

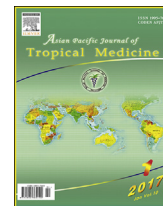
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Measles outbreaks in the Kyeongin area of the Republic of Korea, 2013–2014: A single-center experience in a country of measles elimination

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ABSTRACT

Objective: To identify the source of infection and determine the clinical features and laboratory finding of measles infection.**Methods:** In 27 measles patients, except for 3 adult patients, the rest of 24 pediatric measles cases were analyzed with regard to age, sex, immunization status, transmission routes and molecular genotyping of measles virus. Eighteen measles patients who admitted in isolation ward were set apart to investigate clinical findings and its correlation with laboratory characteristics. Retrospective analysis of cases was conducted in this study.**Results:** Of the 24 pediatric patients, 23 (95.8%) had not received any measles-containing vaccine (MCV). Sixteen of the patients (66.7%) were aged <12 months. The suspicious index case of a girl aged 34 months was not vaccinated with MCV1 and got measles after a trip to Philippines, and molecular genotype was revealed as B3. Measles outbreaks in the community such as a restaurant were followed by this one imported case. According to analysis of 18 patients admitted in isolation ward, the median level of C-reactive protein (CRP) was 0.38 mg/dL and that of lactate dehydrogenase (LDH) was 1200 IU/L. All of the 18 patients had LDH levels above the normal range. Age correlated with CRP ($\rho = 0.528$, $P = 0.024$) and LDH ($\rho = 0.501$, $P = 0.034$). The duration of fever was correlated with the duration of fever before rash ($\rho = 0.898$, $P < 0.01$). The duration of hospitalization was correlated with CRP ($\rho = 0.586$, $P = 0.011$). The white blood cell counts were correlated with the levels of LDH ($\rho = 0.505$, $P = 0.033$), aspartate aminotransferase ($\rho = 0.507$, $P = 0.032$), and alanine aminotransferase ($\rho = 0.481$, $P = 0.043$).**Conclusions:** Early weaning of maternally derived measles antibodies therefore vaccination of MCV1 at a young age from 9 months to 12 months should be considered in situations of early exposure. Furthermore, there is a call for consideration of scheduling an earlier age for the first dose of MMR vaccine in Europe. It is necessary for Korea to investigate the duration of the presence and quantitative analysis of maternal measles antibodies in infants and to reconsider the timing of MCV1.

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1. Introduction

Measles is a serious infection characterized by high fever, cough, coryza, conjunctivitis (the three Cs), and a prominent exanthem. Measles is so highly contagious that approximately 90% of exposed susceptible individuals develop measles. Face-to-face contact is not necessary because viable virus may be suspended in the air for as long as 1 h after a patient with measles leaves a room. Secondary cases from spread of

aerosolized virus have been reported in airplanes, physicians' offices, and hospitals [1].

Before the introduction of measles vaccine into Korea's national immunization program in the 1980s, thousands of Koreans acquired measles each year. Despite the use of vaccination, measles control in Korea remained a public health challenge until the early 2000s [2]. A large measles outbreak occurred in 2000 and 2001; that epidemic involved approximately 55 000 reported measles cases and 7 measles-related deaths. The Korea Advisory Committee on Immunization Practice recommended two doses of measles-containing vaccine (MCV), with the first dose (MCV1) given between 12 and 15 months of age and the second dose (MCV2) given between 4 and 6 years of age. The 5-year National Measles Elimination Plan started in 2001; it ensured high vaccination coverage with two doses of MCV as a school entry requirement, encouraged catch-up vaccination campaigns, and strengthened case-based surveillance with laboratory confirmation including molecular genotyping of the measles virus [3]. As a result, the number of reported measles cases decreased from 23 060 in 2001 to 11 in 2002 and 13 in 2003. After 2003, the annual incidence rate was lower than 1 case per million in the Korean population, indicating that Korea satisfied the criteria for elimination of measles at that time. Korea declared that measles had been eliminated in 2006 [4].

In 2013, the World Health Organization (WHO) [5] finalized its guideline for verification of measles elimination with up-regulation. The first standard addressed the documented duration of the interruption of endemic measles virus transmission. The second was the presence of a high-quality surveillance system that made the first standard reliable. The third was genotyping evidence that supported the interruption of endemic transmission. If the absence of endemic measles virus transmission for more than 36 months was identified in a defined geographical area (*e.g.*, region or country), the WHO verified the elimination of measles. Korea was verified for measles elimination by the WHO Western Pacific Regional Office [6] in March 2014.

However, from April 2013 to July 2014 at Soonchunhyang University Bucheon Hospital, many patients showed symptoms and signs of measles such as fever, cough, coryza, and rash. After laboratory tests were conducted, 27 patients were definitively diagnosed as measles. 3 patients were adult and the rest of 24 patients were infants and children. Bucheon is located between Seoul, the capital city of Korea and Incheon national airport via which 41 million person went through in 2014 [7]. About 88 000 citizens live in Bucheon and population density is 16 330 person/km² that is second highest followed by Seoul [8]. Due to these geographical and demographical factors of Bucheon, measles could be imported by foreigner or returning traveler and then widespread into community, even though Korea was verified for measles elimination.

To investigate the features of the recent measles infection, to stop the spread of the measles outbreak and to identify the source of measles infection, confirmed 24 pediatric measles cases were analyzed with regard to age, sex, immunization status, transmission routes, molecular genotyping of measles virus.

2. Materials and methods

2.1. Case definition and classification

Cases of measles were identified and classified according to the WHO and national guidelines [5]. An illness clinically

compatible with measles is characterized by a generalized maculopapular rash, a temperature above 38.0 °C, and at least one of the three Cs (cough, coryza, and conjunctivitis). A laboratory-confirmed case was defined as a clinical case characterized by at least one of the following: the presence of anti-measles immunoglobulin M (IgM), a 4-fold increase in the anti-measles immunoglobulin G (IgG) titer in acute and convalescent serum specimens, or detection of measles virus nucleic acid by reverse transcription-polymerase chain reaction (RT-PCR).

Imported cases of measles were defined as exposure to measles outside Korea during the 7–18 d before rash onset and exclusion of a local source of infection through investigation of contacts. Import-related measles was defined as a locally acquired infection occurring as part of a chain of transmission originating from an import case as supported by epidemiological or virological evidence or both [5]. Nosocomial cases were defined as confirmed cases in a patient who had contact with another patient confirmed to have measles in a hospital or health care facility during the (7–18) d before rash onset if no other source was identified. A community-acquired case was a confirmed case in a patient who had neither nosocomial nor imported measles.

2.2. Materials and methods

From April 2013 to July 2014, 27 patients were definitively diagnosed as measles according to WHO and national guidelines with clinical presentation and serologic findings. In 27 measles patients, 3 adult patients were excluded at the statistical analysis because they had different epidemiologic and clinical features with the rest of 24 pediatric patients.

Retrospective analysis of the 24 pediatric patients with confirmed measles was conducted by a descriptive cross-sectional study. This study was approved by the institutional review board (IRB) of Soonchunhyang University Bucheon Hospital (SCHBC-IRB-2016-04-010-004).

Confirmed 24 pediatric measles cases were analyzed with regard to age, sex, immunization status, transmission routes and molecular genotyping of measles virus. The immunization status of the 24 children was reviewed through assessment of the medical records of the National Immunization Registry established in 2002. Timely immunization was defined as receiving MCV1 before 15 months of age and MCV2 before 6 years of age.

To collect measles virus and conduct analyses for molecular epidemiological research, we obtained smear samples of the throats of patients. We scraped the posterior pharyngeal wall and tonsil with a cotton swab and placed the swab in virus transport medium. The medium was transferred to the Korea Centers for Disease Control and Prevention (KCDC) for isolation of measles virus from the smear sample, and RT-PCR was then conducted to determine the molecular genotype of the measles virus. Molecular genotyping of measles virus was obligatory because it contributed to the classification of imported and import-related cases of measles [9]. When a physician detects an illness clinically compatible with measles, he or she must notify the authorities in a public health center without delay. When a suspected case was reported, an active laboratory surveillance system by KCDC began to collect samples for laboratory testing using enzyme-linked immunosorbent assay with anti-measles IgM and detection of measles virus nucleic acid by RT-PCR [10].

We statistically analyzed 18 patients admitted in isolation ward with the following parameters: length of hospitalization, duration of fever, complications such as pneumonia, and laboratory findings including white blood cell (WBC) count with differential count, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). We examined correlation of clinical findings with laboratory characteristics.

2.3. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows (Version 20.0; IBM Corp., Armonk, NY, USA). Clinical characteristics such as length of hospitalization and duration of fever were reported as mean \pm SD, but we used median and interquartile range as a supplement because the data did not follow a normal distribution. We performed the Spearman non-parametric test for evaluation of clinical characteristics and laboratory data. Statistical significance was assumed if $P \leq 0.05$.

3. Results

From April 2013 to July 2014, in Soonchunhyang University Bucheon Hospital 27 patients were definitively diagnosed as measles and 3 patients were adult. In three adult patients, one patient was 21 years old and stayed in China and it revealed that he was infected by measles virus H1 type which was wide spread in China at that time. The rest of two adult patients were 29 and 36 years old man infected after trip to Philippines and the genotyping of measles virus was both B3 which was prevalent in Philippines.

Among 27 measles patients, except 3 adult patients, the rest of 24 patients as a population received a confirmed diagnosis of measles in the Department of Pediatrics. The male:female ratio was 3:5 (9 and 15 patients respectively). The patients ranged in age from 5 months to 34 months.

Of the 24 patients, 23 (95.8%) had not received any MCV. Sixteen of the patients (66.7%) were aged <12 months and thus were younger than the age at which MCV1 is recommended by the Advisory Committee on Immunization Practice in Korea. The youngest patients in the population were 5 months of age, at which age it is assumed that passive immunity (*i.e.*, antibodies from the mother) still provides adequate protection.

Four patients with measles were just over 12 months of age (within 1 week after their first birthday). Three patients were aged 16–23 months. Two of these three patients had not yet been vaccinated with MCV1, because of previous treatment of intravenous immunoglobulin for Kawasaki disease and missing of vaccination schedule by parents' mistake respectively. The other patient was a boy aged 17 months who was vaccinated with MCV1 at the age of 12 months but his pneumonia worsened rapidly to acute respiratory distress syndrome with pleural effusion and pneumothorax. He recovered after 2 weeks of ventilator care in the intensive care unit.

We performed case-based investigations and identified the route of transmission of measles infection. We considered that measles virus first imported from another country could be spread from place to place. The sources of measles infection in many cases were ambiguous, but in some cases the origin was clear. The suspicious index case of a girl aged 34 months, the oldest patient

in the population, was not vaccinated with MCV1 because of her parents' individual parenting beliefs. Eleven days after a trip to Philippines, a rash appeared. She was diagnosed with measles, the molecular genotype of measles virus was revealed as B3, which was a prevalent measles virus in the Philippines at that time [11]. An outbreaks were followed by this one imported case in the community such as a restaurant, a day care center, and two hospitals. We established the transmission routes of measles in 10 patients, but in the remaining 14 patients the route of transmission was too vague to be established.

Of the 24 confirmed cases of pediatric measles, the B3 type of measles virus was identified in 21 cases. In 2014, B3 measles virus was widespread in the Eastern Asian area, including the Philippines [11]. RT-PCR did not reveal a specific genotype in the remaining three cases.

Twenty-four measles patients were treated separately with isolation. Five patients were isolated in their own house, a patient was admitted in intensive care unit and 18 patients were hospitalized in the isolation ward. We set apart these 18 measles patients who admitted in isolation ward to investigated clinical findings such as duration of hospitalization and laboratory characteristics such as WBC, CRP, LDH, AST and ALT and correlation of clinical findings and laboratory characteristics. Because data such as duration of hospitalization did not follow the standard normal deviation, it was not efficient to describe these data with average and standard deviation. Thus, we additionally analyzed these data with median and interquartile range (IQR) (Q1 = 25th percentile, Q3 = 75th percentile).

The ages of the 18 patients with measles admitted to the isolation ward ranged from 5 to 34 months, and the mean age was (11.2 \pm 6.7) months (Table 1). The median age of these 18 patients was 10.5 months, and most patients were aged 7–11 months [IQR, (7–11) months]. The length of hospitalization ranged from 4 to 11 d, but mostly 5–7 d [IQR, (5–7) d], and the mean was (6.0 \pm 1.9) d. The duration of fever ranged from 6 to 14 d, but mostly 7–9 d [IQR, (7–9) d], and the mean was (8.3 \pm 2.0) d. We determined that the duration of fever before prominent exanthema was 3–11 d [average, (5.5 \pm 2.0) d]. Most patients had a fever for 4.0–6.5 d before the rash appeared [IQR, (4.0–6.5) d].

Complications in 18 patients admitted to the isolation ward were investigated. The most frequent complication was pneumonia. Eleven patients (61.6%) had croup (laryngotracheobronchitis) with a typical barking cough. Three patients (16.7%) showed wheezy respiration and had bronchiolitis; all were infants aged 5, 7, and 11 months. Seven patients had otitis media (38.9%). Ten patients (55.6%) had acute gastroenteritis. Some patients had more than two complications.

Laboratory findings of these 18 patients were analyzed using the median and IQR because the laboratory data did not follow the standard deviation (Table 2). The median level of CRP was

Table 1

Clinical characteristic of 18 patients with measles in the isolation ward.

Clinical characteristics	Mean \pm SD	Median	25% quartile	75% quartile
Mean age (months)	11.2 \pm 6.7	10.5	7.0	11.0
Hospitalization (d)	6.0 \pm 1.9	5.0	5.0	7.0
Duration of fever (d)	8.3 \pm 2.0	8.5	7.0	9.0
Duration of fever before rash (d)	5.5 \pm 2.0	5.0	4.0	6.5

Table 2

Laboratory findings of 18 patients with measles in the isolation ward.

Laboratory findings	Median	25% Quartile	75% Quartile
WBC count ($\times 10^3/\text{mm}^3$)	7.900	6.295	11.225
CRP (mg/dL)	0.380	0.210	1.060
LDH (IU/L)	1200.000	824.000	1491.000
AST (IU/L)	71.000	59.000	88.000
ALT (IU/L)	26.000	22.000	50.000

0.38 mg/dL [reference, (0.0–0.5) mg/dL] and most CRP values ranged from 0.21 to 1.06 mg/dL [IQR, (0.21–1.06) mg/dL]. An 11-month-old patient was the only one with a significantly high CRP level (10.2 mg/dL) and she had a fever for 14 d and was admitted for 11 d. She experienced multiple simultaneous complications: pneumonia, croup, otitis media, and gastroenteritis. Her WBC count and LDH were also the highest among all 18 patients.

The median level of LDH was 1 200 IU/L [reference, (170–570) IU/L], and a large proportion of LDH levels ranged from 824 to 1 491 IU/L [IQR, (824–1 491) IU/L]. The LDH levels ranged from 575 to 2 710 IU/L; this means that all of the 18 patients with measles who were admitted to the isolation ward had LDH levels above the normal range.

Fourteen of the 18 patients admitted to the isolation ward (77.7%) had an AST level greater than the normal range [reference, (20–60) IU/L]. However, no patients had jaundice or hepatomegaly. The median level of AST was 71 IU/L, and most AST values ranged from 59 to 88 IU/L [IQR, (59–88) IU/L]. The median level of ALT was 26 IU/L, and most ALT values ranged from 22 to 50 IU/L [IQR, (22–50) IU/L]. Elevation of AST was more notable than that of ALT.

Table 3 summarizes the correlations of the clinical characteristics and laboratory findings. Age was not correlated with clinical data such as the duration of hospitalization and duration of fever, but it correlated with CRP ($\rho = 0.528$, $P = 0.024$) and LDH ($\rho = 0.501$, $P = 0.034$). The duration of fever was correlated with the duration of hospitalization ($\rho = 0.567$, $P = 0.014$) and was strongly correlated with the duration of fever before rash ($\rho = 0.898$, $P < 0.01$). The duration of hospitalization and duration of fever before rash were correlated with each other ($\rho = 0.511$, $P = 0.030$). The duration of hospitalization was

correlated with CRP ($\rho = 0.586$, $P = 0.011$). The WBC counts were not correlated with any clinical data, but they were correlated with the levels of LDH ($\rho = 0.505$, $P = 0.033$), AST ($\rho = 0.507$, $P = 0.032$), and ALT ($\rho = 0.481$, $P = 0.043$). AST and ALT, indices of hepatic involvement in measles infection, were very strongly correlated with each other ($\rho = 0.823$, $P < 0.01$), but neither was correlated with any clinical characteristics such as age, duration of hospitalization, or duration of fever.

4. Discussion

In 2007, an outbreak of measles in Korea involving 180 confirmed cases occurred; the median age of patients was 12.5 months [IQR, (10–20) months], and 124 (68.8%) had no history of measles vaccination [12]. Three (1.6%) patients were under 5 months old, 72 (40.0%) were 6–11 months old, and 20 (11.1%) were 12–15 months old and therefore were eligible for MCV1. Infants, representing 41.6% of all case patients, appeared to be at highest risk for measles infection among all age groups. Because the routine vaccination schedule in Korea includes MCV1 at 12–15 months of age, infants were not eligible for vaccination against measles. We can see a similar phenomenon in this study.

We can also see a similar pattern of age composition in measles outbreaks in other countries, especially in advanced countries in which elimination of measles had already been achieved. In the United States, which has the same measles vaccination schedule as Korea, measles elimination was declared by the WHO in 2002. During 2001–2008, however, 557 confirmed cases of measles and 38 outbreaks were reported; the highest incidences of measles were among infants 6–11 months of age and children 12–15 months of age (3.5 and 2.6 cases per 1 million person-years, respectively) [13]. A similar measles outbreak occurred in 2007–2008 in Jerusalem [14]. The age shift in incidence in recent measles outbreaks suggests that we consider whether the measles vaccination policy needs to be changed.

Maternal antibodies against measles are passively transferred to infants. The rising incidence of recent measles outbreaks among infants aged 6–11 months indicates early weaning of maternally derived protection [14]. In a prospective study in Belgium [15] in 2006–2008 to investigate the duration of the presence of maternal antibodies to measles in infants, maternal

Table 3

Spearman correlation matrix of clinical characteristics and laboratory findings in 18 patients with measles who were admitted to the isolation ward.

Variable (ρ)	Age	Duration of hosp.	Duration of fever	Duration of fever before rash	WBC	CRP	LDH	AST	ALT
Age	1.00	–	–	–	–	–	–	–	–
Duration of hosp	0.371 (0.130)	1.000	–	–	–	–	–	–	–
Duration of fever	0.357 (0.146)	0.567 ^b (0.014)	1.000	–	–	–	–	–	–
Duration of fever before rash	0.440 (0.068)	0.511 ^b (0.030)	0.898 ^a (<0.01)	1.000	–	–	–	–	–
WBC	0.273 (0.273)	0.144 (0.568)	0.273 (0.274)	0.342 (0.164)	1.000	–	–	–	–
CRP	0.528 ^b (0.024)	0.586 ^b (0.011)	0.125 (0.622)	0.175 (0.487)	0.226 (0.367)	1.000	–	–	–
LDH	0.501 ^b (0.034)	0.354 (0.150)	0.244 (0.329)	0.318 (0.199)	0.505 ^b (0.033)	0.433 (0.073)	1.000	–	–
AST	0.245 (0.327)	0.159 (0.528)	0.256 (0.305)	0.158 (0.531)	0.507 ^b (0.032)	0.009 (0.971)	0.148 (0.083)	1.000	–
ALT	0.110 (0.664)	0.150 (0.552)	0.230 (0.359)	0.145 (0.565)	0.481 ^b (0.043)	–0.018 (0.943)	0.097 (0.701)	0.823 ^a (<0.01)	1.000

hosp., hospitalization; ρ , correlation coefficient.

^a Correlation is significant at the 0.01 level (two-tailed). ^b Correlation is significant at the 0.05 level (two-tailed).

antibodies, which are transferred passively from the mother, decreased rapidly after birth, particularly when mothers were protected by vaccine-acquired antibody rather than by natural immunity. In that study, the median time to loss of immunity was 2.61 months: 0.97 months for infants of vaccinated women and 3.78 months for infants of naturally immune women. The early loss of maternal antibodies in infants has several implications, so vaccination at a young age should be considered in situations of early exposure such as measles outbreaks or traveling in areas where measles is endemic [15].

In a further detailed prospective seroepidemiologic study conducted from 2005 to 2007 in France [16], where routine measles vaccination had been performed on the same schedule as in Korea for more than 20 years, maternal measles antibodies decreased dramatically in French infants by 6 months of age. As vaccination coverage of the population increases, measles virus circulation declines, and more infants are born with vaccine-induced maternal antibodies. These infants will be protected for a shorter period of time than those in the pre-vaccine era; accordingly, the highest incidences of measles have been observed in infants under 1 year of age in measles outbreaks at Soonchunhyang University Bucheon Hospital at the Kyeongin area in Korea, Jerusalem, the United States, and France [13,14,16]. In consideration shorter time of existence and less quantity of maternally derived measles antibody for infants of vaccinated women than those of naturally immune women, there is an opinion in Europe that infants' protection against measles could be optimized by lowering the age of routine vaccination from 12 to 9 months [16].

There is only a small chance that a massive measles outbreak could occur in Korea because of herd immunity through high vaccine coverage [3]. However, there is still endemic measles transmission abroad, including in eastern Asia (China, the Philippines, Indonesia, and other countries) [6]. Thus, a sudden measles outbreak could occur through the spread of measles virus to the community initiated by imported cases.

Of 24 confirmed pediatric measles cases, 21 (87.5%) were identified as B3. Although we were not able to confirm an epidemiologic link to an internationally imported case, importation of the disease may cause outbreaks and can be a major threat to infants under the recommended age for MCV1.

According to analysis of laboratory findings of 18 measles patients who admitted in isolation ward, all of the LDH levels were above the normal range. Furthermore, the LDH level showed a tendency to increase as the duration of hospitalization increased. Sugaya *et al.* [17] reported that the levels of LDH in patients with measles were frequently increased. On average, LDH of measles patients was increased to $(1\ 147.9 \pm 43.8)$ IU/L, markedly more than in the control group (517.0 ± 15.0) IU/L, $P < 0.001$, in their report. Patients with a high LDH level ($>1\ 500$ IU/L) had longer hospital stays than those with lower values. But in our analysis of measles outbreaks, the levels of LDH were not correlated with the duration of hospital stay and duration of fever. When tissues are damaged by injury or disease, they release more LDH into the bloodstream; thus, LDH could be expected to increase with the destruction of cells [18]. We speculate that the serum LDH level increases due to the destruction of lymphocytes by the measles virus. We actively isolated patients who showed only a high level of LDH as clue to measles infection because the prodromal phase before the rash is highly contagious.

According to a report in 1996 [19], liver dysfunction secondary to measles infection is temporary and rarely

symptomatic; 85% of patients show recovery within 2 weeks after measles infection. According to another report of hepatic involvement in patients with measles in 2003 [20], AST and ALT had a tendency to correlate with age. In our study they did not seem to be correlated with age and it presumed that age distribution from 5 to 34 months are too narrow to show correlation.

Our observations have several potential limitations. First, we are presenting a retrospective analysis of 24 confirmed pediatric measles cases representing a relatively narrow scope of research, and the outbreaks occurred over a short period of time. Second, there is a possibility of other routes of measles transmission that we could not detect.

In conclusion, measles virus was suspected to be imported from abroad and spread to the community, and infants aged 6–11 months, who had not yet received MCV1, were susceptible to measles infection. Measles virus was so highly contagious from 3 d before the appearance of the rash that it was almost impossible to stop the spread of measles transmission by isolation after the rash appeared. Early isolation of patients suspected to have measles (identified by considering symptoms of measles, a history of recent contact with other patients suspected to have measles, and travel to endemic areas such as the Philippines, as well as specific laboratory findings such as elevation of LDH) was important to stop the spread of measles infection. Protection against measles in infants could be optimized both by increasing herd immunity through increased vaccine coverage and by early immunization with MCV at age 6–11 months during measles outbreaks in epidemic areas. In recent reports [13,16] in developed countries in which measles elimination had already been achieved by high vaccination coverage, there is an opinion that the timing of MCV1 needs to be changed by lowering it from 12 to 9 months, considering that maternal measles antibodies decrease dramatically in infants by 6 months of age in post-elimination areas. It is necessary in Korea to investigate the duration of the presence and quantitative analysis of maternal measles antibodies in infants to determine the timing of MCV1 for protection of infants from measles infection, to re-evaluate of immunization policies and to consider of scheduling an earlier age for the first dose of MMR vaccine.

Conflict of interest statement

We declare that we have no conflict of interest.

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