

Original Article

Evaluation of an Expanded Case Definition for Vaccine-Modified Measles in a School Outbreak in South Korea in 2010

Young June Choe^{1*}, Jae Kyung Hu², Kyung Min Song¹, Heeyeon Cho¹, Hee Sook Yoon¹,
Seung Tae Kim¹, Han Jung Lee², Kisoon Kim¹, Geun-Ryang Bae¹, and Jong-Koo Lee¹

¹*Korea Centers for Disease Control and Prevention, Cheongwon-gun, Chungcheongbuk-do; and*

²*Incheon Metropolitan City, Health Social Bureau, Incheon, Republic of Korea*

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SUMMARY: In this study, we have described the clinical characteristics of vaccine-modified measles to assess the performance of an expanded case definition in a school outbreak that occurred in 2010. The sensitivity, specificity, and the positive and negative predictive values were evaluated. Among 74 cases of vaccine-modified measles, 47 (64%) met the original case definition. Fever and rash were observed in 73% (54/74); fever was the most common (96%, 71/74) presenting symptom, and rash was noted in 77% (57/74) of the cases. The original case definition showed an overall sensitivity of 63.5% and a specificity of 100.0%. The expanded case definition combining fever and rash showed a higher sensitivity (72.9%) but a lower specificity (88.2%) than the original. The presence of fever and one or more of cough, coryza, or conjunctivitis scored the highest sensitivity among the combinations of signs and symptoms (77.0%), but scored the lowest specificity (52.9%). The expanded case definition was sensitive in identifying suspected cases of vaccine-modified measles. We suggest using this expanded definition for outbreak investigation in a closed community, and consider further discussions on expanding the case definition of measles for routine surveillance in South Korea.

INTRODUCTION

Measles is a disease presenting with a relatively distinct exanthematous maculopapular rash, characterized by a prodrome of fever, cough, coryza, conjunctivitis, and a pathognomonic enanthem (Koplik spot). The incidence of measles has declined in some countries following the introduction of effective vaccination programs (1). However, measles is still a major public health threat because of its worldwide prevalence and changing epidemiological patterns in countries where vaccines have been widely used (2,3).

South Korea has had a large number of annual measles cases before the introduction of a vaccine into the National Immunization Program in the 1980s (4). However, because of the difficulty in reaching an adequate level of vaccination coverage required to interrupt transmission, the disease prevailed (5). In response to a large nationwide outbreak that occurred in 2001–2002, a school-based catch-up vaccination campaign resulted in a dramatic reduction in the morbidity and mortality of measles (6). Subsequently, implementation of an enhanced measles surveillance system has demonstrated the termination of the endemic circulation of the virus in the country (7). Following these activities, the incidence of measles in South Korea has decreased from

60–100 reported cases per 100,000 persons to less than 1 per 100,000; moreover, the country had declared the elimination of measles in 2006 (5).

Although measles is now considered a disease of the past in South Korea, there have been ongoing reports of sporadic cases of vaccine-modified measles, that is, the occurrence of measles in partially immune persons, which has a mild clinical presentation and, thus, becomes more difficult for clinicians to diagnose as measles (8). Understanding the magnitude of vaccine-modified measles is important because the success of sustaining measles elimination is dependent on a high level of awareness among health-care personnel for the immediate detection and reporting of any suspected measles cases. Because physicians are more likely not to suspect a rash-associated condition as measles because of the sustained elimination of the disease, an expanded surveillance case definition with a higher sensitivity may be required.

The current measles surveillance system operated by the Korean government defines a suspected measles case as “an illness characterized by the presence of all of the following features: morbilliform rash; fever of above 38°C; and one or more of cough, coryza, or conjunctivitis (3C)” (9). Although this case definition has been widely adopted and used in other countries as well, it does not reflect the changing patterns of the epidemiology of measles in the country (10). Moreover, some cases of vaccine-modified measles may not present the typical rash or perhaps even have no overt symptoms at all (11).

Although additional knowledge is required to guide decisions on the expansion of the case definition for measles surveillance in a population with high vaccination coverage, few data currently support this (12). Because the definition for a suspected measles case has a

*Corresponding author: Mailing address: Division of Vaccine Preventable Disease Control and National Immunization Program, Korea Centers for Disease Control and Prevention, Osong Health Technology Administration Complex, 187 Osongsaengmyeong2(i)-ro, Gangneung-myeon, Gangneung-gun, Gangwon-do, 263-951, Republic of Korea. Tel: +82-43-719-7348, Fax: +82-43-719-7379, E-mail: choeyj@yahoo.com

pivotal role in the disease surveillance, assessment of the performance of the current case definition is essential as it may affect the measles control policy in the country.

An outbreak that occurred in a school in 2010 has provided us an opportunity to examine the performance of the case definition for suspected measles in a population.

In this study, we have described the clinical characteristics of vaccine-modified measles to assess the performance of an expanded case definition for suspected measles in a school outbreak.

MATERIALS AND METHODS

Description of the outbreak: The outbreak occurred from May 1 to July 15, 2010, in an all-male junior high school in Incheon, South Korea. There were 878 students enrolled in the school (age range, 13–15 years).

Using a standardized questionnaire, three trained pediatricians interviewed students suspected of having measles about the presence and duration of their symptoms (fever, rash, or 3C). In conjunction with the school nurse and a public health center officer, the duration of symptoms and outcomes of the affected students were followed up.

Study subjects and case definition: The expanded definition for suspected measles that was adopted during this outbreak was “any student attending the school during the outbreak period who presented one or more of following features: fever, rash, cough, coryza, or conjunctivitis.” The students were examined for any rash that started from the back of their ears, as it is considered to be a typical feature in patients with measles infection. All suspected measles cases were identified by the school’s health center through active surveillance.

Laboratory tests were conducted for all suspected cases. The vaccination status of each suspected case was reviewed using the National Immunization Registry Program, which identifies whether the student has received one or more doses of a measles-containing vaccine (\geq MCV1); however, information about whether the students received 1 dose or 2 doses was not available in this registry. Students with no documented history of vaccination or those who were classified as having epidemiologically confirmed measles (defined as a suspected case that had an epidemiological linkage to a laboratory-confirmed case, but with negative laboratory test result) were excluded from analysis. The remaining students (suspected cases with a history of vaccination of \geq MCV1 and those who were not epidemiologically confirmed) were selected for analysis. The participating students with laboratory confirmation were classified as the vaccine-modified measles case subjects, whereas those who had negative laboratory test results were classified as the non-measles case subjects.

Ethical approval is not required in our institution on investigation for routine surveillance data.

Laboratory methods: Laboratory confirmation was defined as a positive test result in any one or more of the following: measles-specific IgM antibody, 4-fold increase of IgG antibody in paired sera, RT-PCR, or virus isolation.

Measles-specific antibody was identified using a measles ELISA test for IgM and IgG (EIA; Siemens

Healthcare Diagnostics Inc., Erlangen, Germany) in all suspected cases. Suspected cases (in students from whom blood specimens were obtained ≤ 72 h after the onset of rash) that were negative for IgM were subjected to a second collection and testing of blood specimens to check the presence of IgM antibody and a change in the IgG titer. Throat swab samples were frozen until shipment for RT-PCR testing and virus isolation.

Data analysis: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated for the following combinations of symptoms and signs: (i) fever and rash and one or more of 3C; (ii) fever and rash; (iii) fever and one or more of 3C; (iv) rash and one or more of 3C; (v) fever; (vi) rash; and (vii) one or more of 3C.

Sensitivity was estimated by the proportion of laboratory-confirmed cases that met the case definition (true positives). This was calculated by dividing the number of laboratory-confirmed cases that met the case definition by the total number of laboratory-confirmed cases. Specificity was estimated by the proportion of non-laboratory-confirmed cases that did not meet the case definition (true negatives). This was calculated by dividing the number of students with negative laboratory test results whose illness did not meet the case definition. PPV was the proportion of signs and symptoms that met each of the case definitions. It was calculated by dividing the number of students who met the case definition that were laboratory-confirmed by the total number of students who met the case definition. NPV was the proportion of those who did not meet the case definition that were not laboratory-confirmed. It was calculated by dividing the number of students who did not meet the case definition that gave negative laboratory results by the total number of students who did not meet the case definition.

RESULTS

Description of the study population: Of the total 878 students in the school, 127 (14.5%) were classified as having suspected measles according to the expanded case definition that was implemented during this outbreak (Fig. 1). Of them, 2 students who had no documented history of vaccination and 17 students who were classified as having epidemiologically confirmed measles were excluded from analysis. Overall, 108 students were included in the analysis, comprising 74 vaccine-modified measles cases and 34 discarded cases. Of the 74 vaccine-modified measles cases, 39 were positive for IgM, 19 showed a 4-fold increase in IgG in the paired sera, and 42 and 11 gave positive results in RT-PCR test and virus isolation, respectively.

Clinical characteristics: Among the 74 cases of vaccine-modified measles, 47 (64%) met the original case definition, which included all of fever, rash, and one or more of 3C (Table 1). When classified according to the combination of symptoms and signs, 73% (54/74) were found to have fever and rash, whereas 77% (57/74) showed fever and one or more of 3C. Among 34 non-measles cases, none met the original case definition. Among the non-measles cases, 12% had fever and rash, 47% had fever with one or more of 3C, and 12% had rash and one or more of 3C.

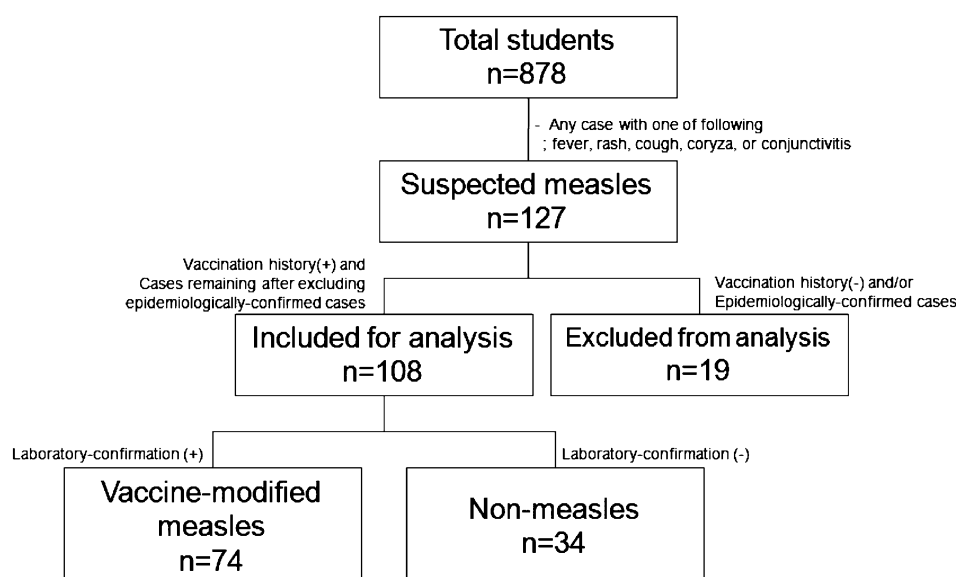


Fig. 1. Enrollment of vaccine-modified measles cases in a school outbreak in Incheon, South Korea, 2010.

Table 1. Clinical characteristics of vaccine-modified measles cases identified in a school outbreak in Incheon, South Korea, 2010

	Vaccine-modified measles n = 74	Non-measles n = 34
Combinations of clinical findings no. (%)		
F + R + 3C	47 (64)	0
F + R	54 (73)	4 (12)
F + 3C	57 (77)	16 (47)
R + 3C	47 (66)	4 (12)
Fever presentation		
no. (%)	71 (96)	27 (79)
duration, mean (days)	4.4 ± 1.5	2.2 ± 1.4
Rash presentation		
no. (%)	57 (77)	8 (27)
duration, mean (days)	4.3 ± 1.6	3.5 ± 2.1
no. rash started from ear (%)	28 (38)	0
≥ One of 3C presentation		
no. (%)	58 (78)	24 (71)
Cough	55 (74)	17 (50)
Coryza	29 (39)	16 (47)
Conjunctivitis	3 (4)	2 (6)
Order of presentation no. (%) ¹⁾		
F = R	14 (26)	2 (50)
F → R	40 (74)	2 (50)
Koplik spot no. (%)	1 (1)	0

¹⁾: Order of presentation indicates chronological order of appearance of fever and rash; F = R indicates fever and rash were noted simultaneously on same day; note that number of cases with both fever and rash were used as denominators for calculation of proportions.

F, fever; R, rash; 3C, cough, coryza, or conjunctivitis.

Fever was the most common presenting symptom in cases of vaccine-modified measles (96%, 71/74) with a mean duration of 4.4 ± 1.5 days; whereas, non-measles cases presented with fever of a shorter duration of 2.2 ± 1.4 days (Table 1). The presence of rash was noted in 77% (57/74) of vaccine-modified measles and 27% of

non-measles cases, with mean durations of 4.3 ± 1.6 days and 3.5 ± 2.1 days, respectively. Only 38% (28/74) of students with vaccine-modified measles had rashes that started from the back of their ears.

The presence of one or more of 3C was found to be similar in vaccine-modified measles and non-measles cases (78% and 71%, respectively) (Table 1). Cough was the most common symptom in vaccine-modified measles cases (74%), followed by coryza (39%) and conjunctivitis (4%).

Among students with vaccine-modified measles, 64% (40/74) have had fever that started earlier than the onset of rash, whereas 26% were found to have fever that developed simultaneously with the onset of rash (Table 1). None of the case subjects had an onset of rash that started earlier than fever development. Only one case of the vaccine-modified measles cases was found to show a Koplik spot that was identified by a pediatrician.

Assessment of the expanded case definition: During the outbreak, the original case definition of suspected measles (all of fever, rash, and one or more of 3C) showed an overall sensitivity of 63.5% and a specificity of 100.0% (Table 2). The PPV and NPV for the original case definition were 100.0% and 55.7%, respectively.

The expanded case definition combining fever and rash showed a higher sensitivity (72.9%) but a lower specificity (88.2%) than the original case definition. The presence of fever and one or more of 3C scored the highest sensitivity among the combinations of signs and symptoms (77.0%), but scored the lowest specificity (52.9%).

When stratified by a single sign or symptom, sensitivity was highest in fever (95.9%) and lowest in rash (77.0%). Specificity was lowest in fever (20.6%), whereas it remained relatively high in rash (76.5%). PPV was highest in rash (87.7%) and lowest in one or more of 3C (70.7%). NPV was highest in fever (70.0%) and lowest in one or more of 3C (38.5%).

Table 2. Sensitivity, specificity, and positive and negative predictive values of different combination of signs and symptoms for vaccine-modified measles cases identified in a school outbreak in Incheon, South Korea, 2010

	Original case definition	Expanded case definitions used during outbreak					
	F + R + $\geq 3C$	F + R	F + $\geq 3C$	R + $\geq 3C$	F	R	$\geq 3C$
Presence of symptoms (measles/non-measles)							
Present	47/0	54/4	57/16	47/4	71/27	57/8	58/24
Absent	27/34	20/30	17/18	27/30	3/7	17/26	16/10
Surveillance quality							
Sensitivity	63.5	72.9	77.0	63.5	95.9	77.0	78.4
Specificity	100.0	88.2	52.9	88.2	20.6	76.5	29.4
PPV	100.0	93.1	78.1	92.2	72.4	87.7	70.7
NPV	55.7	60.0	51.4	52.6	70.0	60.5	38.5

F, fever; R, rash; $\geq 3C$, more than one of cough, coryza, or conjunctivitis; PPV, positive predictive value; NPV, negative predictive value.

DISCUSSION

We found that the expanded case definition was more sensitive in identifying suspected cases of vaccine-modified measles than the original definition. Previously, it was postulated that a sensitive surveillance system that investigates all suspected measles cases is essential in sustaining the elimination of the disease (13,14). However, our study revealed that only 47 of the 74 cases met the original case definition for suspected measles, resulting in a sensitivity of only 63.5%. This finding extends to other studies reporting a lower sensitivity as the incidence of measles cases decreases owing to the wide use of vaccines (15).

Our findings may imply that primary care physicians in South Korea who encounter vaccine-modified measles cases might not consider measles nor do they report these cases to the surveillance system because some of them do not meet the definition for a suspected measles case. This may consequently result in under-reporting of suspected measles cases, which may trigger the endemic circulation that have been postulated in other reports (16,17).

Notifications based on the measles surveillance case definition have been performed since 2001 in the country, when the vaccination coverage for 2 doses of MCV was only 39% (5). Recent surveys have estimated a 2-dose MCV vaccination coverage ranging between 87.8% and 90.0% (18,19). As the vaccination coverage has increased during the last 10 years in South Korea, it is possible that the occurrence of vaccine-modified measles might have become more frequent than in the past. Therefore, an expansion of the conventional case definition for measles, which was established when the vaccination coverage was lower, may be required with the aim to capture more cases of vaccine-modified measles with mild clinical presentations.

We noted that the choice of including different combinations of symptoms and signs can clearly influence the sensitivity, specificity, and PPV of the surveillance case definition. The sensitivity of the case definition did not appear to vary between the two sets of symptoms and signs of fever, rash, and one or more of 3C. However, the specificity appeared highest when including rash, suggesting that rash is not a common present-

ing symptom of the illness in this age group of the study population (20). Moreover, we observed that the PPV decreased remarkably as the case definition was expanded. Our findings indicate that the current case definition for measles surveillance may not sensitively detect the vaccine-modified cases that occur in the country; therefore, there should be a discussion on amending the new expanded case definition for suspected measles in South Korea in the near future.

Our findings are subject to several limitations. First, it represents a relatively limited examination of the epidemiology and clinical presentation of the disease in a specific population of male subjects, who were aged 13–15 years. Therefore, interpretation based on our data should be made with caution. Second, we observed varying clinical presentations in students with a history of \geq MCV1 vaccination; however, we were not able to confirm the number of doses the students received because of the limited registry. Measles infection after vaccination is thought to largely arise from primary or secondary vaccine failure (21). However, the interpretation of the type of vaccine failure in our data is limited because only routine laboratory tests were available during this outbreak. Measurement of IgG avidity would have resulted in a clearer classification between primary and secondary vaccine failures. Finally, because there were only two unvaccinated students, our findings do not compare the clinical characteristics between vaccinated and unvaccinated persons, which could draw a more conclusive picture of the characteristics of vaccine-modified measles as compared with measles infection in unvaccinated individuals.

Despite the limitations of our study, we believe that the expansion of the case definition has increased the number of identified vaccine-modified measles cases that would have been missed if the original case definition was used. It is possible that such cases are not routinely diagnosed in South Korea but were detected during this outbreak. In addition, our experience in this outbreak may represent a “median” of clinical presentation for vaccine-modified measles because three designated physicians observed the clinical presentations throughout the outbreak. On the basis of our findings, the expanded case definition of measles may be used in identifying a significant percentage of measles cases in

South Korea, where the endemic circulation of measles is no longer identifiable.

In conclusion, we report the clinical presentations of vaccine-modified measles to assess an expanded case definition that may provide guidance for clinicians in diagnosing and reporting the changed epidemiology of the disease in South Korea. Thus, we suggest using the expanded case definition of measles for outbreak investigation in closed communities; moreover, further discussions regarding the expansion of the case definition for routine measles surveillance in South Korea should be considered.

Conflict of interest None to declare.

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