

Original Article



Causes of a Low Measles Seroprevalence among Young Healthcare Workers in Korea

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ABSTRACT

Background: Sporadic measles outbreaks have continued to occur in Korea, mainly in adults in their 20s and 30s, most notably in 2014 and 2019. We here evaluated the possible causes of a low seroprevalence of measles by testing young healthcare workers (HCWs).

Materials and Methods: This study was conducted in a 2,743-bed tertiary-care hospital in Seoul between 2020 and 2021. We performed a measles antibody test (chemiluminescence immunoassay), measured the IgM/IgG index ratio, and conducted an avidity test at 1-month after Measles-Mumps-Rubella (MMR) vaccination in HCWs who had been seronegative for measles. Measles vaccination histories were obtained from the national vaccine registry.

Results: Of the 3,173 HCWs newly employed in our hospital during the study period, 54 with a negative measles IgG at commencement were enrolled. Thirty six (67%) of these subjects were female, and the median age was 25 years (interquartile range [IQR]: 24 - 27). Forty nine (91%) showed seroconversion at 1 month after the first vaccination. Of these individuals, 38 received both measles IgM and IgG test, and all had an IgM/IgG index <1. Of the 49 seroconverters, all HCWs showed a high avidity index. According to the national immunization registry, 45 (83%) received at least 2 doses of an MMR vaccination.

Conclusion: Secondary vaccine failure may underlie vaccine failure in young Korean adults. HCWs born after 1985 with a negative measles antibody may need only a single dose booster vaccination rather than a 2-dose vaccination regimen.

Keywords: Measles; Measles-Mumps-Rubella vaccination; Vaccine failure; Healthcare workers

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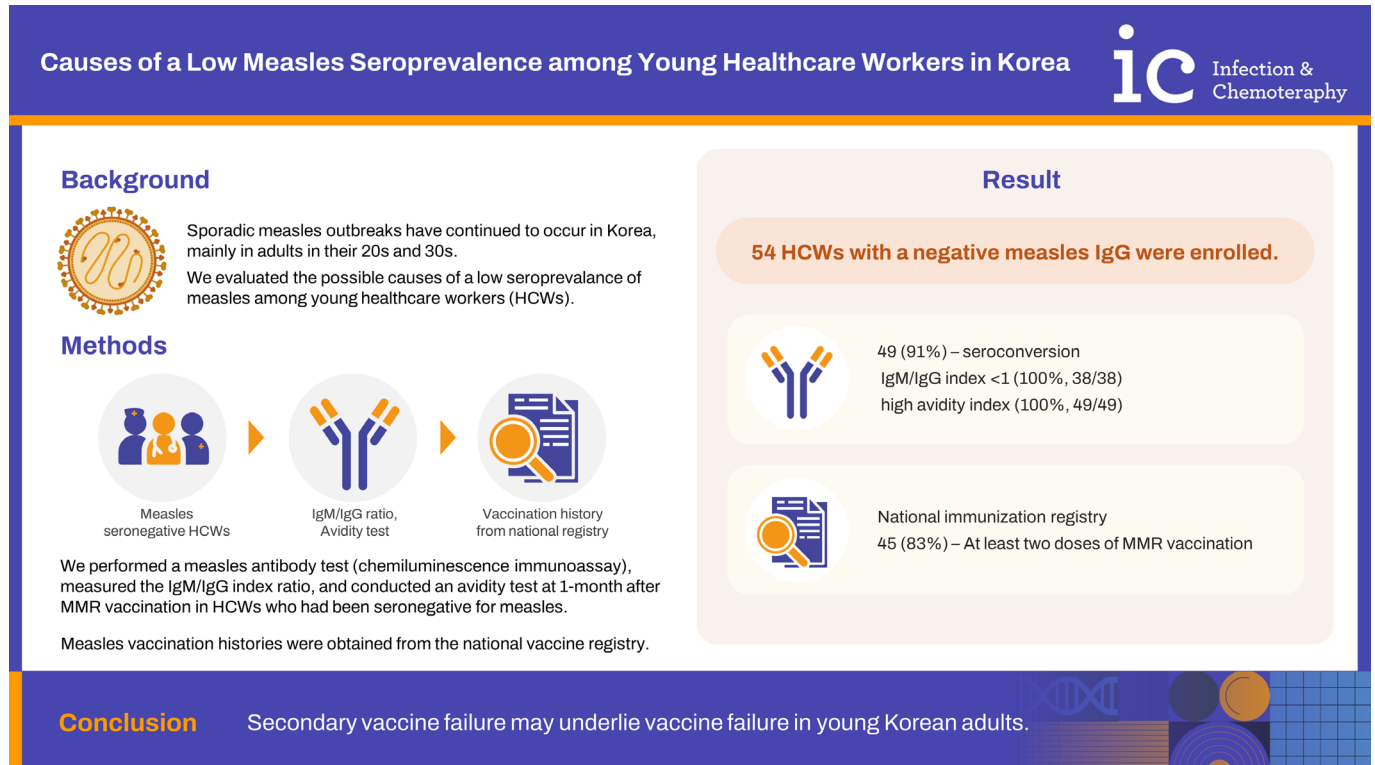
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GRAPHICAL ABSTRACT



INTRODUCTION

Measles has been declared eliminated from Korea since 2006, but sporadic outbreaks have continued due to imported cases and nosocomial transmission [1, 2]. Of note in particular, 442 cases arose in 2014 and 194 cases in 2019 due to outbreaks. Recent measles cases in Korea have arisen in pediatric patients who have never been vaccinated but also in young adults in their 20s and 30s who have [2, 3]. A large national outbreak of measles in South Korea involving more than 55,000 cases occurred between 2000 and 2021. The Korean government subsequently implemented a national measles elimination program, including catch up measles and rubella (MR) vaccinations and a keep-up program (policy of vaccination certification as a school entry requirement) [1, 4]. As a result of this scheme, more than 95% of young Korean adults born after 1985 have received a 2-dose Measles-Mumps-Rubella (MMR) vaccination [1]. However, measles cases are still arising in young Korean adults aged in their 20s and 30s.

Recent studies and our own previous report found that the measles seroprevalence is low in young adults in Korea, resulting in an under-immunity pocket [5-8]. The reason for this phenomenon is unclear but secondary

vaccine failure (*i.e.*, waning immunity after measles vaccination) and primary vaccine failure (no antibody response after vaccination due to problems in the process of vaccine production or distribution, or in the vaccination procedures) are possible causes [9]. Hence, we here evaluated the possible cause of a low seroprevalence of measles antibodies in young healthcare workers (HCWs) at our own tertiary hospital.

MATERIALS AND METHODS

1. Setting and definition

This study was conducted from 2020 to 2021 for newly employed HCWs at 2,743-bed tertiary-care hospital in Seoul, Korea. The immunization program for new employees at our hospital includes a universal screening test for the measles antibody and two-dose MMR vaccination for any individuals showing a negative IgG result from this test according to the KDCA's guideline. Seronegative HCWs who agreed to participate in the study was enrolled.

At 1-month after the first MMR vaccination among the participating seronegative HCW subjects, we conducted further measles antibody testing, and thereby determined

the IgM/IgG index ratio, using chemiluminescence immunoassays (LIAISON Measles IgG and LIAISON Measles IgM; DiaSorin, SpA, Italy), and also a measles IgG avidity assay (Euroimmun, Lubeck, Germany), as per the manufacturer's protocol in each case.

In accordance with the methodology of a prior study [10], we here defined an IgM/IgG ratio >1 as an indicator of primary vaccine failure, and of <1 as indicative of secondary vaccine failure. The relative avidity index (RAI) in our current investigation was as defined by the assay manufacturer's guidelines as follows: the RAI percentage denotes the extinction of the sample with urea treatment divided by extinction of the sample without urea treatment, multiplied by 100. An RAI $<40\%$ indicated low avidity antibodies, of between 40% and 60% indicated equivocal results, and of $>60\%$ indicated high avidity antibodies.

We obtained measles vaccination histories for our present subjects from the national vaccine registry.

2. Ethics statement

The study protocol was approved by our Institutional Review Board (2019-1590). Informed consent was obtained from participants.

RESULTS

During the study period, 3,173 HCWs were newly employed at our hospital, of which 167 had a negative measles IgG test. Of these seronegative cases, 54 agreed to enroll in this investigation (Fig. 1), among which 36 (67%) were females, and the median age was 25 years (interquartile

range [IQR]: 24 - 27). Fifty (93%) of these study subjects were born after 1990 and remaining 4 were born from 1978 to 1981. Forty nine (91%) showed seroconversion at 1 month after the first vaccination. Of these individuals, 38 received both measles IgM and IgG test, and all had an IgM/IgG index <1 . Of the 49 seroconverters, all HCWs showed a high avidity index (mean \pm SD, 80.8 ± 8.8).

The measles vaccination record in the Korean national vaccine registry showed that 45 (83%) of our study subjects had a documented vaccination record during their childhood, and 9 (17%) did not (Fig. 2). Of these 9 HCWs without childhood records, four were born from 1978 and 1981, and of the remaining five who were born after 1990, 3 had a history of one-dose vaccination as an adult. In addition, of the 45 HCWs who had been vaccinated during their childhood, 11 received one or two-dose MMR vaccination again at an adult age. Hence, 3 (6%) had a documented history of receiving 4 doses of MMR vaccination, 8 (15%) received 3 doses, 34 (63%) received 2 doses, and 3 (6%) received 1 dose, and the remaining 6 (11%) had no documentation of vaccination. In addition, the 48 HCWs with a vaccination record had received their MMR vaccination at a median of 18 years (IQR: 7 - 20) prior.

DISCUSSION

Our present study showed that HCWs with a negative measles IgG had an IgM/IgG index <1 and a high avidity index one month after MMR vaccination. This suggests the possibility that secondary vaccine failure may be responsible for most vaccine failure cases among young adults in Korea. While immunity after infection by the

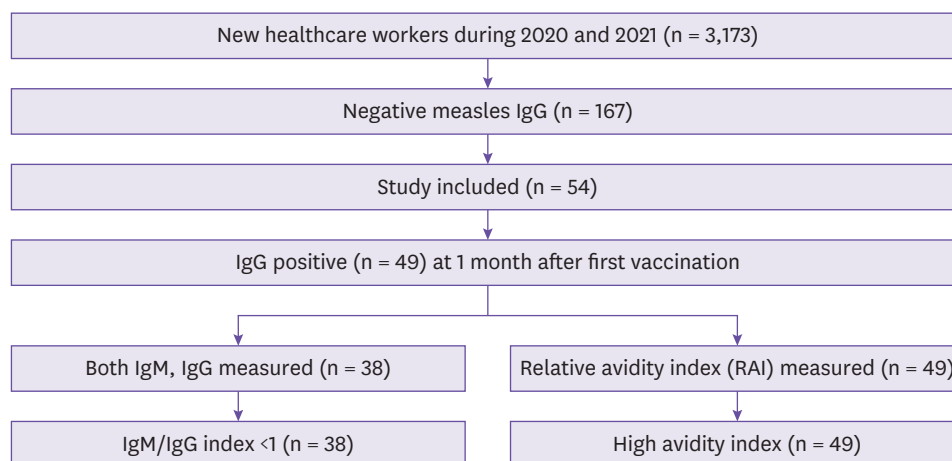


Figure 1. Study flowchart and IgM/IgG index ratio and avidity test results for measles immunity among the study population.

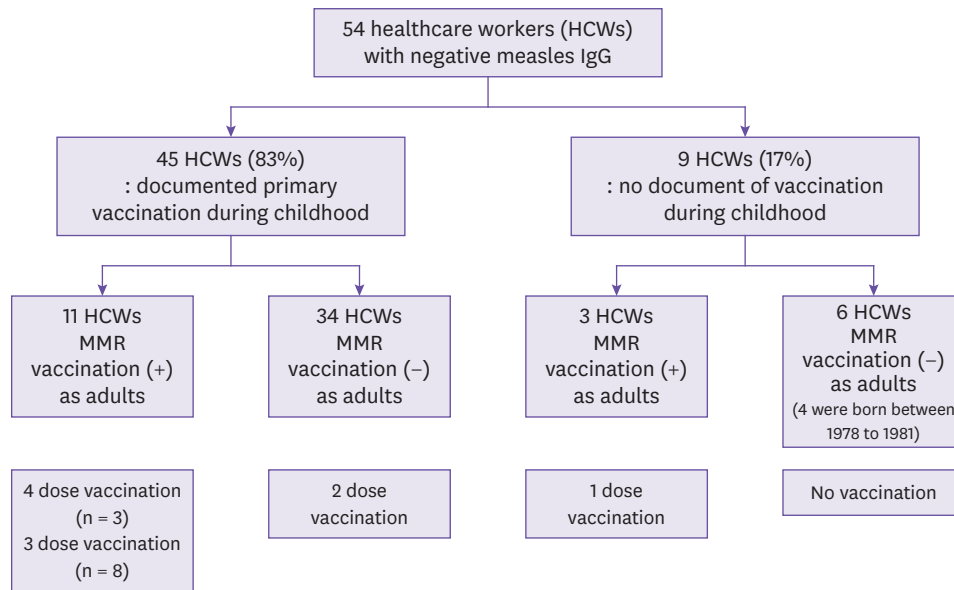


Figure 2. Prior measles vaccination history of the study population according to the national vaccination registry.

wild-type measles virus may persist [11], the longevity of protection after vaccination without natural infection is unknown. The antibody titer decreases more rapidly from a vaccination alone than following a natural infection [12, 13]. According to the measles seroprevalence study conducted by the Korea Disease Control and Prevention Agency in 2010 and 2014, the seropositivity rate in 2014 was lower than that in 2010 for people in the same birth year, indicating the possibility of waning immunity against measles [14]. Similarly, Korean birth cohorts from 1994 - 1996 showed a low seroprevalence for measles antibodies (64% for IgG titer ≥ 320 mIU/mL) in a study performed in 2010 [15]. However, the possibility of primary measles vaccine failure (due to problems in the process of vaccine production or distribution, or in the vaccination procedures) arising from the mass vaccinations in Korea in 2001 cannot be ruled out. Our present study findings suggest that secondary vaccine failure (waning immunity) is a plausible cause of the low seroprevalence of measles in young adults. Similar to our current observations, other studies conducted in Korea have found that most (89 - 99%) HCWs who are seronegative for measles have high avidity results at one month after vaccination [16, 17], again suggestive of secondary vaccine failure. The presence of pockets of measles-susceptible populations in Korea raises concerns regarding the higher risk of future outbreaks, and also with regard to the maintenance of herd immunity among HCWs, which is vital to preventing measles transmission in a healthcare setting. Antibody testing for new HCWs, who are mostly young adults, and

adequate booster vaccinations for seronegative HCWs, are warranted.

In Korea, seronegative HCWs are recommended to receive two doses of the MMR vaccination [18]. Those born after 1985 received two doses of the measles vaccine due to the national vaccination program and the resulting school entry requirements. Therefore, the reasons why two doses of the MMR vaccination are needed is unclear. Data on the efficacy of four doses of MMR vaccination are limited. In cases of secondary vaccine failure, cell-mediated immunity and memory cell responses have an important role in the protection against measles, even when these individuals have no antibody response [12]. Five (9%) seronegative participants after a MMR vaccination may be non-responders or they may develop antibody later, as previously reported [19]. Additionally, one of the five seronegative individuals did not have any vaccination record, and we may test his or her antibody after a single dose of MMR vaccination. All 49 seroconverted HCWs had results suggestive secondary vaccine failure. Therefore, our present data suggest that a single dose booster MMR vaccination for seronegative young HCWs is more appropriate than a two dose protocol.

Our study had several limitations of note. First, it was a single center study with a small number of participants. Second, the national vaccine registry in Korea may be inaccurate, especially in relation to the early 2000s, due to the possibility of missing records. Particularly, four

participants without vaccination record who were born between 1978 and 1981 may receive measles vaccination. Third, we did not perform a plaque reduction neutralization test (PRNT). Protection against measles cannot be determined using an IgG measurement alone, and it is known that a neutralization antibody test is the most reflective of the level of immunity. Also as high neutralizing antibody responses (PRN titers >30,000) have been observed in secondary vaccine failures, PRN titers can also differentiate secondary from primary vaccine failures [12]. Finally, since the avidity test is not standardized, the results may vary depending on the kit used [20].

In conclusion, secondary vaccine failure may be the reason for low seroprevalence of measles among young adults in Korea. Hence, HCWs in particular with a negative measles antibody test results who were born after 1985 can receive a single booster vaccination rather than a two-dose vaccination.

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Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: JJ, SHK. Methodology: HC, SKC, MJK, JJ. Data curation: JJ, SKK, JJ. Formal analysis: JJ. Writing -

original draft preparation: HC, JJ. Writing - review and editing: EOK, MJK, YPC, SHC, SOL, YSK, SHK.

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