



## An increasing, potentially measles-susceptible population over time after vaccination in Korea



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### ABSTRACT

**Background:** In Korea, measles occurs mainly in infants <12 months of age, who are unvaccinated. In addition, vaccine populations, including adolescents and young adults, can become infected through importation. Thus, the question arises whether the current level of herd immunity in Korea is now insufficient for protecting against measles infection.

**Methods:** Age-specific measles seroprevalence was evaluated by performing enzyme immunoassays and plaque reduction-neutralization tests on 3050 subjects aged 0–50 years (birth cohort 1964–2014) and 480 subjects aged 2–30 years (birth cohort 1984–2012).

**Results:** The overall seropositivity and measles antibody concentrations were 71.5% and 1366 mIU/mL, respectively. Progressive decline in antibody levels and seropositivity were observed over time after vaccination in infants, adolescents, and young adults. The accumulation of potentially susceptible individuals in the population was confirmed by comparing data from 2010 and 2014 seroprevalence surveys. The statistical correlation between measles incidence and measles seronegativity was determined.

**Conclusions:** Waning levels of measles antibodies with increasing time post-vaccination suggests that measles susceptibility is potentially increasing in Korea. This trend may be related to limitations of vaccine-induced immunity in the absence of natural boosting by the wild virus, compared to naturally acquired immunity triggered by measles infection. This study provides an important view into the current measles herd immunity in Korea.

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### 1. Introduction

Measles is a highly contagious vaccine-preventable disease caused by the measles virus. Since a vaccine against measles became available in 1963, accelerated immunization activities

**Abbreviations:** CIs, confidence intervals; EIA, enzyme immunoassay; GMT, geometric mean titer; KCDC, Korea Centers for Disease Control and Prevention; KNHANES, Korea National Health and Nutrition Examination Survey; MCV, measles-containing vaccine; MMR, measles, mumps, and rubella; ND<sub>50</sub>, 50% neutralizing antibody end-point titers; PRNT, plaque-reduction neutralization test; WHO, World Health Organization.

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have reduced the global incidence and mortality of measles. Many countries have successfully eliminated measles by following a routine vaccination program [1,2].

In Korea, the measles-containing vaccine (MCV) became available in 1965, and the trivalent measles, mumps, and rubella (MMR) vaccine was introduced in early 1980s. A 2-dose MMR vaccination schedule was recommended beginning in 1997, with the first dose given at 12–15 months of age and the second dose given at 4–6 years of age. Before the introduction of a measles vaccine, large number of measles cases were reported annually in Korea. Owing to the occurrence of large, nationwide measles outbreaks with approximately 55,000 cases of measles and 7 deaths during 2000–2001, the government implemented the 5-year National Measles Elimination Plan that included the measles vaccination “catch-up campaign” and “keep-up” programs in 2001. The

catch-up immunization program targeted 5.86 million children aged 8–16 (March 1985–February 1994 birth cohort) who did not have documented evidence of receiving the MCV vaccine, and the keep-up program maintained >95% 2-dose MCV coverage by requiring the achievement of 2-dose MMR vaccination before entering elementary school by all children aged 7 years [1,3,4]. As a result of national efforts to control measles, the reported numbers of measles cases decreased to 0.93 cases/million people during 2008–2013 and 2-dose MMR vaccination coverage had been maintained at >95% since 1996. In March 2014, the World Health Organization (WHO) verified that measles had been eliminated in Korea [1,4]. Although measles had been eliminated in Korea, the resurgence of measles outbreaks related to imported and import-associated measles cases occurred during 2013–2014. Most patients with measles were infants aged <1 year, but measles cases were also identified in patients aged 13–24 old who had received a 2-dose measles vaccination [4]. Measles outbreaks among highly vaccinated populations have been observed in many countries [5–7]. Such outbreaks in a population with high 2-dose measles vaccine coverage may be related to a vaccine-handling issue (cold chain issue), the vaccination strategy (number of doses, age of vaccination), host immunity (waning immunity, suboptimal immunity), and environmental factor (heavy exposure) [5,8,9].

By investigating the seroprevalence of measles in Korea, we provide a significant window into current measles herd immunity to better understand the prevalence of measles susceptibility underlying measles outbreaks in Korea.

## 2. Material and methods

### 2.1. Serum samples

A total of 3050 residual serum specimens were provided in 2014, including sera from 1000 patients aged <10 years by a private diagnostic laboratory, and sera from 2050 patients aged 10–50 years were obtained from the fifth Korea National Health and Nutrition Examination Survey (KNHANES VI-1st), which was conducted by the Korea Centers for Disease Control and Prevention (KCDC) [10]. The serum samples from the private diagnostic laboratory were collected for medical diagnosis and health screening, and the other samples from the KNHANES were collected to assess the health and nutritional status of Koreans. In total, 3050 sera (50 per age group, by months for infants <12 months of age and by years for healthy individuals aged 1–50 years) were stored at –20 °C until investigation. We excluded samples referred for the diagnosis of measles, mumps, rubella, or human immunodeficiency virus. Personal and confidential information were removed, except for demographic information including age and gender. Specific vaccination documents were not available for individuals in this study population.

### 2.2. Detection of measles virus-specific IgG antibodies in enzyme immunoassays

Measles virus-specific IgG antibodies were detected using an enzyme immunoassay (EIA) kit (Enzygnost® anti-Measles Virus/IgG, Siemens Healthcare Diagnostics, GmbH Marburg, Germany) on the BEP® III automated system (Siemens Healthcare Diagnostics), according to the manufacturer's instructions. The sample results were classified as follows: optical density (OD) >0.2 was deemed positive, 0.1–0.2 was equivocal, and <0.1 was negative. Serum samples with equivocal results were re-tested in duplicate and classified based on the results with a majority. Positive delta ODs were then converted to international units using the  $\alpha$ -method, as specified by the manufacturer.

### 2.3. Analyzing neutralizing-antibody concentrations against measles virus

Measles virus neutralizing antibody titers were determined by performing a modified plaque-reduction neutralization test (PRNT) [11]. All sera were heat inactivated at 56 °C for 30 min, and serially diluted 4-fold and incubated in the presence of 25–35 plaques of Edmonston strain for 2 h at 37 °C. The virus/serum mixtures were then added in triplicate to a Vero/hSLAM cell monolayer growing in a 24-well plate, after which the plate was incubated at 35 °C for 1 h. Viral inocula were removed and overlay medium was added. The plate was incubated for an additional 4 days, the overlay medium was removed, and culture overlay medium containing neutral red was added. The plate was incubated for another 1 day, and the medium was decanted. The cells were fixed with 4% paraformaldehyde. The 50% neutralizing antibody end-point titers (ND<sub>50</sub>) were calculated using the Kärber formula, and those results were standardized against the WHO 3rd International Standard (NIBSC code 97/648) with an antibody concentration of 3000 mIU/ml.

### 2.4. Statistical analyses

Statistical analysis and graph constructions were performed using SAS software (version 9.3; SAS Institute, Cary, NC) and Prism software (version 6.0; GraphPad software Inc., San Diego, CA). We analyzed proportions and 95% confidence intervals (CIs) of measles seroprevalences in the study population. Correlations were calculated using Pearson's and Spearman's correlation coefficients.  $P < 0.05$  was considered to reflect statistical significance.

## 3. Results

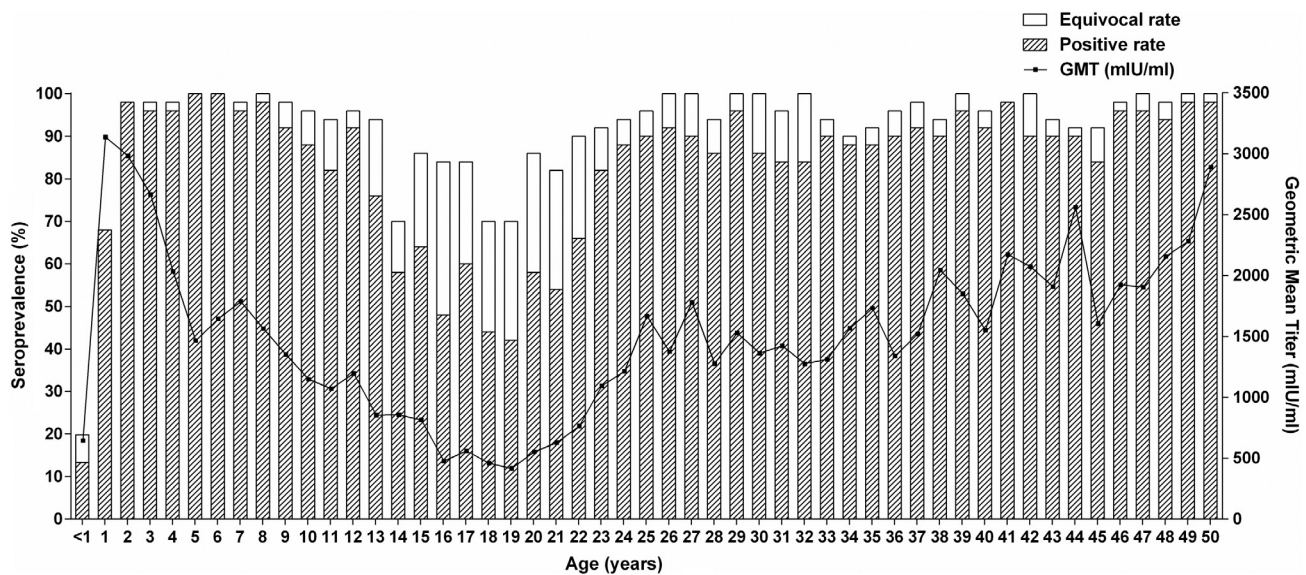
### 3.1. Measles seroprevalence in Korea

The seroprevalence of antibodies against measles virus was analyzed in 3050 serum samples, of which 1575 (51.6%) were from male and 1475 (48.4%) from females, by an indirect IgG EIA. The prevalence of measles IgG antibodies by age group is shown in Table 1. The overall seropositivity of measles in the study population was 71.5% (95% CI, 69.6–73.4), and 8.6% (95% CI, 5.2–12.0) were equivocal. Young children (aged 1–6 years) presented the highest seropositivity of 93.0% (95% CI, 90.0–96.0) and a GMT of 2175 mIU/mL (95% CI, 1961–2412). The lowest seropositivity and GMT values of 48.5% (95% CI, 38.6–58.4) and 478.3 mIU/mL (95% CI, 421–543.3), respectively, were detected in adolescents (aged 16–19 years) in this study (Table 1). No significant differences were observed in seropositivity rates between males and females in any age group (data not shown). The age-specific measles seropositive proportion and distribution of GMT antibodies are presented in Fig. 1. The highest seropositivity of IgG antibodies was detected in 5- and 6-year-old children. Measles seropositivity gradually decreased from 100% in children aged 5 and 6 years to 42% (95% CI, 20.9–63.1) in the 19-year-old age group. This decline recovered steadily to >80% seropositivity for measles in individuals aged 23 years and over. The GMTs of antibodies indicated a pattern similar to that found with seroprevalence, and the highest GMT level was observed in infants aged 1 year (3137.5 mIU/mL), who most likely had received 1-dose of the MMR vaccine at 12–15 months. Among young children aged 1–5 years, the GMT decreased sharply from 3137.5 mIU/mL at 1 year of age to 1464.5 mIU/mL at 5 years of age. The GMT levels displayed significant linearity ( $P < 0.001$ ), dropping from 1786.5 mIU/mL at 7 years of age to 415.9 mIU/mL at 19 years of age, but the subsequent rates of decline were slower than those in children aged 1 to 5 years

**Table 1**  
Seroprevalence of measles by age group, Republic of Korea, 2014.

Age group	Year of birth	No. tested	Proportion seropositive % (95% CI)	Proportion equivocal % (95% CI)	Geometric mean titer mIU/mL (95% CI)
<1	2014	550	13.3 (5.5–21.1)	6.5 (0–14.6)	643.5 (530.7–780.3)
1–6	2008–2013	300	93.0 (90.0–96.0)	0.7 (0–11.9)	2175 (1961–2412)
7–12	2002–2007	300	91.3 (88.0–94.7)	5.7 (0–16.7)	1336 (1205–1482)
13–15	1999–2001	150	66.0 (56.7–75.3)	17.3 (2.8–31.9)	840.1 (699.1–1010)
16–19	1995–1998	200	48.5 (38.6–58.4)	28.5 (16.8–40.2)	478.3 (421–543.3)
20–24	1990–1994	250	69.6 (62.8–76.4)	19.2 (8.1–30.3)	822.1 (721.6–936.6)
25–29	1985–1989	250	90.8 (87.0–94.6)	7.2 (0–19.1)	1517 (1333–1727)
30–39	1975–1984	500	88.8 (85.9–91.7)	7.2 (0–15.6)	1526 (1390–1675)
40–50	1964–1974	550	93.3 (91.1–95.4)	3.8 (0–12.0)	2065 (1895–2252)
Total	1964–2014	3050	71.5 (69.7–73.4)	8.6 (5.2–12.0)	1366 (1309–1426)

Abbreviation: CI, confidence interval.



**Fig. 1.** Age-specific distribution of seroprevalence and GMT of measles IgG antibodies in Korea in 2014. The sample size was 50 for each age group, except for infants <12 months of age, where the sample size was 550.

after receiving the 2-dose of the MMR vaccine. These declines gradually rose back to measles antibody GMTs of >1200 mIU/mL in those aged 25 years and over (Fig. 1).

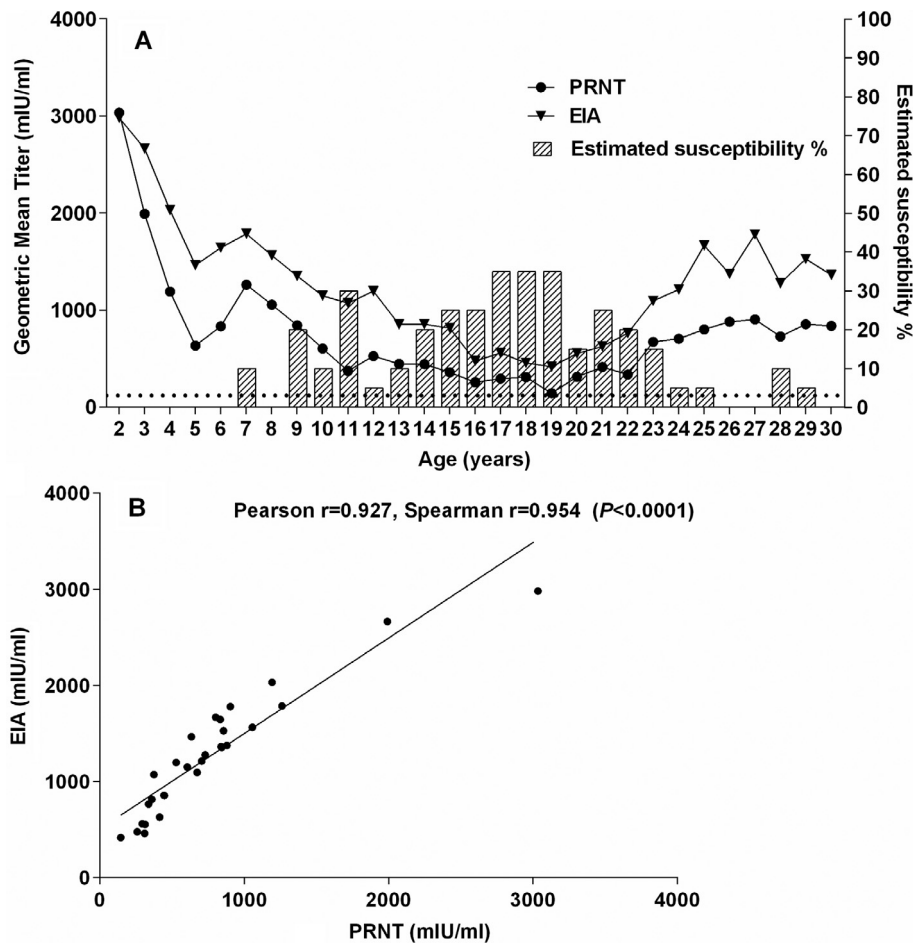
### 3.2. Neutralizing antibody concentrations

In total, 480 specimens were randomly selected from 3050 sera tested by EIA and analyzed by PRNT for measles neutralizing-antibody concentrations. Fig. 2 shows the distribution of neutralizing-antibody concentrations determined in the PRNT and EIA for IgG antibody titers among individuals in the study population aged 2–30 years. The potential measles-susceptibility rate was estimated using the 120 mIU/mL threshold of potential susceptibility and correlations between the values from the PRNT and EIA experiments. A high agreement was observed between IgG titers from the EIA and PRNT experiments, with Pearson's and Spearman's correlation coefficients of 0.9271 and 0.954, respectively ( $P < 0.0001$  for both). The lowest neutralizing-antibody concentration (145 mIU/ml) was detected in the 19-year-old group, with 7 (35%) individuals showing potential susceptibility ( $\leq 120$  mIU/mL), but only 1 being negative ( $< 8$  mIU/mL).

### 3.3. Comparison of seroprevalence between in 2010 and 2014

This measles seroprevalence study of samples obtained in 2014 was compared to data from a previous study conducted in 2010 by

the KCDC [12], which showed an overall seropositivity for measles of 78.2% in 1400 sera from individuals aged 24–47 months (2007–2008 birth cohort) and 7–18 years (1992–2003 birth cohort). The 2010 and 2014 studies were conducted using the same methods and a comparable EIA kit in the identical laboratory. Fig. 3A and B shows changes in seropositivity and antibody titers that occurred in each age group after 4 years from 2010 to 2014. The seropositivity and measles antibody GMT for the 2014 study population was significantly lower ( $P < 0.0001$  in both cases) compared to the 2010 study population, and reduction values in the 2014 and 2010 study populations were 16.4% (95% CI, 12.32–20.56) and 401.7 mIU/mL (95% CI, 225–578.5), respectively (Fig. 3A and B). Fig. 3C and D presents the distribution of seropositivity and antibody titers for each age group at the time of investigation. The lowest seropositivities and GMT were observed in different age groups, i.e., in the 15-year-old group (61%, 632.81 mIU/mL) from the 2010 data set and in the 19-year-old group (42%, 415.9 mIU/mL) from the 2014 data set (Fig. 3C and D). A potential susceptibility window was found, with seropositivity rates <80% among the group aged 11–18 years in 2010, which had shifted and expanded to the group aged 13–22, 4 years later in 2014 (Fig. 3C). The trend of decreased measles antibody titers with increasing time post-vaccination occurred in both years ( $r = 0.9597$ ,  $P < 0.0001$ ), but the proportion of the population with a low antibody titer was greater in 2014 than in 2010 (Fig. 3D).



**Fig. 2.** Age-specific IgG levels (determined in EIAs) or neutralizing antibody titers (determined in PRNTs) versus the estimated measles susceptibility (A) and correlations between the values from the PRNT and EIA experiments calculated using Pearson's correlation coefficient (B). EIA, enzyme immunoassay; PRNT, plaque-reduction neutralization test.

### 3.4. Measles outbreak and seroprevalence

In 2014, a measles outbreak occurred in Korea and 442 cases of measles infection were confirmed. When classified by aged group, a significant correlation was observed between measles antibody seronegativity and the number of reported measles cases ( $r = 0.8886$ ,  $P < 0.0001$ ) (Fig. 4). Most cases occurred in infants, adolescents, and young adults, with 176 (39.8%) cases occurring in individuals aged  $\leq 1$  years and 185 (41.9%) cases among individuals aged 13–24 years. Peak seronegativity rates were observed in the age groups under 1 year (76.2%), 13–15 years (16.7%), 16–18 years (20.7%), and 19–21 years (20.7%) (Fig. 4).

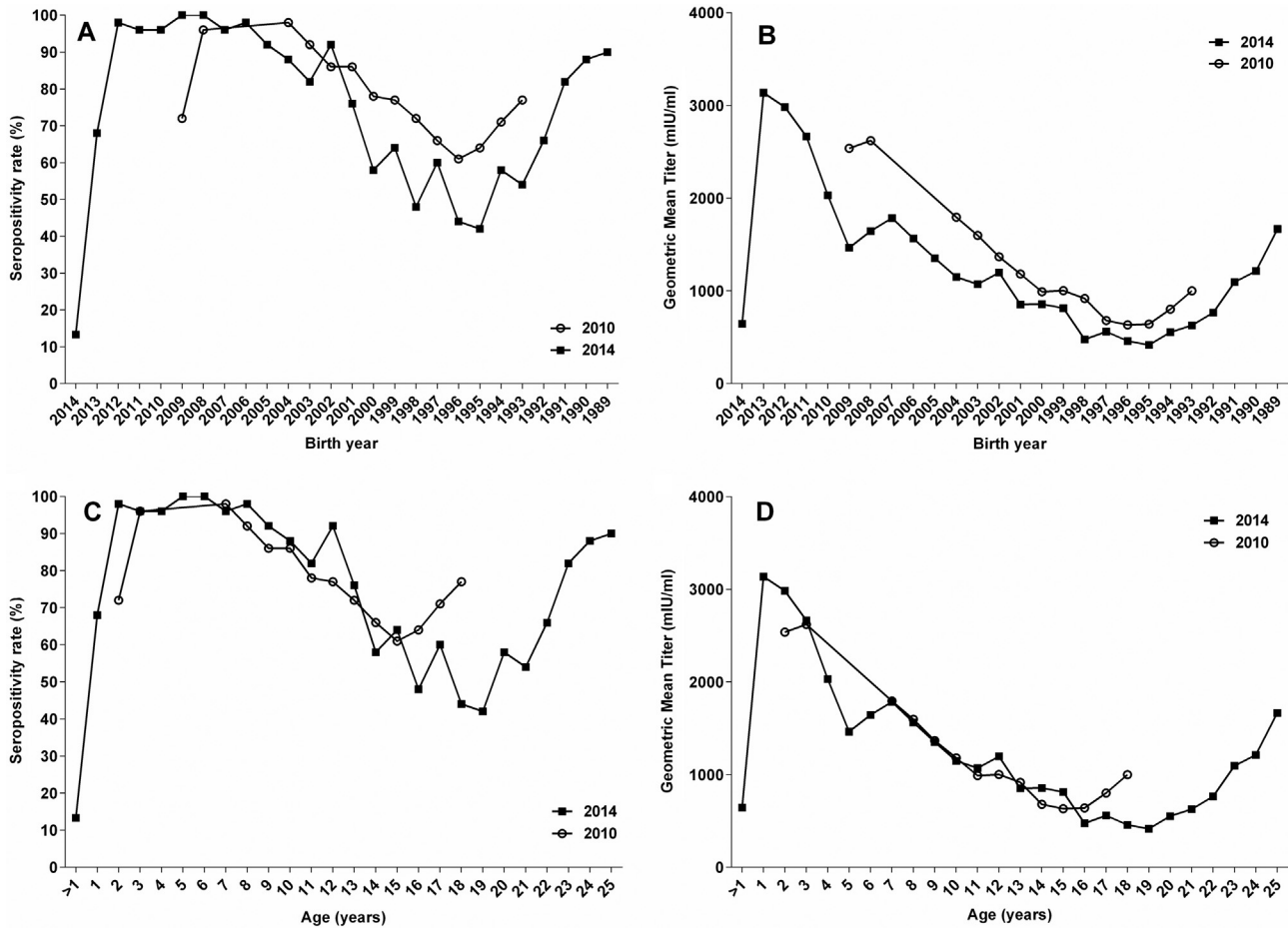
### 3.5. Passive immunity to measles in infants during the first year of life

The infants aged under 12 months had very low seroprevalence and measles antibody GMT values of 13.3% (95% CI, 5.5–21.1) and 643.5 mIU/mL (95% CI, 788.4–1485.5), respectively. The seropositivity of IgG antibodies was 76.0% (95% CI, 62.4–89.6) in infants aged 1 month, which decreased to 8.0% (95% CI, 0–34.6) in infants aged 3 months. The measles antibody GMT was 841.0 mIU/mL (95% CI, 679.0–2155.2) in infants aged 1 month, which dropped abruptly to 369.5 mIU/mL (95% CI, 0–2010.9) in infants aged 3 months. After 4 months of age, seropositivity and measles antibody levels were very low, and detectable measles-specific antibodies were not observed after 8 months (Fig. 5).

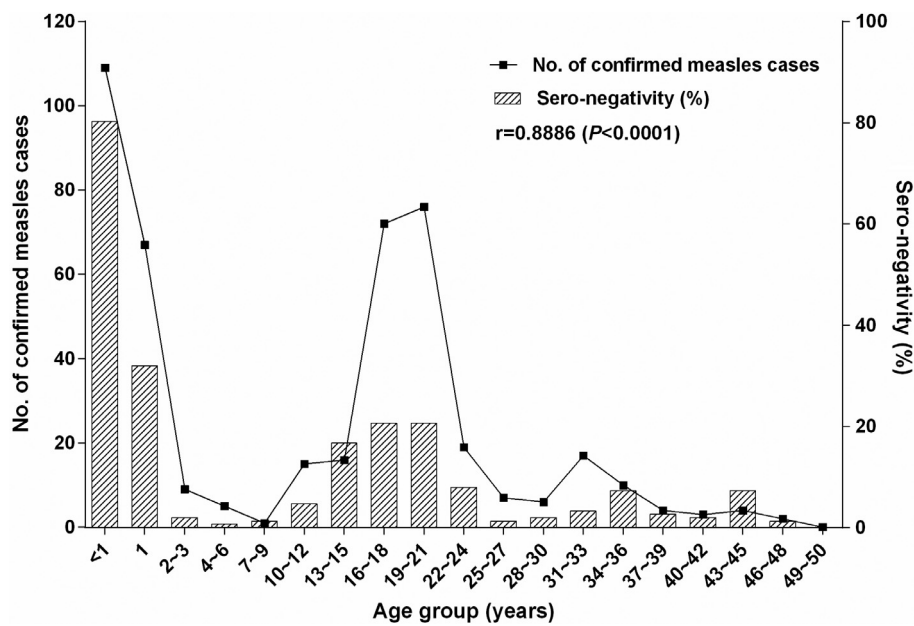
## 4. Discussion

Despite high measles vaccination coverage by a successful national vaccination program, small outbreaks have occurred following the importation from other countries in recent years, even though the circulation of wild measles viruses in Korea has been stopped since 2010 [4,13]. Such outbreaks have affected mostly unvaccinated people, but they also occurred in adolescents and young adults who had been previously vaccinated against measles [4,13]. During 2010–2016 in Korea, 36.2% of individuals with confirmed measles infection were unvaccinated, 46.8% were vaccinated previously (10.5% with 1-dose, 36.2% with 2-dose), and vaccination information was not available for 17% of infected individuals (data not shown).

The existence of potential factors underlying vaccine failure, such as waning immunity, was suggested by data generated in previous studies on measles outbreaks in highly vaccinated populations [5,6,8,9]. A rise in the proportion of seronegative individuals with lowering antibody levels over time since the last vaccination was observed in our study, and this proportion had shifted and expanded towards older individuals with lowering seropositivity and antibody levels being present over time. Similar findings have been reported in other countries. For example, the antibody-avidity indexes and concentrations decreased by 8% and 58%, respectively, 22 years after a 2-dose MMR vaccination in a Finland study [14]; the measles IgG GMTs decreased to 934, 251, and 144 mIU/ml in 2001–2003, 1990–1993, and 1994–1995,



**Fig. 3.** Seroprevalence of measles in 2010 and 2014. The distribution of seropositive rates (A) and GMT (B) by birth cohort (1984–2014) were compared between 2010 and 2014. The seroprevalence data between 2010 and 2014 were compared for seropositivity (C) and GMT levels (D) of measles-specific antibodies, according to the age group, during this investigation.



**Fig. 4.** Relationships between measles sero-negativity and confirmed measles cases by age groups in Korea in 2014. Correlations between sero-negativity and the number of confirmed measles cases were calculated using Pearson’s and Spearman’s correlation coefficients.

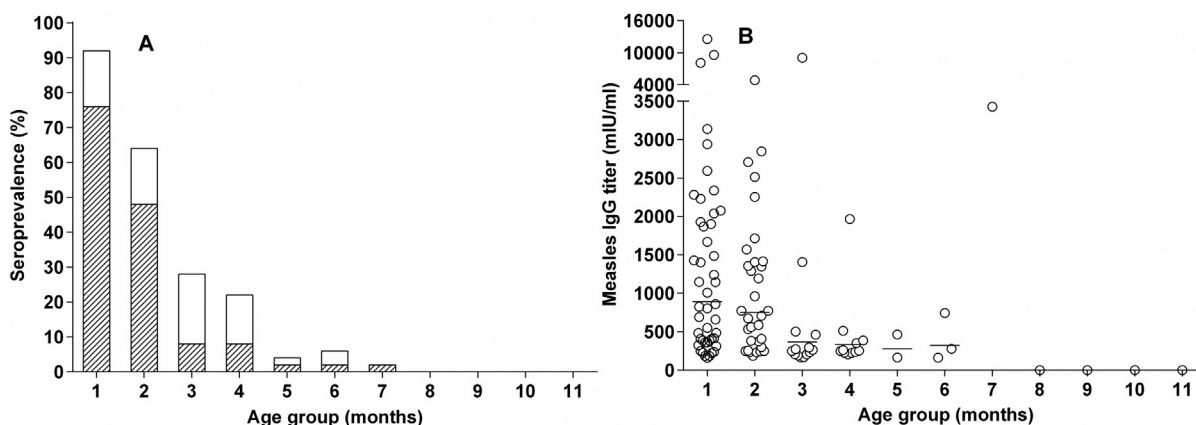


Fig. 5. Seroprevalence (A) and GMT (B) of measles IgG antibodies in infants aged <12 months.

respectively, in a study conducted in Portugal [15]; and declining neutralizing measles-antibody titers were detected in both kindergarteners and middle schoolers, 5 years and 10 years after a secondary vaccine dose (2814 decreased to 641 mIU/ml, and 1672 decreased to 737 mIU/ml, respectively) in a study conducted in the United States [16]. The neutralizing antibody titer is related to protection a measles virus infection, and PRN titers of  $\geq 120$  mIU/mL are thought to be protective against measles [17]. Age-specific, potential susceptibility was calculated using a cut-off value of  $\leq 120$  mIU/mL, and adolescents and young adults presented higher susceptibility rates compared to other age groups.

In the 20–29-year-old age group, higher seropositivity and GMT were detected than in the 13–19-year-old age group that was estimated to have been administered a measles and rubella vaccine through the catch-up vaccination program in 2001 [1,3,18]. These data can be interpreted to mean that the catch-up campaign was an appropriate strategy for progressing toward measles-elimination goals in Korea. The group aged 30–50 years, whose immunity against measles was presumably acquired naturally by previous exposure to wild measles virus, presented higher seroprevalence and antibody concentrations than did other age groups, except for the 1–12-year-old age group. Our observations that long-term and higher antibody levels were present following natural infection than after vaccination agree with data from other previously published studies [2,19].

Measles epidemics have been and still observed in other countries with low vaccination coverage, and the measles outbreaks through importation is continuously reported in countries that have eliminated measles such as Korea [4,20,21]. The measles-importation risk still exists, especially in individuals with suboptimal immunity. Several reports have warned that the susceptibility to measles infection may be rising because of waning vaccine-induced immunity over time after vaccination, in the absence of natural boosting by circulating measles viruses [22,23]. Our data showed good agreement between the incidence of measles and the susceptible age groups (adolescents and young adults) with measles seronegativity observed, suggesting the potential accumulation of measles-susceptible individuals in the population due to waning immunity, which may pose increased risk for measles outbreaks following measles importation from other endemic countries.

Cell-mediated immunity may protect against measles virus infection by promoting viral clearance, recovery from acute disease, and the persistence of long-term immunity [24–26]. Measles-avidity assays may provide valuable information for assessing the occurrence of measles in highly vaccinated popula-

tions by identifying vaccine failure [5,27,28], although these issues we not addressed in this study.

In this study, passively acquired maternal measles antibodies declined significantly and expired at 8 months after birth in Korean infants. Several studies of early waning of maternal measles antibodies in infants were published in recent years, and such waning may be related to low maternal measles titers, a limitation of vaccine-induced immunity compared with naturally developed immunity after wild measles virus infection, and the absence of natural boosters [29–33]. Because an increasing number of women have acquired immunity by vaccination instead of natural measles infection due to decreasing opportunities for wild virus exposure, the immunity gap in measles protection occurring between the loss of passive immunity derived from the mother and immunity acquired from the first vaccination can be amplified. As a consequence, the proportion of infants susceptible to measles infection increases progressively.

Earlier immunization (<12 months) has been suggested as a means for solving the problem that antibodies passively acquired from vaccine-induced maternal immunity do not persist long term [32,34,35]. Measles-endemic countries such as China, India, Philippines, and France have implemented measles vaccination programs in infants under 12 months of age [36]. Although earlier vaccination in infants before 12 months of age can reduce the susceptibility to measles, better seroconversion rates and antibody levels were observed when the MMR vaccine was administered at 12 months of age [35,37,38]. The WHO recommends administering the 1-dose of the MMR vaccine to infants aged 12 months in countries with low rates of measles transmission, but in the endemic countries, the WHO advises that the first vaccination should be given at 9 months of age and the second vaccination given at 15–18 months [39]. The waning of measles antibodies in adolescents and young adults after vaccination and in infants after birth but before the first vaccination, and the limitation of vaccine-induced immunity in measles-eliminated environments versus acquired immunity by natural infection were confirmed in our age-specific seroprevalence study. These findings suggest that an increasing proportion of measles-susceptible individuals is occurring with increasing time post-vaccination in Korea. Testing this hypothesis require further studies with data from the continuative seroprevalence survey at 3–4-year intervals to determine the accumulating measles susceptibility in Korean population. In addition, cell-mediated immune responses to measles and IgG antibody-avidity studies are needed to provide a better understanding of measles occurrences in vaccinated populations.

## Ethical approval

Ethical approval (approval no. 2014-11EXP-05-P-E) for this study was obtained from the Institutional Review Board of the KCDC.

## Potential conflicts of interest

None of the authors have a commercial or other association that might pose a conflict of interest.

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