Need for a third dose of measles containing vaccine among young-aged healthcare workers in measles elimination setting

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I am much honoured to present this manuscript entitled "**Need for a third dose of measles containing vaccine among young-aged healthcare workers in measles elimination setting**" to distinguished scholars as you.

Considering the threat of measles outbreaks in South Korea during 2018-2019, effective measures to control outbreaks is a priority. Several reports revealed that recent measles outbreaks were attributed to a low seropositivity among highly vaccinated young adults. Still, whether additional dose of measles containing vaccine (MCV) has a role as booster is questionable and its clinical significance is unclear. I, therefore, evaluated the immune response of a third dose of MCV among young-aged healthcare workers who have received two doses of MCV in the past.

I thank all the nursing and laboratory staff and physicians who supported this project. Finally, I give credit to all the patients included in the study. I would like to thank professor Jun Yong Choi for his dedication to this manuscript.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Several reports revealed that recent measles outbreaks among highly vaccinated young adults were largely attributed to waning immunity. Still, whether additional dose of measles containing vaccine (MCV) has a role as booster is questionable. I evaluated the immune response of a third dose of MCV among healthcare workers (HCWs) in a Korean hospital. Hospital-wide measles seroprevalence was assessed by enzyme-linked immunosorbent assay (ELISA). Furthermore, to evaluate the immunogenicity of a third dose of MCV, measles neutralizing antibody and immunoglobulin G (IgG) avidity index were determined before and after a third dose in seronegative young-aged HCWs. Among 3,277 HCWs, 3,033 (92.6%) had anti-measles IgG. Seropositivity was lowest in HCWs aged 20-24 years, of whom, HCWs presumed to receive a third dose of MCV had higher seropositivity than those who received a presumed second dose (89.5% vs 75.4%). Measles neutralizing antibody titers were significantly higher in HCWs who had anti-measles IgG after previous two doses of MCV than those who did not. A third dose of MCV was administered to 18 HCWs who did not have anti-measles IgG after two doses, and the neutralizing

antibody titers significantly increased 4 weeks and 1 year after the third vaccination. At 4-weeks post vaccination, four-fold rise in neutralizing antibody levels were observed in 14 (77.8%), and subjects with medium (121-900 mIU/mL) or high (>900 mIU/mL) level of neutralizing antibody titers were 18 (100%) and 14 (77.8%), respectively. Although the neutralizing antibody titers decreased 1 year post vaccination, levels were significantly higher compared with baseline and 17 (94.4%) subjects still remained at medium or high level. High avidity index (>60%) was observed in all subjects at 4 weeks and 1 year after vaccination. Although routine administration of additional MCV is not necessary to maintain measles immunity in countries which have achieved the measles elimination, a third dose of vaccine can be used as an intervention to prevent transmission in outbreak setting, especially for young adults who failed to respond to the second dose.

Keywords: measles, seroprevalence, measles vaccine, immunogenicity, antibody response

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I. INTRODUCTION

Measles is a highly contagious viral disease characterized by febrile rash [1]. Before the development of measles vaccine in 1963, measles killed more than 2 million people each year worldwide [2]. In the 1980s, as measles vaccine became widely available, the incidence and mortality rates of measles decreased significantly. Globally, the number of reported measles cases annually decreased 85% between 2000 and 2016, from 853,479 to 132,137, and the number of estimated measles deaths decreased 84%, from 550,100 to 89,780. It is estimated that 20.4 million deaths were prevented owing to measles vaccination during this period [3].

In South Korea, the incidence rate of measles gradually declined after measles vaccine was available in 1965. The second dose of measles containing vaccine (MCV) have been introduced in 1997 and then measles cases further decreased to less than 100 per year [4]. After a nationwide measles outbreak occurred during 2000-2001, in which approximately 55,000 cases were reported, Korean

government implemented the National Measles Elimination 5 Year Program. Owing to national efforts, the incidence rates reached to less than 1 per million people and South Korea declared the elimination of measles [5].

Recently, measles has been resurgent and outbreaks occurred worldwide [6]. During 2018-2019, hospital-associated measles outbreaks occurred in South Korea [7, 8]. Although young-aged healthcare workers (HCWs) in Korean hospitals are expected to have received two doses of MCV in the past, many of transmissions were attributed to HCWs in their 20s who had exposed to measles patients. Recent studies showed that the lowest measles antibody positive rates were observed among young-aged HCWs in South Korea [9-12]. These findings suggest that waned vaccine-induced immunity contributes to measles transmission among highly vaccinated young adults in outbreak setting.

Although two doses of measles-mumps-rubella (MMR) vaccine provides sufficient immunity against mumps, as well as measles, a third dose of MMR has been administered during mumps outbreaks [13-15]. A third dose may be used to improve immunity against measles in outbreak settings among seronegative HCWs. Still, there is limited study determining the immunogenicity of a third dose of MCV. Therefore, I assessed the antibody responses after a third dose of MCV among young-aged HCWs in South Korea.

II. MATERIALS AND METHODS

1. An additional dose of measles containing vaccine

The study was conducted in Ajou University Hospital, a tertiary care teaching hospital, Suwon, South Korea. Since 2011, new employees in the hospital were requested to receive one dose of MCV at least if they could not provide the

evidence of immunity to measles which include one of followings: (1) documented two dose of MCV; (2) laboratory confirmed past measles infection; (3) positive results of measles antibody.

2. Measles seroprevalence study

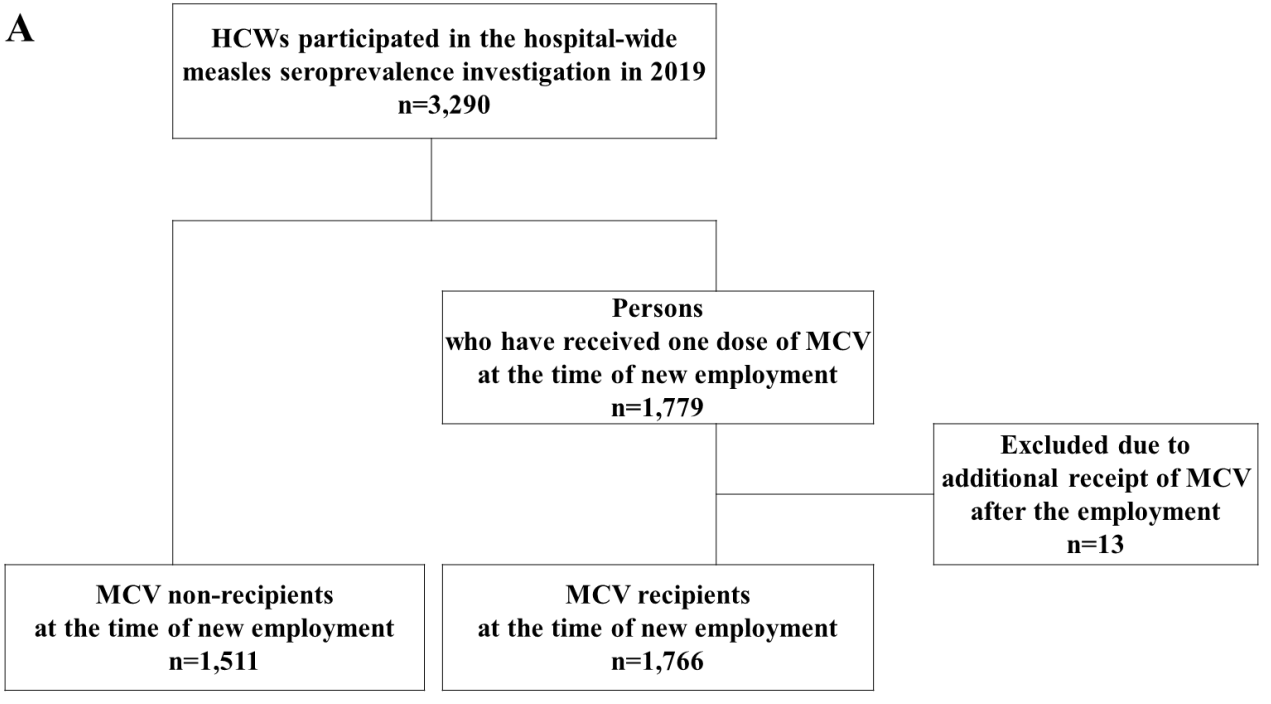
Hospital-wide investigation was implemented to determine the measles seroprevalence from July to August, 2019. 3290 HCWs participated in the measles seroprevalence study (Figure 1A). Of them, 1511 (45.9%) subjects did not receive MCV at the employment. Among 1779 (54.1%) subjects who had received MCV at the employment, 13 subjects were excluded because they had received additional MCV after the employment for another reasons. Based on historical changes of measles vaccination program in South Korea [4], subjects were classified according to the likelihood of having get vaccinated with two dose of MCV in the past, as follows: (1) 20-24 age, most likely; (2) 25-33 age, likely; (3) 34-39 age, less likely; (4) 40-49 age, unlikely; (5) ≥50 age, most unlikely.

3. Third dose of measles containing vaccine study

Invitation messages using e-mail were sent to subjects who did not receive MCV at the employment to determine immune response of a third dose of MCV. Among HCWs born after 1985, subjects who verified the vaccination status of two MCV doses during childhood received third dose of MCV and were willing to participate in the study were included. Following cases were excluded: (1) their household members who had been diagnosed with measles in the past; (2) persons who had already received MCV at least 3 times; (3) receipt of any other vaccination within 30 days; (4) persons contraindicated to MCV. Between October 2019 and February 2020, 18 subjects with negative or equivocal results for antibody to measles and 26 subjects with positive results were enrolled in this study (Figure 1B).

I obtained information on demographic factors, comorbidities, and date of first and second vaccination to measles. A third dose of MCV (MMRII; Merck & Co.) was administered to subjects without anti-measles IgG at first visit and blood samples were collected before (baseline), 4 weeks after, and 1 year after a third dose of MCV. They were questioned about local reactions and systemic reactions after vaccination at 4 weeks visit. Subjects with positive anti-measles IgG were required to take only one blood sampling at first visit (Figure 1B).

A



B

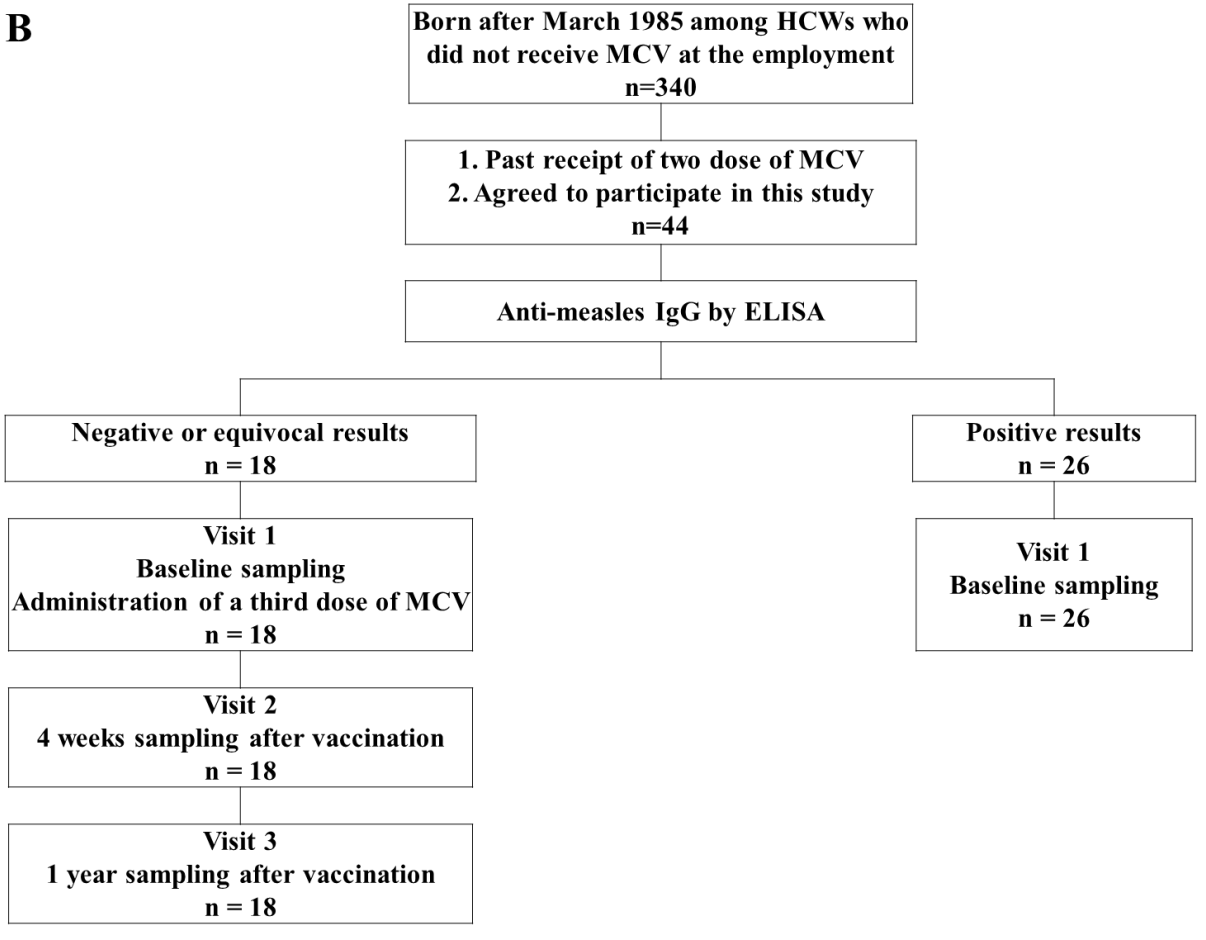


Figure 1. Flow chart of study population. A, Study of measles seroprevalence among healthcare workers (HCWs) according to receipt of one dose of measles containing vaccine (MCV) at the time of new employment. B, Study for determining immunogenicity and safety of a third dose of measles containing vaccine. ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G.

4. Laboratory methods

A. Enzyme-linked immunosorbent assay

Anti-measles virus IgG was determined in subjects included in measles seroprevalence study. Test was performed by enzyme-linked immunosorbent assay (ELISA) kit using the Chorus Measles IgG (Diesse Diagnostica Senese Spa, Italy). The results were expressed as an index, ratio between the optical density value of the test sample and that of the cut-off. Serum samples was categorized as positive (>1.2), equivocal (0.8-1.2), and negative (<0.8), according to manufacturer's instructions. All serum samples were re-tested in duplicate if equivocal results were obtained. After re-testing, the results were classified with based on the values with a majority.

B. Plaque reduction neutralization test

Measles neutralizing antibody were measured in samples collected from subjects enrolled in third dose of MCV study by plaque reduction neutralization (PRN) test, as previously described [16]. Low passage Edmonston wild type measles virus was used as challenge virus. All serum samples were serially diluted four-fold starting from 1:4 to 1:4096 after heat inactivation at 56℃ for 30 min. Challenge virus diluted to present 25-35 plaques per well was added to the serum dilution. Virus/serum mixtures were incubated at 37℃ for 2 h, then transferred on 24-well plate containing Vero cell monolayer. After incubating 37℃ for 2 h, the inoculum was removed and overlay media containing carboxymethylcellulose was added. The well was transported again incubator for 5 days and overlay media was decanted at the end of incubation period. 1% crystal violet was added in each well for staining for 20-30 min after cell fixation. The 50% neutralizing antibody end-point titer (ND50) were determined for all serum samples using the Kärber method. Titers were standardized against the WHO 3rd International Standard Reference Serum (NIBSC code 97/648) with measles

antibody concentration of 3000 mIU/mL, so PRN titer of 1:8 was expressed in 8mIU/ml. Serum samples was classified as negative (<8 mIU/mL), low (8-120 mIU/mL), medium (121-900 mIU/mL), and high (>900 mIU/mL), as described at previous studies [17]. Serum samples with PRN titer >120 mIU/mL were considered as seropositive, as described at previous studies [18, 19]. Seroconversion was defined as ≥four-fold increase in PRN titer against measles after vaccination between paired serum samples.

C. Avidity test

Measles IgG avidity test was performed in serum samples with neutralizing antibody titers ≥8 mIU/mL by a commercial enzyme immunoassay (EUROIMMUN, Lübeck, Germany) according to manufacturer's instruction. The results were expressed as relative avidity index (RAI) that was calculated as the percentage of IgG values in sera treated with and without urea. Samples with RAI of <40% were classified as low avidity, those between 40% and 60% as equivocal, and those above 60% as an indication of high avidity.

5. Statistical analysis

Categorical variables were presented as numbers with percentages and compared using Chi-square test or Fisher's exact test. Continuous variables were presented as medians with interquartile range (IQR) and compared using Mann-Whitney U test. All statistical analyses were performed using SPSS software version 25 (SPSS Institute Inc., Chicago, IL, USA). A two-sided p-value of < 0.05 was considered statistically significant.

6. Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-SMP-19-310), and the protocol adhered to the tenets of

the Declaration of Helsinki. All of the study participants provided written informed consent.

III. RESULTS

1. Measles seroprevalence study

Among 3277 serum samples tested by ELISA, 3033 (92.6%) were positive for measles antibody and 129 (3.9%) were equivocal. Age-specific seropositivity of HCWs were presented in Figure 2. Since none of subjects who did not receive MCV at the employment were born in 1998, seropositivity for those could not calculated. There was an increasing trend in measles seropositivity with age in both subjects who had received MCV at the employment and who did not. According to age group, the highest seropositivity was observed in subjects of age group ≥50 who most unlikely completed vaccination with two dose of MCV in the past. There was no significant difference in seropositivity between subjects who had received MCV at the employment (100%) and who did not (94.7%) in this age group (Table 1). In contrast, seropositivity was lowest in subjects of age group 20-24 who most likely get vaccinated with two dose of MCV in the past. Seropositivity was significantly higher in subjects who had received MCV at the employment compared with those who did not (89.5% vs 75.4%, P = 0.01).

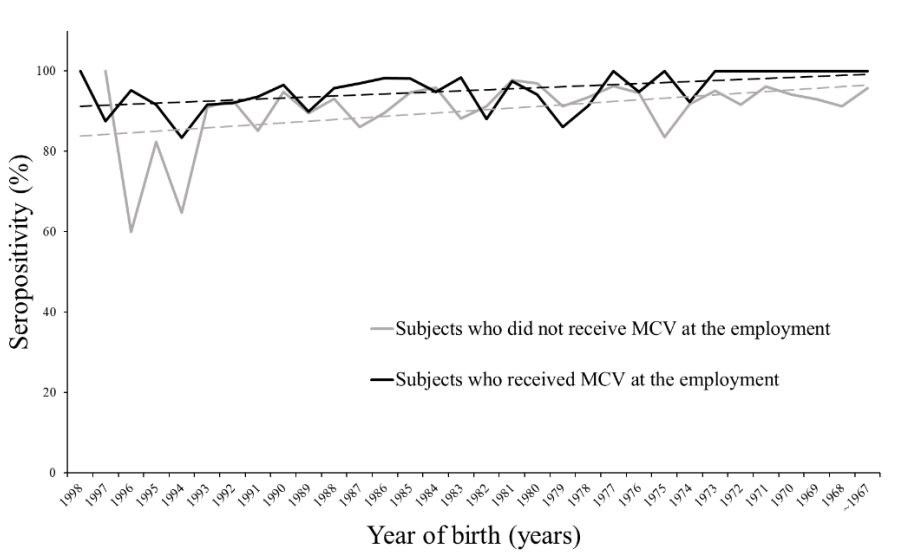


Figure 2. Age-specific seropositivity between healthcare workers who received one dose of measles containing vaccine (MCV) at the time of new employment and non-recipients. The dotted line shows a trend in seropositivity by year of birth. Since no one born in 1998 among subjects who did not receive MCV at the employment, seropositivity could not calculated for those.

Table 1. Comparison of measles seroprevalence between healthcare workers who received one dose of measles-mumps-rubella at the time of new employment and did not, by age group

Age group	Year of birth	MCV non-recipients at the time of new employment				MCV recipients at the time of new employment				*P*
		Subjects, no.	Positive, no. (%)	Equivocal, no. (%)	Negative, no. (%)	Subjects, no.	Positive, no. (%)	Equivocal, no. (%)	Negative, no. (%)	
20-24	1994-1998	57	43 (75.4)	7 (12.3)	7 (12.3)	391	350 (89.5)	20 (5.1)	21 (5.4)	0.01
25-33	1985-1993	303	275 (90.8)	15 (5)	13 (4.3)	984	923 (93.8)	32 (3.3)	29 (2.9)	0.19
34-39	1979-1984	342	319 (93.3)	12 (3.5)	11 (3.2)	271	254 (93.7)	8 (3)	9 (3.3)	0.93
40-49	1969-1978	657	609 (92.7)	27 (4.1)	21 (3.2)	111	107 (96.4)	3 (2.7)	1 (0.9)	0.31
≥50	≤1968	152	144 (94.7)	5 (3.3)	3 (2.0)	9	9 (100)	0 (0)	0 (0)	0.779[a]
Total	1953-1998	1511	1390 (92.0)	66 (4.4)	55 (3.6)	1766	1643 (93.0)	63 (3.6)	60 (3.4)	0.46

[a]By the Fisher's exact test

2. Third dose of MCV study

Similar demographic characteristics were observed between subjects with and without anti-measles IgG (Table 2). All subjects have get vaccinated with first dose of MCV between 12 and 15 month. Median years since vaccination with second dose of MCV in subjects without anti-measles IgG were 18.2 (IQR 18.1-18.9), which was similar to that in subjects with anti-measles IgG (18.2, IQR 18.1-18.2). Baseline PRN antibody level was significantly lower in subjects without anti-measles IgG (130 mIU/mL, IQR, 45.5-259.5 mIU/mL) than those with anti-measles IgG (4096.5 mIU/mL, IQR, 2410.8-7417.0 mIU/mL) ($P < 0.001$). However, no significant differences were detected in baseline avidity index level between both groups (69.2%, IQR, 61.6-77.3% vs 72.5%, IQR, 67.3-76.5%).

Eighteen subjects without anti-measles IgG get received third dose of MCV. All of those completed the whole schedule of study that required to collect blood samples before and 4 weeks and 1 year after vaccination. No serious adverse events were detected during the study period. 3 subjects reported local adverse events, a pain at the injection site. 1 subject reported systemic adverse event, flu-like symptoms (febrile sense, headache, and myalgia). All reported adverse events were mild and resolved within 4 weeks following vaccination.

After third dose of MCV, seroconversion rates were 77.8% and 61.1% at 4 weeks and 1 year, respectively (Figure 3A). Four week after third dose of MCV, PRN antibody titer significantly increased from 130 mIU/mL (IQR, 45.5-259.5 mIU/mL) to 1478.50 mIU/mL (IQR, 831.50-2521.00 mIU/mL). Although PRN titer declined at 1 year following vaccination, by 635.50 mIU/mL (IQR, 295.75-988.25 mIU/mL), the level remained significantly higher than that of baseline (Table 3 and Figure 3B). Similar trend was observed in seropositivity rates and high PNR titer (>900 mIU/mL) rates (Figure 3C). At 4-weeks post vaccination, all subjects had PRN antibody titer >120 mIU/mL, considered as seropositive, and subjects with high level of PRN titer 14 (77.8%). Although the rates of

seropositivity and high PNR titer declined at 1 year post vaccination, 17 (94.4%) subjects still remained seropositive status. All of subjects had high avidity index from 4 weeks after vaccination. No significant differences were observed in avidity index at 4 weeks and 1 year, compared with baseline level (Figure 3D).

Table 2. Baseline characteristics of subjects, who have completed vaccination with two dose of MCV in the past, according to negative/equivocal and positive results for measles IgG by ELISA

	Negative/equivocal results (n=18)	Positive results (n=26)	*P*
Age, years, median (IQR)	28 (24-31)	30 (28-31)	0.426
Female, no. (%)	16 (88.9)	25 (96.2)	0.347
BMI, kg/m^2, median (IQR)	20.35 (19.71-23.94)	23.37 (20.02-25.77)	0.136
1st MCV at 12-15 month, no. (%)	18 (100)	24 (100)	>0.999
Time since 2nd MCV, years, median (IQR)	18.20 (18.13-18.88)	18.16 (18.13-18.18)	0.166
Time since 2nd MCV, days, median (IQR)	6644.0 (6619.0-6892.25)	6629.50 (6617.75-6636.25)	0.166
Baseline avidity index, %, median (IQR)	69.23 (61.6-77.34)	72.49 (67.30-76.48)	0.427
Baseline neutralizing antibody level, mIU/mL, median (IQR)	130 (45.50-259.50)	4096.50 (2410.75-7417.00)	<0.001

IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; MCV, measles containing vaccine

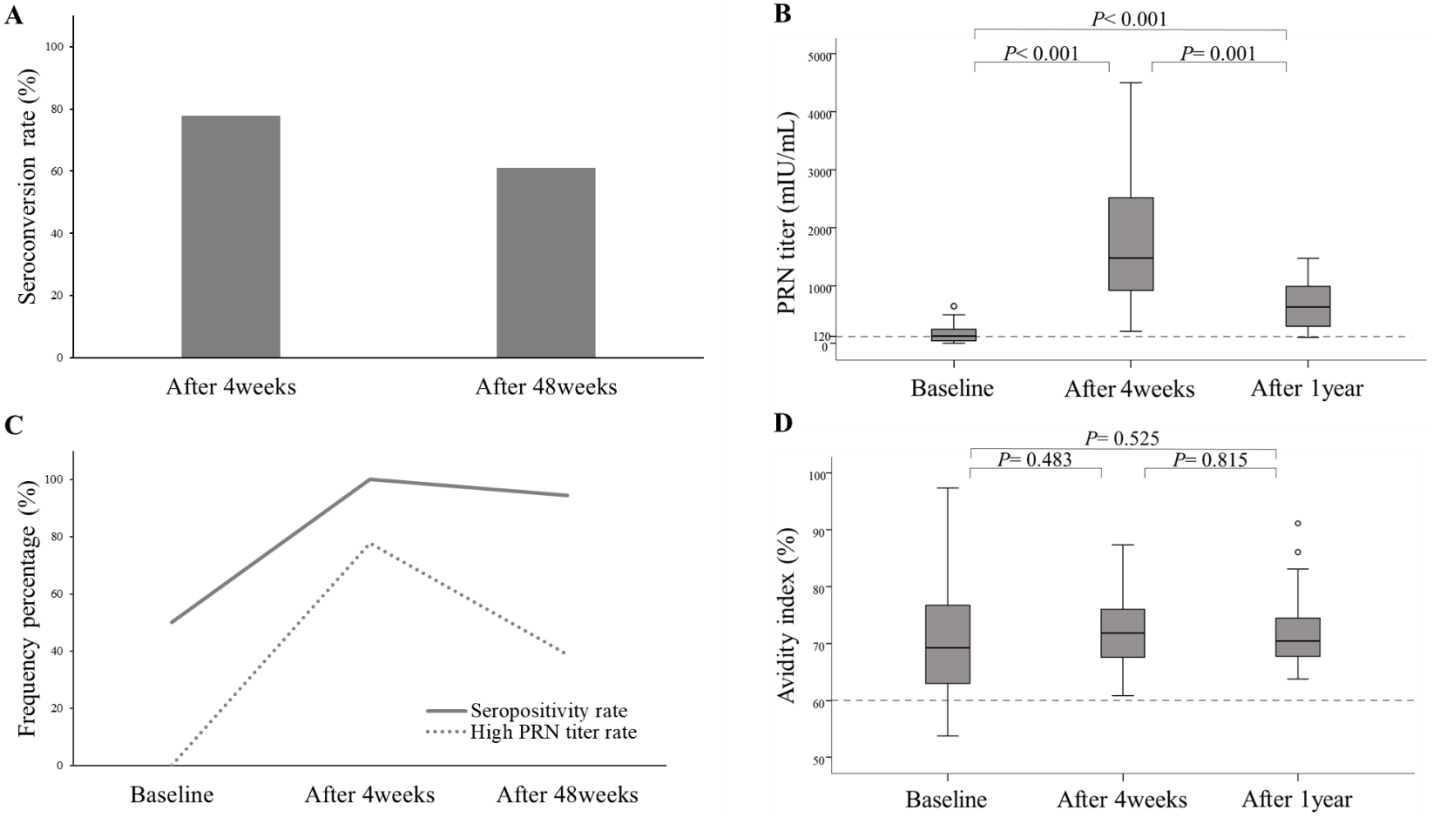


Figure 3. Immune response in healthcare workers (born after March 1985) who had negative or equivocal IgG results by ELISA after receipt of a third dose of measles containing vaccine. Seroconversion (four-fold rise in neutralizing antibody

titer) rates (A), PRN titer (B), seropositive rate of neutralizing antibody and high PNR titer (>900 mIU/mL) rate (C), and avidity IgG antibody index (D) before (baseline) and after (4 weeks and 1 year) vaccination. IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; PRN, plaque reduction neutralization.

Table 3. ELISA Measles virus neutralizing antibody concentrations by PRN assay and avidity IgG antibody index before (baseline) and after (4 weeks and 1 year) a third dose of measles containing vaccine in 18 subjects who had negative or equivocal results for measles IgG by ELISA

Subject	Baseline				4 weeks after a third dose of MCV				1 year after a third dose of MCV			
	PRN titer, mIU/mL	Results	Avidity index, %	Results	PRN titer, mIU/mL	Results	Avidity index, %	Results	PRN titer, mIU/mL	Results	Avidity index, %	Results
A	44	low	53.7	equivocal	1517	high	76.5	high	987	high	63.7	high
B	291	medium	63.9	high	1198	high	72.2	high	642	medium	67.7	high
C	46	low	69.2	high	1911	high	73.4	high	502	medium	66.6	high
D	66	low	63.6	high	500	medium	60.8	high	149	medium	75.5	high
E	494	medium	57.9	equivocal	917	high	64.1	high	519	medium	64.9	high
F	86	low	62.9	high	2270	high	65.7	high	936	high	66.0	high
G	249	medium	57.0	equivocal	2516	high	69.8	high	1052	high	70.3	high
H	225	medium	68.0	high	4502	high	87.3	high	629	medium	91.1	high
I	7	negative	NC	NC	208	medium	82.7	high	107	low	83.1	high
J	9	low	76.8	high	356	medium	75.2	high	135	medium	69.2	high

K	648	medium	75.8	high	2536	high	67.6	high	1469	high	74.3	high
L	34	low	77.9	high	1145	high	70.6	High	280	medium	70.2	high
M	232	medium	74.5	high	575	medium	71.5	high	301	medium	69.6	high
N	102	low	74.6	high	3312	high	70.6	high	992	high	70.7	high
O	85	low	97.3	high	1440	high	66.2	high	551	medium	72.9	high
P	222	medium	80.9	high	3384	high	79.5	high	1209	high	74.5	high
R	158	medium	85.1	high	1103	high	73.5	high	887	medium	73.1	high
Q	642	medium	60.3	high	1743	high	76.0	high	911	high	86.1	high

PRN, plaque reduction neutralization; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay

IV. DISCUSSION

Most HCWs (92.6%, 3033/3277) in the hospital had anti-measles IgG and the seropositive rates were lowest in age group 20-24. The MMR vaccination program for new employees who did not have the evidence of measles immunity increased the seropositivity in young-aged HCWs. Measles neutralizing antibody titers were significantly lower in 18 subjects who did not have detectable anti-measles IgG after the previous two doses of MCV than 26 subjects with anti-measles IgG. However, among 18 subjects without anti-measles IgG, a significant increase in the PRN titers occurred 4 weeks and 1 year after the third dose of MCV. At 1-year post-vaccination, neutralizing antibody levels were significantly higher compared with baseline and most subjects (94.4%) still remained over medium level of PRN titers.

Most subjects had high avidity IgG antibodies at baseline, and high avidity IgG presented in all samples collected at 4 weeks after third dose. After vaccination, low avidity IgG is observed for about 6-8 weeks, and it takes more than 3 months for development of high avidity IgG [20]. Therefore, high avidity IgG detected shortly after vaccination provides laboratory evidence of past immunologic experience with measles from immunization. These findings could be interpreted that waning immunity occurred after two doses among subjects in this study. Meanwhile, the seropositivity rate was higher among HCWs in age group 25-33 than those in age group 20-24 despite waning immunity. A certificate of two doses of measles vaccination was required at entering elementary school in South Korea since 2001. As a result, almost all HCWs in age group 20-24 had to submit a certificate at school entry, and therefore they are estimated to acquire only vaccine-induced immunity against measles through two doses of MCV. In contrast, most of subjects in age group 25-33 received the second dose through catch-up vaccination during nationwide measles outbreak occurred in their school

years, 2000-2001. Therefore, they might have chance to boost their immunity against measles through natural infection during nationwide measles outbreak. The number of measles cases confirmed during the outbreak (approximately 55,000) may not be enough to have an effect on seroprevalence among them. However, it must be considered a possibility that large numbers of measles cases were not diagnosed, because many adolescents might present atypical symptoms due to receipt of one dose of MCV in childhood. MCV provides significant immune response against measles to vaccine recipients and almost all persons who failed to respond to the first dose develop antibodies after the second dose [21, 22]. However, since vaccine-induced antibody titers decline over time and detectable antibody level persists longer after natural infection than post-vaccination [23-26], higher seropositivity was observed among subjects in age group 25-33 than those in age group 20-24.

Recently, measles outbreaks have been occurred among highly vaccinated populations [27-29]. In outbreak settings, administration of MCV has been recommended to susceptible persons to prevent disease and transmission. However, data are insufficient to recommend for the use of a third dose to seronegative persons who have received two doses. I demonstrated the higher seropositivity in young-aged HCWs who received a presumed third dose than in those who were estimated to receive two doses previously. Moreover, boost effect of a third dose of MCV on measles neutralizing antibody levels were detected in persons with secondary vaccine failure. Significant boost in measles immunity occurred 4 weeks after a third dose of MCV and remained at 1 year after vaccination. Although the antibody levels decreased at 1 year post-vaccination, levels of most subjects were above 120 mIU/mL, which is considered as protective level of measles neutralizing antibody [18]. Fiebelkorn et al indicated that third dose of MCV is unlikely to be effective for maintaining measles immunity, but they agreed with boost effect of third dose of MCV in persons who failed to respond to the second dose [17]. Therefore, a third dose of MCV to persons with

waned vaccine-induced immunity may be used as an effective intervention to limit the spread of measles in outbreaks settings.

Safety of a third dose of MCV has been well described in other studies that evaluated the role of a third dose of MMR in mumps outbreaks [30]. Third dose were well-tolerated and no serious adverse events were reported. Among young adults who received a third dose, symptoms, such as lymphadenopathy, diarrhea, headache, and arthralgia, were reported, but episodes were mild and developed at low rates. Similar to these safety data, only mild and transient adverse events were also reported in this study, and there was no serious adverse event during study period.

IgG results by ELISA did not consistent with neutralizing antibodies by PRN test in this study. There were no samples with positive results by ELISA at baseline, but neutralizing antibodies were positive in 50% of baseline samples. It could be explained by difference in methods. Target antigen is whole measles virus in ELISA. In contrast, PRN assay measures neutralizing antibody against measles virus surface glycoproteins mainly hemagglutinin protein [31, 32]. Therefore, PRN test is more sensitive to detect measles antibodies compared with ELISA. The false negative results of ELISA are more likely to be observed in samples with low titers of neutralizing antibody [33]. This finding was also observed in this study.

This study has some limitations. First, I recruited only young-aged HCWs born after 1985 because they were likely to have received two doses of MCV. Therefore, there is a possibility of selection bias. Second, although this study provides the evidence on immunogenicity and safety of third dose of MCV in healthy young adults, I could not evaluate the vaccine effectiveness. Future studies are needed to evaluate the effectiveness of the third dose of MCV in measles outbreak setting in highly vaccinated persons. Third, cellular immunity was not investigated in this study. Both humoral and cellular measles immunity play an important role in preventing measles. I am preparing the study that

evaluate the cellular immunity after third dose of MCV using T-cell assays.

V. CONCLUSION

Data for the safety and immunogenicity of a third dose of MCV shown in this study give an important evidence for use of a boosting shot in highly vaccinated population. Although routine administration of a third dose of MCV is not necessary to maintain measles immunity in countries which have achieved the measles elimination, health departments may need to consider using of it to persons with waned vaccine-induced immunity for measles outbreak control in intense-exposure or vulnerable settings.

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ABSTRCT (IN KOREAN)

홍역 퇴치 국가에서 젊은 의료기관 종사자들에게 3 차 홍역 백신 투여의 필요성

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김용찬

홍역 예방접종을 어린 시절에 마친 젊은 성인들의 낮은 혈청 양성률이 문제가 되고 있고 이는 최근 발생하고 있는 홍역 유행의 원인으로 지목된다. 아직까지 이들에게 홍역 백신을 추가적으로 투여하는 것이 홍역에 대한 면역력을 향상시키는 지를 확인한 연구는 드물다. 본 저자는 국내 일개 병원에서 의료기관 종사자들을 대상으로 3차 홍역 백신 접종의 면역 반응을 평가하였다. 연구가 진행되었던 병원에서 enzyme-linked immunosorbent assay (ELISA)를 진행하여 전체 의료기관 종사자들의 홍역 혈청 유병률을 확인하였다. 또한, 3차 홍역 백신 접종의 면역원성을 평가하기 위해서, 혈청 음성인 젊은 연령 대상자들에게 3차 홍역 백신 투여 전후의 홍역 바이러스 중화 항체 및 immunoglobulin (IgG) 결합력 지수를 확인하였다. 홍역 혈청 유병률 조사에 포함된 3,277명 중 3,033명 (92.6%)가 홍역에 대한 IgG 항체를 가지고 있었다. 항체 양성률은 20-24세의 연령 그룹에서 가장 낮았고, 그 중 홍역 백신을 3회 접종했을 것으로 추정되는 사람들에서 2회 접종했을 것으로 추정되는

사람들보다 더 높은 항체 양성률이 확인되었다 (89.5% vs 75.4%). 과거 2회의 홍역 예방접종을 완료한 후 홍역에 대한 IgG 항체가 확인된 이들은 항체가 확인되지 않은 이들보다 더 높은 홍역 바이러스 중화 항체 역가를 가지고 있었다. 2회 홍역 예방접종 후 홍역에 대한 IgG 항체가 확인되지 않았던 18명에게 3차 홍역 백신을 투여하였고, 3차 접종 4주와 1년 후에 중화 항체 역가가 유의미하게 증가하였다. 3차 백신 접종 4주 후, 14명 (77.8%)에서 4배 이상의 중화 항체 역가 상승이 관찰되었고, 중간 (121-900 mIU/mL) 혹은 높은 (>900 mIU/mL) 수준의 역가를 갖는 대상자는 각각 18명 (100%)과 14명 (77.8%) 이었다. 백신 접종 1년 후 중화 항체 역가가 감소하였지만 백신 접종 전과 비교하면 여전히 의미 있게 높았고, 17명 (94.4%)의 대상자는 여전히 중간 혹은 높은 수준의 역가를 유지하였다. 백신 접종 4주와 1년 후 모든 대상자에서 높은 IgG 결합력 지수 (>60%)가 확인되었다. 3차 홍역 백신은 홍역 퇴치 국가에서 홍역 면역을 유지하기 위해 일괄적 투여는 필요하지 않지만, 2차 접종 후에도 홍역에 대한 IgG 항체가 형성되지 않은 젊은 성인들 중심으로 발생하는 홍역 유행 발생 시 전파를 방지하기 위한 대책으로 투여를 고려해 볼 수 있겠다.

핵심되는 말: 홍역, 홍역 혈청 유병률, 홍역 백신, 면역원성, 항체 반응