Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 1 May 2017
Received in revised form 16 June 2017
Accepted 18 June 2017
Available online xxxx

Keywords:
Measles
Neutralizing antibody
Seroprevalence
Waning immunity

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 though 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.

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 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

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_{50}, 50% neutralizing antibody end-point titers; PRNT, plaque-reduction neutralization test; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.vaccine.2017.06.058
0264-410X/

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 KNHNES 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 α-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_{50}) 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 internals (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

Please cite this article in press as: Kang HJ et al. An increasing, potentially measles-susceptible population over time after vaccination in Korea. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.06.058