaks.

For detecting measles patients promptly, molecular amplification methods for MeV genome may be useful in measles outbreaks dominated by M-Me cases. We detected 38 M-Me cases with mild symptoms or fever using molecular amplification methods. On the other hand, low IgM positivity of measles patients suggests that antibody tests are unsuitable for detecting measles patients promptly, especially M-Me patients who had only mild symptoms (Fig. 4). Previous studies showed that assaying IgM in patients early in the clinical course would not be useful for diagnostic purposes (24, 25). The importance of molecular amplification methods for MeV may rise with the increase in M-Me cases by the progression of measles control worldwide.

Our study had several limitations. First, misdiagnosed measles cases might
exist because people with mild symptoms and with no idea that they contacted a measles patient would not suspect measles 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 catarrh onset. Third, vaccination histories might be mistaken because some of them were unclear about the time they received the vaccination and the contents of the vaccination. We should further investigate IgG, and IgG avidity to clarify the immunological status of patients at the time of diagnosis (26). The last limitation is that we considered PrC C as the infectious source of the facility according to the activity histories of PrC C and two associates (Fig. 3). Moreover, we considered that the two associates developing M-Me were not related to the measles transmission because preceding studies indicated that the transmissibility of M-Me was low (12, 13).

**Conclusion**

The measles outbreak in Yamagata Prefecture, Japan, 2017 was induced by an imported case and was transmitted mainly by three unvaccinated patients as PrCs, including the index case. In Japan, people with insufficient immunity for MeV, especially those aged 20–39 years, should receive additional doses of measles vaccine to prevent epidemics and importations of measles. Furthermore, to correctly and rapidly
diagnose measles patients, public health officials and healthcare providers should make efforts to detect all measles cases using epidemiological and genetic approaches.

**Acknowledgement**

We sincerely thank the public health nurses and all staff for their dedication in dealing with issues during this outbreak. This research was supported in part by the Research Program on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED).

**Conflict of interest**

None to declare.
References


18. Giesecke J. Primary and index cases. Lancet. 2014;384:2204


Figure legends

**Fig. 1** The epidemic curve of 60 measles cases, by day of symptom onset, Yamagata Prefecture, Japan, March–April 2017

**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 two nodes represents MeV transmission. Nodes are assembled according to the place of infection and divided into three districts by broken lines. PrC: Primary case

* Eight 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.
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.
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</th>
<th>Modified measles</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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 -9 yrs</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>10-19 yrs</td>
<td>4 (18.2)</td>
<td>5 (13.2)</td>
<td></td>
</tr>
<tr>
<td>20-29 yrs</td>
<td>6 (27.3)</td>
<td>13 (34.2)</td>
<td></td>
</tr>
<tr>
<td>30-39 yrs</td>
<td>4 (18.2)</td>
<td>16 (42.1)</td>
<td></td>
</tr>
<tr>
<td>40-49 yrs</td>
<td>5 (22.7)</td>
<td>3 (7.9)</td>
<td></td>
</tr>
<tr>
<td>≥50 yrs</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.
**Table 2** Characteristics of seven primary cases of measles, and the number and places of transmissions they produced

<table>
<thead>
<tr>
<th>PrC*</th>
<th>Age</th>
<th>Sex</th>
<th>Measles type</th>
<th>Vaccination status</th>
<th>Symptomatic period†</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>None</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>Unknown</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>

*Primary case

†Duration between the day of symptom onset and the day of specimen collection
Fig. 2
Fig. 3

- **PrC A**
- **PrC B**
- **PrC C**
- **PrC D**
- **PrC E**
- **PrC F**
- **PrC G**

**Measles**

- Driving school
- Hotel

**Modified measles**

- Shonai
- Murayama
- Okitama

- Dotted circle indicates a facility

- Symbols indicate different conditions:
  - *: Measles
  - †: Modified measles

Accepted Manuscript
Fig. 4

The bar chart shows the number of patients with positive and negative outcomes over different days after symptom onset. The y-axis represents the number of patients, while the x-axis shows the days after symptom onset.