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Correlates of laboratory-confirmed measles in Japan, 2011–2015

Aika Watanabe [a,b], Tomoe Shimada [a,*], Takuri Takahashi [a], Yuzo Arima [a], Hitomi Kinoshita [a], Takehiko Saitoh [a], Kazuhiko Kanou [a], Tamano Matsui [a], Tomimasa Sunagawa [a], Keiko Tanaka-Taya [a], Kazunori Oishi [a]

[a] Infectious Diseases Surveillance Center, National Institute of Infectious Diseases, 1–23–1 Toyama, Shinjuku, Tokyo 162–8640, Japan
[b] Department of Epidemiology for Infectious Diseases, Osaka University Graduate School of Medicine, 2–2 Yamadaoka, Suita, Osaka 565–0871, Japan

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ABSTRACT

Background: With the progressive decline in the incidence of measles in Japan, its diagnosis has become challenging, with fewer physicians having experience in examining measles patients. We aimed to determine the correlates of laboratory-confirmed measles to help physicians improve their measles diagnosis.
Methods: This study was conducted using the National Epidemiological Surveillance of Infectious Disease (NESID) system data during 2011–2015. Among clinically suspected measles patients reported to NESID, measles virus (MV)-positive patients were compared with MV-negative patients. The odds ratios (OR) and associated 95% confidence intervals (CI) were determined using logistic regression.
Results: A total of 4168 laboratory-tested patients were notified to NESID. We analysed 618 MV-positive patients (median age, 17 years; interquartile range [IQR], 4–30 years) and 600 MV-negative (median age, 10 years; IQR, 1–29 years) patients after excluding those that met the exclusion criteria or were reported during the rubella epidemic period (the 18th epidemiological week of 2012 to the 46th week of 2013). Having an epidemiological link with a measles patient within 14 days of onset (OR, 14.9; 95% CI, 10.0–23.3), a history of recent international travel (OR, 11.7; 95% CI, 6.9–19.9), and unvaccinated/unknown vaccination status for measles-containing vaccine (MCV; OR, 3.7; 95% CI, 2.3–5.7) were significantly associated with MV-positive status. International travel (adjusted OR, 10.2; 95% CI, 5.9–17.7) and unvaccinated/unknown MCV vaccination status (adjusted OR, 5.8; 95% CI, 3.5–9.8) remained significantly associated with MV-positive status after adjusting for age, sex, and each other.
Conclusion: In low-incidence Japan, having an epidemiological link, international travel, and lack of MCV vaccination were correlates of laboratory-confirmed measles. The findings of this study could potentially improve the clinical diagnosis of measles, which can lead to more efficient testing and earlier laboratory confirmation.

1. Introduction

Measles, caused by the measles virus (MV), is an acute and highly contagious disease mainly characterised by high fever and cough followed by the appearance of systemic maculopapular rash [1]. It can lead to serious illness, life-long complications, and death [2]; however, it is preventable by vaccination [3]. In Japan, a one-dose measles-containing vaccine (MCV) schedule was implemented in 1978, which was changed to a 2-dose schedule in 2006. The first dose (MCV1) is administered between 12 and 24 months of age, and the second dose (MCV2) between 5 and 6 years of age (i.e., a year prior to entering elementary school). In response to a large measles outbreak in 2007, the National Measles Elimination Plan was approved in December 2007. In accordance with this plan, measles became a notifiable disease that requires reporting through the National Epidemiological Surveillance of Infectious Disease (NESID) system under the Infectious Diseases Control Law of Japan in January 2008 [4,5]. In addition, a nationwide 5-year catch-up campaign of measles-rubella vaccination targeting age groups of 12–13 and 17–18 years was initiated in April 2008 as a temporary measure after measles outbreaks occurred in school-age populations [5]. Following these efforts, the number of

Abbreviations: MV, measles virus; MCV, measles-containing vaccine; MCV1, first dose of MCV; MCV2, second dose of MCV; NESID, National Epidemiological Surveillance of Infectious Disease; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range, IgM, immunoglobulin M; PPV, positive predictive value.

* Corresponding author.
E-mail address: tomoes@niid.go.jp (T. Shimada).

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confirmed measles cases in Japan has decreased dramatically since 2009, and the indigenous MV genotype D5 strain has not been detected since May 2010 [6]. Consequently, based on the established criteria, the Measles Regional Verification Commission for the World Health Organization Western Pacific Region verified that Japan had achieved measles elimination in March 2015 [7,8]. However, during the years of progress prior to measles elimination and in the years following, local transmission following MV importation continued to be observed [9–13]. In a country with a low incidence of measles, a timely and accurate measles diagnosis has become more difficult for physicians who have little experience in examining measles patients [14–15]. Given the high incidence of measles-like diseases, physicians may face challenges in the differential diagnosis when confronted with patients presenting with rash and fever, and knowledge about the indicators for increasing the index of clinical suspicion is needed. Therefore, we conducted this study to identify the correlates of laboratory-confirmed measles, based on the national surveillance data. Our study findings can assist clinical and public health practitioners because such studies examining correlates of measles have been limited, especially in countries that are in a transitional phase towards measles elimination.

2. Materials and methods

2.1. Case definition and classification

The measles case definition for NESID is based on clinical signs/symptoms and laboratory findings. Clinically, a patient is diagnosed with measles when presenting with fever, rash, and catarrh signs (e.g., cough, coryza, or conjunctivitis). Laboratory-confirmed measles is defined as a patient with any of the aforementioned clinical signs/symptoms fulfilling any of the following laboratory criteria [16]: detection of measles-specific immunoglobulin M (IgM) titre, detection of MV by reverse transcription polymerase chain reaction or isolation of MV in cell culture [17]. MV detection, isolation, and genotyping are performed mainly at designated local governmental public health institutions. It is recommended that these clinical specimens (i.e., blood, urine, and throat samples) for measles test be collected at an appropriate time: the specimens for IgM testing are required to be obtained between 4 and 28 days after rash onset, and the specimens for MV detection and isolation to be obtained within 7 days after rash onset [18].

2.2. Study design

This study was conducted based on measles patients notified after the last detection of MV genotype D5 strain in Japan in 2010. We extracted the following data from measles patients notified in the NESID system between 1 January 2011 and 31 December 2015: age, sex, clinical signs/symptoms, laboratory findings, date of illness onset, MCV vaccination status, dates of MCV vaccination, international travel history within 14 days of illness onset, laboratory test results, dates of specimen(s) collection, and suspected location of MV exposure. An epidemiological link, defined as having a record of a contact history with a suspected/confirmed measles patient, was also assessed from the case reporting form. Among clinically suspected measles patients reported to NESID, those with a positive result for any of the measles tests listed in the laboratory criteria were defined as "MV-positive patients" (laboratory-confirmed cases) and those with a negative result were defined as "MV-negative patients"(discarded cases). Patients with any of the following were excluded: (1) tested for any specimen (s) obtained at an inappropriate (i.e., outside the aforementioned appropriate time) and/or an unknown time (with respect to time since disease onset) (however, those that tested positive for MV (n = 22) were included even if sampled during an inappropriate time); (2) tested for MV but had no results available (i.e., blanks); (3) tested positive for MV vaccine strain [i.e., detection of MV vaccine strain (genotype A) or IgM-positive result, but had received MCV 8 days to 6 weeks prior to sample collection [19]]; (4) did not meet the notification criteria, or (5) had duplicated data.

2.3. Data analysis

We first described the frequency and distribution of the demographic and epidemiological characteristics of the MV-positive and MV-negative patients. We examined the association of these characteristics with laboratory-confirmed measles status by calculating odds ratios (OR) with their associated 95% confidence intervals (CI). Following univariate logistic regression, an exploratory multivariate logistic regression model was constructed.

All variables with a large and significant OR in the univariate analysis were included in the multivariate regression model; age and sex were included regardless of its significance in the univariate analysis or changes to the OR estimates of the other covariates. Variables with a high proportion of unknown status records (i.e. having an epidemiological link to a measles patient or the suspected location of MV-exposure) were not included in the model due to the large proportion of missing data and potential for sparse data bias. All adjusted ORs (aOR) were simultaneously adjusted for all other factors included in the model.

As a large rubella outbreak had occurred from late 2013 to March 2014 in Japan [20], we stratified the data by epidemic and non-epidemic periods for rubella to examine the effect of the rubella epidemic on measles detection. An epidemic period for rubella was defined as the weeks where the weekly number of rubella patients was >2 standard deviations of the mean number of patients in the study period for at least 3 consecutive weeks. A non-epidemic period for rubella was defined as a period outside the defined epidemic periods. We conducted a sensitivity analysis based on the data stratified by epidemic vs. non-epidemic period to determine any differences between the two periods. Data were cleaned and analysed using Microsoft Excel 16.0 and SAS 9.4 (SAS Institute Japan Ltd., Tokyo, Japan). Statistical significance was assumed at a p value <0.05; all p values were 2-sided. Chi-squared and Fisher's exact test (where appropriate) were used for comparing the distribution of categorical data between MV-positive and MV-negative patients.

2.4. Ethics

Ethical approval was not necessary because this study was conducted for public health purposes and based on national surveillance data.

3. Results

A total of 4719 suspected measles patients were notified in the NESID system during the study period from 2011 to 2015 (Fig. 1). Of these, 4168 (88%) were laboratory-tested for measles. We excluded 2150 (52%) patients based on the exclusion criteria: 1726 patients were tested for specimen(s) obtained at an inappropriate and/or unknown time (i.e., specimens obtained too early or late); 390 patients had no test results available for MV (i.e., "blanks"); 42 patients tested positive for the MV vaccine strain; 7 patients did not meet notification criteria; and 5 patients had duplicated data. The epidemic period for rubella was identified from the 18th epidemiological week of 2012 to the 46th week of 2013. The remainder of the study period was defined as the non-

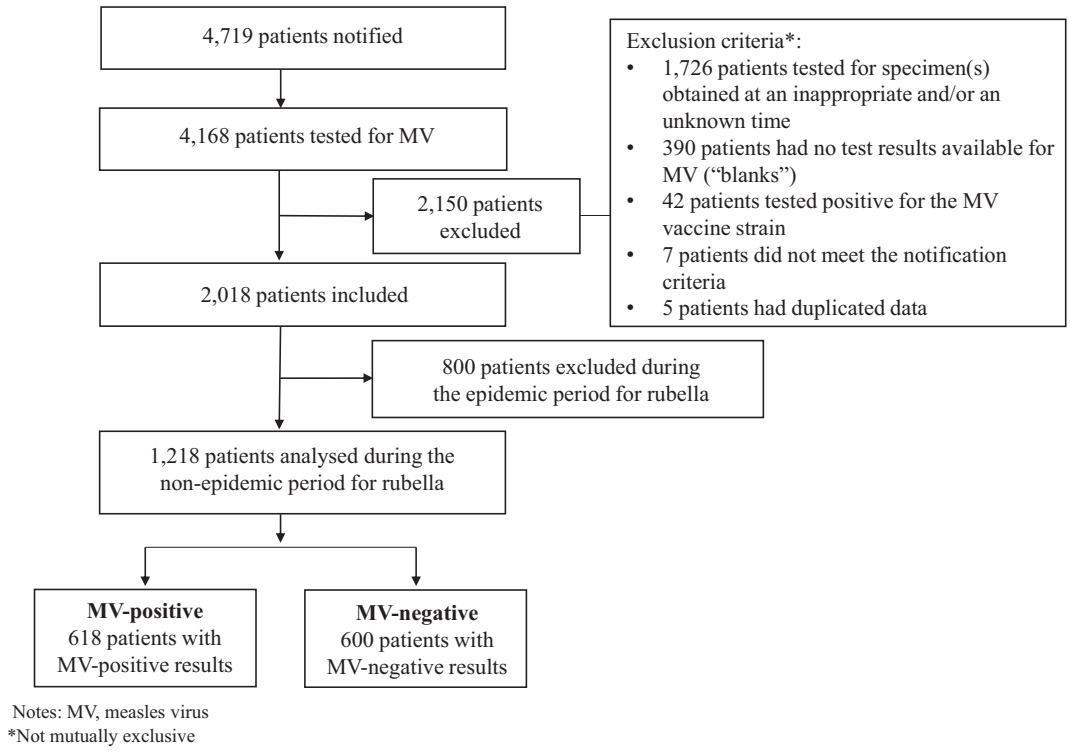

Fig. 1. Flow diagram of MV-positive and MV-negative patients, Japan, 2011–2015.

epidemic period for rubella (the 1st week of 2011 to the 17th week of 2012 and the 47th week of 2013 to the 53rd week of 2015). A higher proportion of measles-negative patients in the epidemic period for rubella were male (70%), older (age ≥ 26 years; 56%), and had unknown MCV vaccination status (64%) compared to those in the non-epidemic period (Supplement 1). Based on the sensitivity analysis of the stratified data, the ORs for sex, age, and vaccination status differed by >10% between the periods. Furthermore, rubella virus was detected in significantly more measles-negative patients during the epidemic (96%, 298/312) than the non-epidemic (39%, 23/59) period for rubella (χ^2 test, $p < 0.05$; Supplement 2), indicating that the measles-negative group during the epidemic period was driven by characteristics of rubella patients, and thus considerably different compared to the non-epidemic periods for rubella. Therefore, we excluded a total of 800 patients from the rubella epidemic period, and a total of 1218 patients (618 MV-positive and 600 MV-negative) from the non-rubella epidemic period were included in the analyses. The demographic characteristics, except for sex, differed significantly between the 2 groups (Table 1).

MV-positive patients were older [median age, 17 years; interquartile range (IQR), 4–30 years] than MV-negative patients (median age, 10 years; IQR, 1–29 years). Among MV-positive patients, there were 176 (29%) adults aged 26–39 years (born during 1972–1989), and 62 (10%) were infants aged <1 year (before the age of eligibility for MCV1). However, relative to other age groups, the positive predictive value (PPV) of testing MV-positive was higher among patients aged 5–14 years (61%, 123/203, born during 1997–2010) and 26–39 years (61%, 176/290).

Regarding MCV vaccination status, a higher proportion of MV-positive patients were unvaccinated for MCV (50%) and only a small proportion had received 2 doses of MCV (5%). Among both MV-positive and MV-negative patients, approximately 30% of patients reported an unknown MCV vaccination status.

International travel within 14 days of onset was reported for 150 (24%) MV-positive patients. The majority of MV-positive (56%) and MV-negative patients (95%) did not have any recorded information for epidemiological link.

Based on the univariate analyses, an epidemiological link with measles (OR, 14.9; 95% CI, 10.0–22.3), international travel within 14 days of onset (OR, 11.7; 95% CI, 6.9–19.9), and unvaccinated/unknown MCV vaccination status (OR, 3.7; 95% CI, 2.3–5.7) were significantly associated with MV-positive status. After restricting the analysis to those with a known MCV vaccination status, unvaccinated (OR, 5.3; 95% CI, 3.3–8.4) patients were more strongly associated with MV-positive status.

In addition, suspected locations of MV-exposure including the home (OR, 4.6; 95% CI, 1.7–12.2) and hospital (OR, 3.6; 95% CI, 1.2–10.6) were significantly associated with MV-positive status compared to nursery/school. Based on the multivariate analysis, patients with an unvaccinated/unknown MCV vaccination status (aOR, 5.8; 95% CI, 3.5–9.8) and having an international travel history (aOR, 10.2; 95% CI, 5.9–17.7) were significantly associated with laboratory-confirmed measles (Table 2). Unvaccinated status (aOR, 10.2; 95% CI, 5.9–17.7) was more strongly associated after restricting the analysis to patients with a known MCV vaccination status.

4. Discussion

By analysing national surveillance data, we determined that having an epidemiological link, unvaccinated status, and international travel history were correlates of laboratory-confirmed measles in Japan during 2011–2015. This information can help improve clinical detection of measles, leading to more efficient testing and earlier laboratory confirmation and public health response.

An incomplete or unvaccinated/unknown MCV vaccination status was significantly associated with laboratory-confirmed measles patients. In a recent national surveillance report, about 90% of measles patients had incomplete MCV vaccination (including those with unknown MCV vaccination status) [21]. In Japan, a

Table 1
Demographic characteristics of patients during the non-epidemic period for rubella (n = 1218), Japan, 2011–2015.

	MV-positive (n = 618) n (%)	MV-negative (n = 600) n (%)	p value
Sex			
Male	319 (51.6)	325 (54.2)	0.37
Age			
<1 year	62 (10.0)	59 (9.8)	<0.05
1–4 years	102 (16.5)	191 (31.8)	
5–14 years	123 (19.9)	80 (13.3)	
15–25 years	110 (17.8)	92 (15.3)	
26–39 years	176 (28.5)	114 (19.0)	
40–49 years	34 (5.5)	40 (6.7)	
≥50 years	11 (1.8)	24 (4.0)	
MCV vaccination status			
Unvaccinated	311 (50.3)	149 (24.8)	<0.05[a]
1 dose of measles-containing vaccine	80 (12.9)	176 (29.3)	
2 doses of measles-containing vaccine	29 (4.7)	73 (12.2)	
Unknown	198 (32.0)	202 (33.7)	
International travel history			
Yes	150 (24.3)	16 (2.7)	<0.05[a]
No	465 (75.2)	578 (96.3)	
Unknown	3 (0.5)	6 (1.0)	
Record of epidemiological link			
Yes	272 (44.0)	30 (5.0)	<0.05
No	346 (56.0)	570 (95.0)	
Suspected location of MV-exposure			
Home	123 (19.9)	8 (1.3)	<0.05 [b,c]
Hospital	73 (11.8)	6 (1.0)	
Nursery/school	37 (6.0)	11 (1.8)	
Workplace	10 (1.6)	2 (0.3)	
Others	31 (5.0)	3 (0.5)	
Unknown/blank	344 (55.7)	570 (95.0)	

MV, measles virus; MCV, measles-containing vaccine.
[a] Analysed excluding 'Unknown'.
[b] Analysed excluding 'Others' and 'Unknown/blank'.
[c] Fisher's exact test.

Table 2
Univariate and multivariate analyses of factors associated with laboratory-confirmed measles patients during the non-epidemic period for rubella (n = 1218), Japan, 2011–2015.

	Crude odds ratio [95% CI]	Adjusted odds ratio [95% CI]
MCV vaccination status		
Unvaccinated/unknown	3.7 [2.3–5.7]	5.8 [3.5–9.8]
1 dose of measles-containing vaccine	1.1 [0.7–1.9]	2.2 [1.2–3.9]
2 doses of measles-containing vaccine	Reference	Reference
International travel history		
Yes	11.7 [6.9–19.9]	10.2 [5.9–17.7]
No/unknown	Reference	Reference
Record of epidemiological link		
Yes	14.9 [10.0–22.3]	–
No	Reference	–
Suspected location of MV-exposure		
Home	4.6 [1.7–12.2]	–
Hospital	3.6 [1.2–10.6]	–
Workplace	1.5 [0.3–7.8]	–
Nursery/school	Reference	–

Adjusted odds ratios were adjusted for sex, age, vaccination status, and international travel history.
CI, confidence interval; MV, measles virus; MCV, measles-containing vaccine.

routine vaccination record is issued by clinicians who provide vaccination and should be kept by vaccinees and/or their guardians. MCV vaccination status should be confirmed by such documentation rather than the patient's memory, to verify vaccination status and increase the PPV of clinical measles diagnosis that incorporates confirmed vaccination status information.

Recent international travel was also significantly associated with laboratory-confirmed measles patients. In fact, international travel has permitted multiple MV importations from endemic countries into countries or areas that have achieved elimination. The United States and Australia reported that as many as 95–100% of measles cases were related to international travel. Examples of large measles outbreaks following an imported case include the 2014 Disneyland outbreak in the United States [22] and the 2012 outbreaks in Sydney, Australia [23,24].

In 2016, over 24 million foreigners visited Japan and 16 million Japanese had travelled abroad [25]. Based on the available information provided by the Japan National Tourism Organization

[26], visitors to Japan who travelled from measles-endemic areas accounted for at least 44% of all visitors in 2017. At least 43% of all Japanese overseas travellers went to measles-endemic areas in 2015. Given the high transmissibility of measles, MV importation is expected under such situations; therefore, we strongly recommend that physicians inquire of recent international travel history when examining patients presenting with fever and rash. Having detailed travel history information can help improve differential diagnosis by considering the likelihood of measles.

According to the univariate analysis, having a record of epidemiological link was strongly associated with laboratory-confirmed measles. In May 2014, the Ministry of Health, Labour and Welfare notified that local governments are required to report any evidence of an epidemiological link obtained through outbreak investigation. The PPV for having a record of an epidemiological link was considerably high (90%). However, the majority of reported patients had no epidemiological link information available. In addition to imported cases who would not have a link, this information was not mandatory on the reporting form, and it might also have been difficult to identify the epidemiological link due to the high transmissibility of measles. To obtain more available information of an epidemiological link from suspected patients, any evidence of epidemiological link obtained from confirmed patients through outbreak investigation (i.e., contact tracing) should be shared rapidly during an outbreak.

While completeness of this information was low, the high PPV is plausible and expected given that the majority of those with a recorded epidemiological link are those who were contacts of a laboratory-confirmed patients. Therefore, having an epidemiological link also serves as helpful information for physicians who suspect measles. Nonetheless, we strongly believe that the existence or otherwise of an epidemiological link does not affect public health response. The national guideline for measles response states that a single suspected measles case should be investigated and trigger a prompt response to avoid further transmission.

There were laboratory-confirmed patients without all three measles-like symptoms (88/618, 14%), namely modified measles, defined by NESID. We assumed that physicians do not usually suspect measles when they encounter modified measles and would therefore not test the patient for measles. Having an epidemiological link to a measles patient should be an important clue for diagnosis in such cases. In fact, 49 (56%) out of 88 modified measles patients had an epidemiological link to a measles patient.

We selected the nursery/school as the reference group when evaluating suspected locations of MV exposure with the assumption that most schoolchildren had completed 2 doses of MCV. Compared to the reference group, the home and hospital were significantly associated with laboratory-confirmed measles. The household has often proved to be a high-risk setting for measles transmission if family members are susceptible to measles due to continuous close-contact among family members [27]. Among patients infected at home, at least 17% had family members with measles-like symptoms who had recently visited a measles-endemic area. It is important to note that there are certain vulnerable populations when regarding the household as a high-risk location of MV exposure. In a recent report, imported MV cases spread from persons living in Japan who returned from travelling abroad [9,28]. Some foreigners living in Japan are a vulnerable population who frequently miss routine vaccinations because of language barriers. In order to maintain a high MCV coverage at the community level, health authorities must carefully follow-up these vulnerable groups to ensure that they receive their routine vaccinations.

Hospitals, including emergency departments, can also be a high-risk setting for MV exposure and measles transmission due to susceptible occupants. Nosocomial transmission of measles has been frequently reported and has played a crucial role in the transmission of infection and generation of many cases, especially in countries nearing measles elimination [29,30]. The risk of transmission from a measles patient to susceptible individuals may be increased in settings where health care workers have less experience with measles and therefore, have less suspicion for the disease that has become unusual in a low-incidence setting [30]. Misdiagnosis or delayed diagnosis of a measles case might result in MV spread due to inadequate infection control measures [14]. Early suspicion and rapid detection of potential measles exposure is always the first step to limiting further spread of MV. To maintain measles elimination status, a sensitive surveillance system with high data quality and high vaccination coverage (>95%) are essential.

We believe our findings will help physicians improve clinical diagnosis for the early identification of measles. The strength of our study is that we performed a comparison between MV-positive and MV-negative patients based on laboratory results among those who sought healthcare and received a laboratory test, thus limiting potential biases introduced by differences in healthcare seeking behaviour (laboratory-confirmed outcomes are confirmed only after accessing healthcare).

Furthermore, stratifying patients by the epidemic/non-epidemic period for rubella and restricting the analysis to the non-epidemic period also helped to ensure more generalisable results for the correlates of laboratory-confirmed measles, based on the usual situation. The PPV between these periods [epidemic period, 66/800 (8%); non-epidemic period, 618/1218 (51%)] was substantially different, with MV-negative patients during the epidemic period for rubella strongly associated with rubella positivity. As the correlates during the rubella-epidemic period were strongly affected by the characteristics of these rubella patients (Supplement 1), including these results would have changed our comparison group from an MV-negative one to essentially a rubella-positive comparison group.

There were several potential limitations in our study. First, our comparison was performed between MV-positive and MV-negative patients. The calculated ORs could be biased as these MV-negative patients were different from a random sample of healthy controls from the source population. However, our approach is practically useful for clinicians, as these are the very patients that they encounter. The results can inform diagnosis when they encounter a patient with a measles-like syndrome.

Second, almost half of the patients notified to NESID were excluded from our study. Among them, 1726 patients were excluded because they were tested using specimens that were obtained during an inappropriate and/or unknown period and the distribution of their true MV status remains unknown. We assumed that false negative patients, who can be a source of measles infection, may have been included in the excluded group. In order to conduct accurate surveillance, specimens should be collected during the appropriate period, and therefore, the dates of rash onset and specimen collection should be accurately recorded. Third, there was a possibility of underreporting some clinical patients in this study. For example, earlier, not all measles-negative patients were reported due to differences in the notification policy among local governments; after 2013, all health practitioners were required to report any suspected measles patients to local health officials within 24 h. Fourth, we expected that the majority of patients aged 5–14 years would be protected against MV infection compared to other age groups because the MCV2 vaccination coverage of this age group was estimated as 92–94% [31]. However, this age group (61%) had a high PPV similar to the 26–39 year age group (61%). A potential reason for the high PPV may be that the physicians were being more specific and selective in suspecting and testing patients aged 5–14 years with rash and fever because children in this age group were generally assumed

to have a high vaccine coverage of MCV2 and thus be of low MV infection risk.

Despite these limitations, we have identified correlates from the national data that could aid in the diagnoses of measles in suspected patients in Japan, with the potential to increase efficiency and the PPV of laboratory-testing for measles in a low-incidence setting.

5. Conclusions

In conclusion, having an epidemiological link to measles patients, lack of MCV vaccination, and recent international travel history were strongly associated with laboratory-confirmed measles. The findings of this study have the potential to improve the clinical detection of measles by physicians, which can lead to more efficient and earlier laboratory confirmation. We recommend that physicians increase their index of suspicion by seeking information about the above factors whenever they examine patients presenting with rash and fever, especially in countries progressing towards measles elimination. Studies to determine correlates of laboratory-confirmed measles in the post-elimination era are also needed in order to maintain measles elimination status.

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Conflicts of interest

The authors have no financial interests relevant to this article to disclose.

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Author contributions

Aika Watanabe, Tomoe Shimada, and Kazunori Oishi initiated and designed the study. Takuri Takahashi, Hitomi Kinoshita, Takehiko Saitoh, Kazuhiko Kanou, and Tomimasa Sunagawa collected and cleaned the data. Aika Watanabe and Tomoe Shimada analysed the data. Aika Watanabe, Tomoe Shimada, Yuzo Arima, Tamamo Matsui, and Keiko Tanaka-Taya interpreted the data. Aika Watanabe, Tomoe Shimada, and Kazunori Oishi wrote the first draft of the manuscript. All authors read, commented, and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.011.

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