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Case-based surveillance enhanced with measles virus detection/genotyping is essential to maintain measles elimination in Aichi Prefecture, Japan

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ABSTRACT

Background: Japan was verified as having achieved measles elimination by the Measles Regional Verification Commission in the Western Pacific Region in March 2015. Verification of measles elimination implies the absence of continuous endemic transmission. After the last epidemic in 2007 with an estimated 18,000 cases, Japan introduced nationwide case-based measles surveillance in January 2008. Laboratory diagnosis for all suspected measles cases is essentially required by law, and virus detection tests are mostly performed by municipal public health institutes. Despite relatively high vaccination coverage and vigorous response to every case by the local health center staff, outbreak of measles is repeatedly observed in Aichi Prefecture, Japan.

Methods: Measles virus N and H gene detection by nested double RT-PCR was performed with all specimens collected from suspected cases and transferred to our institute. Genotyping and further molecular epidemiological analyses were performed with the direct nucleotide sequence data of appropriate PCR products.

Results: Between 2010 and 2014, specimens from 389 patients suspected for measles were tested in our institute. Genotypes D9, D8, H1 and B3 were detected. Further molecular epidemiological analyses were helpful to establish links between patients, and sometimes useful to discriminate one outbreak from another. All virus-positive cases, including 49 cases involved in three outbreaks without any obvious epidemiological link with importation, were considered as import-related based on the nucleotide sequence information. Chain of transmission in the latest outbreak in 2014 terminated after the third generations, much earlier than the 2010–11 outbreak (6th generations).

Conclusion: Since 2010, almost all measles cases reported in Aichi Prefecture are either import or import-related, based primarily on genotypes and nucleotide sequences of measles virus detected. In addition, genotyping and molecular epidemiological analyses are indispensable to prove the interruption of endemic transmission when the importations of measles are repeatedly observed.

1. Introduction

Measles is a highly contagious disease caused by measles virus (MeV) [1]. Recently, both global and local measles control has achieved significant success [2,3]. Although measles is still a major cause of child death, estimated global mortality in 2013 is 145,700, fell by 75% from 544,200 in 2000 [4]. For the Western Pacific Region including Japan the elimination goal was set on 2012, and achievement of elimination was recently verified for Japan by the Measles Regional Verification Commission [3].

Aichi Prefecture, populated with 7.4 million as of November 2014, is one of the 47 second level administrative units in Japan (population: 127 million). It is located at the central area of the Honshu Island and is a major component of the third most industrialized and densely populated area of the nation. Until recently, measles was common in Japan including Aichi Prefecture, and outbreaks occurred each year during 1999–2003 [5,6]. Measles cases exported from Japan to the United States

Abbreviations: MeV, measles virus; MCV, measles-containing vaccine; NESID, National Epidemiological Surveillance Of Infectious Diseases; POC, point-of-care; RT-PCR, reverse transcription-polymerase chain reaction; SIA, supplementary immunization activity.

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Table 1
Numbers of measles cases reported annually from Aichi Prefecture compared with corresponding national data of Japan, and number of cases tested for measles virus by Aichi Prefectural Institute of Public Health between 2008 and 2014.

Calendar year	Japan	Aichi Prefecture			
	Case number (per million)	Case number (per million)	Number of cases less than 1 year of age (%)	Number of cases with MeV tests[a]	Genotypes[b]
2008	11,012 (85.4)	198 (26.6)	17 (8.6)	1	D5
2009	732 (5.7)	28 (3.9)	5 (17.9)	1	None
2010	447 (3.5)	32 (4.3)	2 (6.3)	22	D9
2011	439 (3.4)	32 (4.3)	2 (6.3)	62	D9
2012	293 (2.3)	39 (5.2)	3 (7.7)	118	D8
2013	232 (1.8)	25 (3.3)	4 (16.0)	103	B3, D9, H1
2014	463 (3.6)	46 (6.2)	8 (17.4)	84	B3, H1
Total		400	41 (10.3)	391	

[a] Number of tests performed by Nagoya City Public Health Institute are not included. Discarded cases based on laboratory findings and/or clinical courses are included.
[b] Test results performed by Nagoya City Public Health Institute are not included.

[7] and other countries were often noticed. In order to intensify measles control in Japan, second dose of measles-containing vaccine (MCV) was introduced in 2006, and case-based surveillance requiring confirmation with laboratory diagnosis, i.e., detection of the virus by RT-PCR/isolation and/or detection of measles virus-specific IgM antibody, was introduced in 2008. In addition, 5-year nation-wide supplementary immunization activity (SIA) targeting 13 and 18-year age groups was conducted in 2008–2012 [8]. Subsequently, number of measles cases in Japan dropped rapidly from 11,012 in 2008 to 732 in 2009. In Table 1, annual incidence of measles reported from Japan and from Aichi Prefecture between 2008 and 2014 is summarized. Measles incidence per million in Aichi Prefecture did not decrease since 2010, despite higher 1st dose MCV coverage in 2008–2013 (94.9–97.8%) than the national average [http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/hashika.html#20111231 in Japanese].

Control of measles requires both high vaccine coverage (more than 95%) and the presence of a well performing surveillance system. As a local public health institute, we are in charge of virus detection tests. Furthermore, virological information that is useful to determine the epidemiological link for each measles patient would be welcomed by physicians and public health officials. With the rapid decrease of annual reported number of measles cases, MeV detection and further laboratory information including the viral genotype and detailed molecular analysis data became feasible in Aichi Prefecture. Since 2010, we accept almost any sample for MeV detection obtained from every suspected measles case, including blood/serum of the patient collected before the onset of rash.

This paper describes the results of viral detection tests and sequence analyses (e.g., genotyping) on suspected measles cases, with emphasis on those involved in outbreaks, during recent 5 years (January 2010–December 2014) performed in our institute together with relevant epidemiological data. We also discuss the impact of virus information on the documentation of elimination status of the disease.

2. Methods

2.1. Virus detection and genotyping

Samples of throat swab, urine, blood were collected from patients suspected for measles and from susceptible contacts with confirmed measles patients in Aichi Prefecture, and were transferred to our laboratory. Patients diagnosed in Nagoya City (population: 2.3 million) within Aichi Prefecture are included in the annual case numbers described in Table 1, while laboratory tests for these patients were performed independently by Nagoya City Public Health Institute and their results are not included in this paper.

In most cases, samples were transferred to our laboratory immediately following collection. Some samples, especially sera collected at the disease onset (often before rash onset and therefore measles had not been considered) from the index patient, were retrieved a few weeks after storage in the refrigerator.

Nested double RT-PCR protocol for measles virus N and H genes, and the determination of measles virus genotype [9] by the nucleotide sequence of the relevant amplified product of NP region has been described elsewhere [10].

MeV isolation was attempted with PCR-positive samples using Vero-hSLAM cell line [11]. As a part of the National Epidemiological Surveillance Of Infectious Diseases (NESID) Japan, detection of rubella virus [10], parvovirus B19 and other viruses including enteroviruses and influenza viruses was also attempted with those samples negative for measles virus.

2.2. Collection of patient information

Diagnosis for each measles case based on both clinical and laboratory information was finalized by the reporting physician. Since 2010, every case confirmed as measles in Japan is subjected to a vigorous epidemiological investigation conducted by local health center(s). Epidemiological and clinical information of the patients described in this paper was limited to the information available from NESID system, except for those already reported in public, e.g., in the monthly publication of Infectious Agents Surveillance Report (IASR).

3. Results

3.1. Increase in number of samples for measles virus detection

Before June 2010 in Aichi Prefecture, reports of measles cases by physicians were mostly based on serology (detection of MeV-specific IgM). Requests for MeV detection were rare, e.g., only two patients were tested for MeV detection in 2008 and 2009 (Table 1). Requests for MeV detection gradually increased after the first successful MeV detection in an outbreak initiated by an imported measles case from the Philippines involving two nosocomial transmissions in two clinics (ID 1 in Table 2A). In this outbreak, MeV genotyping of the index patient (the imported case) was possible by direct sequencing of the RT-PCR product of the serum specimen that had been collected from the patient shortly after the disease onset (with fever before onset of rash) and stored at 4 °C for 26 days. The serum specimen was retrieved after the confirmation of second generation cases. Since 2013, samples from almost all patients suspected of measles in Aichi Prefecture are brought in to our institute for virological tests.