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Original Article

The third dose of measles-containing vaccine induces robust immune responses against measles in young seronegative healthcare workers who had previous two-dose measles vaccination

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ABSTRACT

Background: Despite the low measles antibody positivity rate among young healthcare workers (HCWs) who have previously received two doses of a measles-containing vaccine (MCV), whether an additional dose of MCV acts as a booster remains unknown. Thus, we aimed to evaluate the immune responses to a third dose of MCV in young HCWs.

Methods: Hospital-wide measles seroprevalence was assessed using enzyme-linked immunosorbent assay (ELISA). The immunogenicity of a third dose of MCV was determined in young seronegative HCWs (born between 1986 and 1997) who had previously received a two-dose measles vaccination.

Results: A total of 3033 (92.6%) HCWs had anti-measles immunoglobulin G. The lowest seropositivity rate was observed in HCWs aged 20–24 years (87.7%). In this group, HCWs who received a third dose of MCV had higher seropositivity than those who received a second dose (89.5% vs. 75.4%). A third dose of MCV was administered to 18 HCWs who did not have anti-measles IgG despite two doses. Neutralizing antibody titers increased significantly 4 weeks after the third vaccination. Although neutralizing antibody titers decreased 1 year post vaccination, 17 (94.4%) HCWs had medium (121–900 mIU/mL) or high (> 900 mIU/mL) levels. Furthermore, the third dose of MCV increased the measles virus-specific T-cell effector function.

Conclusions: The third dose of MCV induced a strong immune response against measles in young seronegative HCWs who had previously received a two-dose measles vaccination.

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Introduction

Measles is a highly contagious viral disease characterized by a febrile rash [1]. Before the development of the measles vaccine, the disease caused more than 2 million deaths worldwide annually [2]. In the 1980 s, as the vaccine became widely available, the incidence and mortality rates of measles decreased significantly. Between 2000 and 2017, the annual number of reported measles cases and deaths globally both decreased by 80%, from 853,479 to 173,330 and from 545,174 to 109,638, respectively. During this period, approximately 19.3 million deaths were prevented by vaccination [3]. However, measles has resurged, and outbreaks have occurred worldwide between 2018 and 2019 [4]. During that period, South Korea also experienced measles outbreaks, and many cases developed in healthcare facilities, which played a major role in measles

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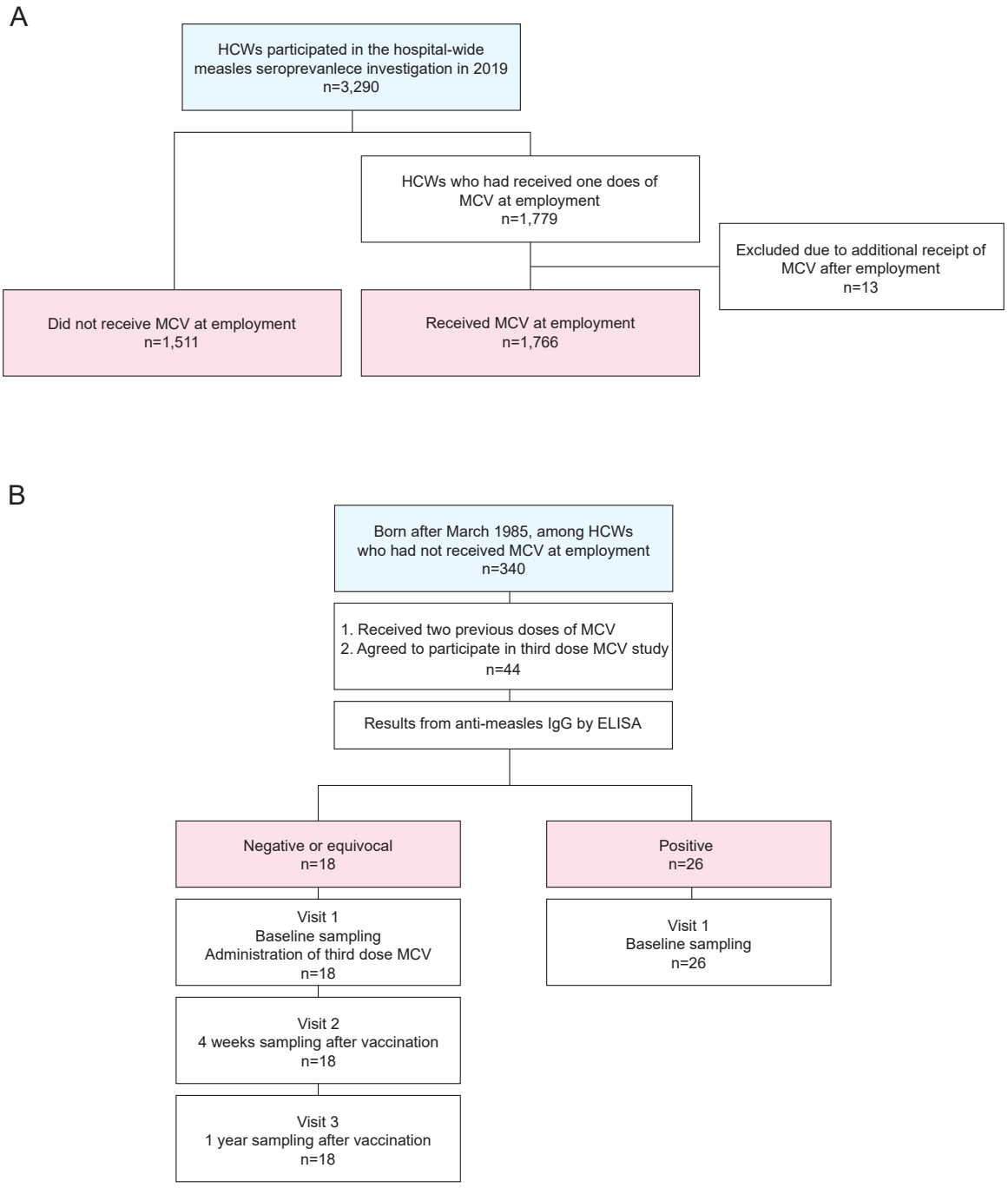

Fig. 1. Flow chart of study inclusion. A, Study of measles seroprevalence among healthcare workers (HCWs) according to receipt of one dose of measles-containing vaccine (MCV) at the time of new employment. B, Study of immunogenicity and safety of a third dose of MCV. ELISA, enzyme-linked immunosorbent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

outbreaks because of their enclosed and crowded environments [5,6]. Therefore, minimizing nosocomial transmission is an important control measure to prevent the spread of measles.

Achieving a high level of herd immunity among healthcare workers (HCWs) through two doses of a measles-containing vaccine (MCV) is the most effective strategy for reducing nosocomial transmission of measles [7]. However, the low positivity rate for measles antibodies observed among young HCWs is a major concern in South Korea, even though they were expected to have previously received two doses of MCV [8–12]. In South Korea, a two-dose measles vaccination with measles-mumps-rubella was included in the national immunization program in 1997, with the first and second doses administered to children aged 12–15 months and 4–6 years, respectively. Since the nationwide measles outbreak in 2000–2001, the Ministry of Health and Welfare has implemented policies aimed at increasing the two-dose measles vaccination rate in children to > 95%. As part of this effort, in 2001, a follow-up vaccination program targeted 5.7 million school-aged children who had not received a second measles vaccine dose. These children were vaccinated with the measles-rubella vaccine. Additionally, since 2001, certification for the two-dose measles vaccination has been mandatory for all preschool-aged children before they enter elementary school [13]. Therefore, young HCWs born after 1985 are likely to have received two doses of MCV in the past.

Although two doses of MCV effectively prevent measles, vaccine-induced immunity against measles wanes over time [14]. Available

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evidence suggests that immunity acquired by natural infection persists longer than that obtained by vaccination, and the protective effect of the measles vaccine may decrease over time after receiving two doses without boosting through natural infection [14,15]. We believe that this waning immunity may have occurred in previously vaccinated young HCWs, as demonstrated in another study in Korea [11].

Currently, information regarding the effectiveness of a third dose of MCV to boost waning immunity against measles is limited. In particular, whether seronegative HCWs who have received a previous two-dose measles vaccination should receive a third dose needs to be determined. In the present study, we aimed to evaluate the effect of a third dose of MCV on the measles antibody positivity rates among HCWs using a seroprevalence survey conducted in a large hospital. We also aimed to determine the immunogenicity of a third dose of MCV in young seronegative HCWs who had previously received two doses of the measles vaccine.

Material and methods

Study design and population

This prospective study was conducted at a tertiary care teaching hospital in Suwon, South Korea. During the study period, no measles outbreaks occurred in the study hospital and the surrounding area. In other words, apart from the measles vaccine, there are limited opportunities to influence immunity against measles among HCWs. Since 2011, new hospital employees have been requested to receive one dose of MCV if they cannot provide evidence of immunity to measles, which includes the following: (1) documented two doses of MCV, (2) laboratory-confirmed past measles infection, and (3) positive results from measles antibody testing.

Measles seroprevalence study

A hospital-wide measles seroprevalence study was conducted between July and August 2019. Anti-measles virus immunoglobulin G (IgG) was assessed using enzyme-linked immunosorbent assay (ELISA). The details of the laboratory procedures are described in the supplementary data. A total of 3290 HCWs participated in the measles seroprevalence study (Fig. 1A), among which 1511 (45.9%) did not receive MCV at employment. Of the 1779 (54.1%) HCWs who received MCV at employment, 13 were excluded because they received additional MCV after employment for other reasons. Based on changes in the measles vaccination program in South Korea [16], HCWs were classified according to the likelihood of having received two doses of MCV in the past: (1) 20–24 years born in 1994–1998, most likely; (2) 25–33 years born in 1985–1993, likely; (3) 34–39 years born in 1979–1984, less likely; (4) 40–49 years born in 1969–1978, unlikely; (5) ≥ 50 years born before 1969, most unlikely.

Administration of a third dose of MCV in seronegative HCWs

After the seroprevalence survey, e-mail invitations were sent to HCWs who had not received MCV at employment. Among the HCWs born after 1985, those who received two doses of MCV during childhood were eligible for the study to determine their immune response to a third dose of MCV. The following cases were excluded: (1) past occurrence of measles within the household, (2) receipt of MCV more than three times, (3) receipt of any other vaccination within 30 days, and (4) contraindication to MCV. Between October 2019 and February 2020, 18 HCWs with negative or equivocal results for measles antibodies (cohort 1) and 26 HCWs with measles antibodies (cohort 2) were enrolled (Fig. 1B).

Patient information such as demographic factors, comorbidities, and dates of previous measles vaccination were obtained. A third dose of MCV (MMRII; Merck & Co.) was administered to cohort 1 at the first visit, and blood samples were collected before (baseline), 4 weeks after, and 1 year after the third dose. Participants were questioned about local and systemic reactions after vaccination during the 4-week visit. In cohort 2, blood collection was performed only during the first visit. The humoral immune response was evaluated by measuring neutralizing antibody titers and IgG avidity against measles. Intracellular cytokine staining and flow cytometry were performed to determine the cellular immunity against measles. The details of the laboratory procedures are described in the supplementary data.

Statistical analysis

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

Results

Measles seroprevalence among HCWs

Among the 3277 serum samples tested using ELISA, 3033 (92.6%) were positive for measles antibody, and 129 (3.9%) were equivocal. Age-specific seropositivity is shown in Fig. 2. We observed an increasing trend in measles seropositivity with age in HCWs who had received MCV at employment and in those who had not. The highest seropositivity was observed in HCWs aged ≥ 50 years, who were most unlikely to have completed vaccination with two doses of MCV in the past. No significant difference in seropositivity was observed between HCWs who had received MCV at employment (100%) and those who had not (94.7%) in the ≥ 50 years age group (Table 1). In contrast, HCWs aged 20–24 years, who were most likely to have completed vaccination with two doses of MCV in the past, had the lowest seropositivity. Seropositivity was significantly higher in HCWs who received MCV at employment, which is presumed to be the third dose of MCV, than in those who did not (89.5% vs. 75.4%, $P = 0.01$).

Safety and immunogenicity of a third dose of MCV

Baseline characteristics of subjects

Similar demographic characteristics were observed in cohorts 1 and 2 (Table 2). All participants received their first dose of MCV between the age of 12 and 15 months old. The median time since vaccination with a second dose of MCV in cohort 1 was 18.2 years (IQR 18.1–18.9), similar to that in cohort 2 (18.2 years, IQR 18.1–18.2). The baseline plaque reduction neutralization (PRN) antibody level was significantly lower in cohort 1 (130 mIU/mL, IQR 45.5–259.5 mIU/mL) than in cohort 2 (4096.5 mIU/mL, IQR 2410.8–7417.0 mIU/mL; $P < 0.001$). However, no significant differences were detected in the baseline avidity index level between the two cohorts (69.2%, IQR 61.6–77.3% vs. 72.5%, IQR 67.3–76.5%).

Safety of a third dose of MCV

In cohort 1, 18 participants received a third dose of MCV and completed the study with regard to blood sample collection before, 4 weeks after, and 1 year after vaccination. No serious adverse events (AEs) were observed during the study period. Three participants reported local AEs and pain at the injection site, and one reported a systemic AE and flu-like symptoms (febrile sensation, headache, and

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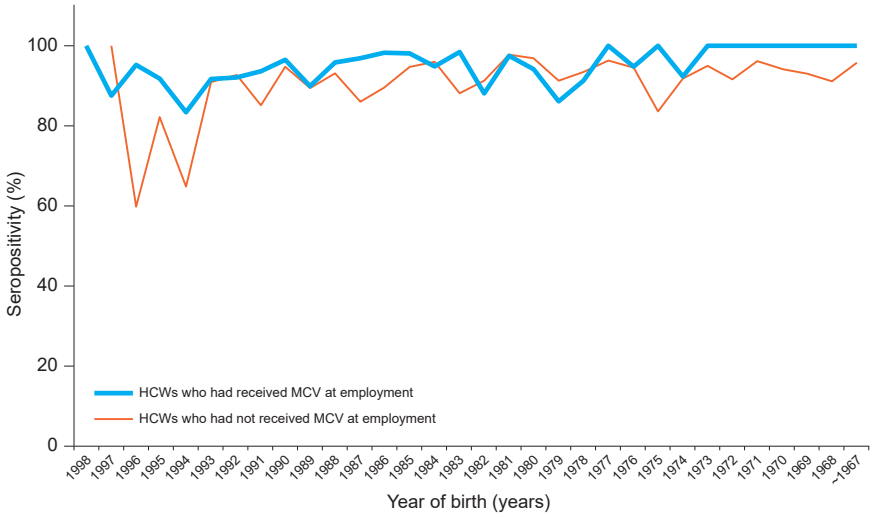

Fig. 2. Age-specific seropositivity between healthcare workers (HCWs) who received one dose of measles-containing vaccine at the time of new employment and those who did not. No HCWs who had not received MCV at employment were born in 1998, so the seropositivity is not presented.

myalgia). However, all reported AEs were mild and were resolved within 4 weeks of vaccination.

Humoral immune response after a third dose of MCV

Seroconversion rates were 77.8% and 61.1% at 4 weeks and 1 year after the third dose of MCV, respectively (Fig. 3A). Four weeks after the third dose, the 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 the PRN titer declined by 635.50 mIU/mL (IQR 295.75–988.25 mIU/mL) 1 year following vaccination, the level remained significantly higher than baseline (Table S1 and Fig. 3B). A similar trend was observed for seropositivity rates and high PNR titers (> 900 mIU/mL) (Fig. 3C). Four weeks post vaccination, all participants had PRN antibody titers of > 120 mIU/mL, which were considered seropositive, and 14 (77.8%) participants had high PRN titers. Although the seropositivity rates and high PNR titer declined 1 year after vaccination, 17 (94.4%) participants remained seropositive. All participants had a high avidity index 4 weeks after vaccination. No significant differences were observed in the avidity index at 4 weeks and 1 year compared to the baseline (Fig. 3D).

A third dose of MCV increases measles specific T cell effector functions

We analyzed the baseline frequency of measles virus-specific $CD4^+$ T cells in cohorts 1 and 2 using intracellular cytokine staining (ICS). In ICS, peripheral blood mononuclear cells (PBMCs) were *ex vivo* stimulated with measles virus-infected Vero cell lysate and stained for IFN γ and TNF (Fig. S1). The baseline frequency of IFN γ^+ cells among the $CD4^+$ T cells was significantly lower in cohort 1 than in cohort 2 (Fig. 4A). Likewise, that of TNF^+ cells among $CD4^+$ T cells tended to be lower in cohort 1 than that in cohort 2, although this difference was not statistically significant (Fig. 4B). After the third dose of MCV in cohort 1, we analyzed the changes in the frequency of IFN γ^+ and TNF^+ cells among $CD4^+$ T cells at 4 weeks and 1 year post vaccination. Although the frequency of IFN γ^+ cells did not change significantly (Fig. 4C), the frequency of TNF^+ cells among $CD4^+$ T cells significantly increased at 1 year post vaccination compared to baseline (Fig. 4D).

In $CD8^+$ T cells, the baseline frequency of IFN γ^+ (Fig. 4E) and TNF^+ (Fig. 4F) cells tended to be lower in cohort 1 than in cohort 2; however, the difference was not significant. After the third dose of MCV in cohort 1, the frequency of IFN γ^+ cells among $CD8^+$ T cells significantly increased at 1 year post vaccination compared to that at 4 weeks post vaccination (Fig. 4G). The frequency of TNF^+ cells among $CD8^+$ T cells showed similar kinetics; nonetheless, the difference was not statistically significant (Fig. 4H). In summary, the third dose of MCV increased measles-specific $CD4^+$ and $CD8^+$ T-cell effector functions in HCWs without anti-measles IgG after two doses.

Discussion

Immunity against measles wanes, and detectable antibody levels decline over time after two doses of MCV [17–20]. Currently, evidence on the use of a third dose of the measles vaccine to boost waning vaccine-induced immunity is limited. The results of the present study showed that a presumed third dose of MCV increased seropositivity in young HCWs, among whom there were concerns regarding waning measles immunity. Additionally, we identified the boosting effect of a third dose of MCV on humoral and cellular immunity in young seronegative HCWs who had previously received

Table 1
Comparison of measles seroprevalence in healthcare workers who received one dose of MCV at the time of new employment and healthcare workers who did not according to age group.

Age group	Year of birth	Did not receive MCV at employment				Received MCV at 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.

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Table 2
Baseline characteristics of healthcare workers who previously completed vaccination with two doses of MCV 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, measle-containing vaccine.

two doses of the measles vaccine. The third dose of MCV showed acceptable safety and reactogenicity.

In the recent measles outbreak in South Korea, the majority of cases occurred in infants who had not yet received the measles vaccine and in young HCWs who were exposed to measles patients in hospitals [21]. Young HCWs are expected to have previously completed two doses of measles vaccination, based on the national measles vaccination program [16,19,22]. However, they had the lowest positivity rates in several measles seroprevalence surveys conducted in South Korea [8–10,12,19,23–25], as shown in our study. These findings may be due to vaccine-induced immunity waning over time, and the fact that immunity acquired by natural infection persists longer than that obtained by vaccination [17–20].

We also demonstrated the effects of a third dose of MCV. The anti-measles IgG positivity rate was 14.1% higher in young HCWs who received the presumed third dose of MCV than in those who did not. Additionally, the third dose of MCV also boosted measles-neutralizing antibody levels in young HCWs. Significant increases in measles-neutralizing antibody levels occurred 4 weeks after the third dose of MCV and remained until 1 year after vaccination. Although the neutralizing antibody levels decreased 1 year after vaccination, the levels in most participants were > 120 mIU/mL, which is considered a protective level of measles-neutralizing antibody [26]. Moreover, we identified enhanced measles virus-specific T-cell effector functions after a third dose of MCV. Previous studies have already reported the immunogenicity of a third dose of MCV in seronegative persons after two doses. However, most of these studies only measured humoral immunity. Although one study has demonstrated cellular immunity [27], the authors measured the relative proportion of simple IFN γ-producing T cells, which exhibit low sensitivity and specificity. We used a more sophisticated assay, namely, intracellular cytokine staining, to measure the polyfunctionality of measles antigen-specific T cells. This method has higher accuracy and enables a more comprehensive assessment of T

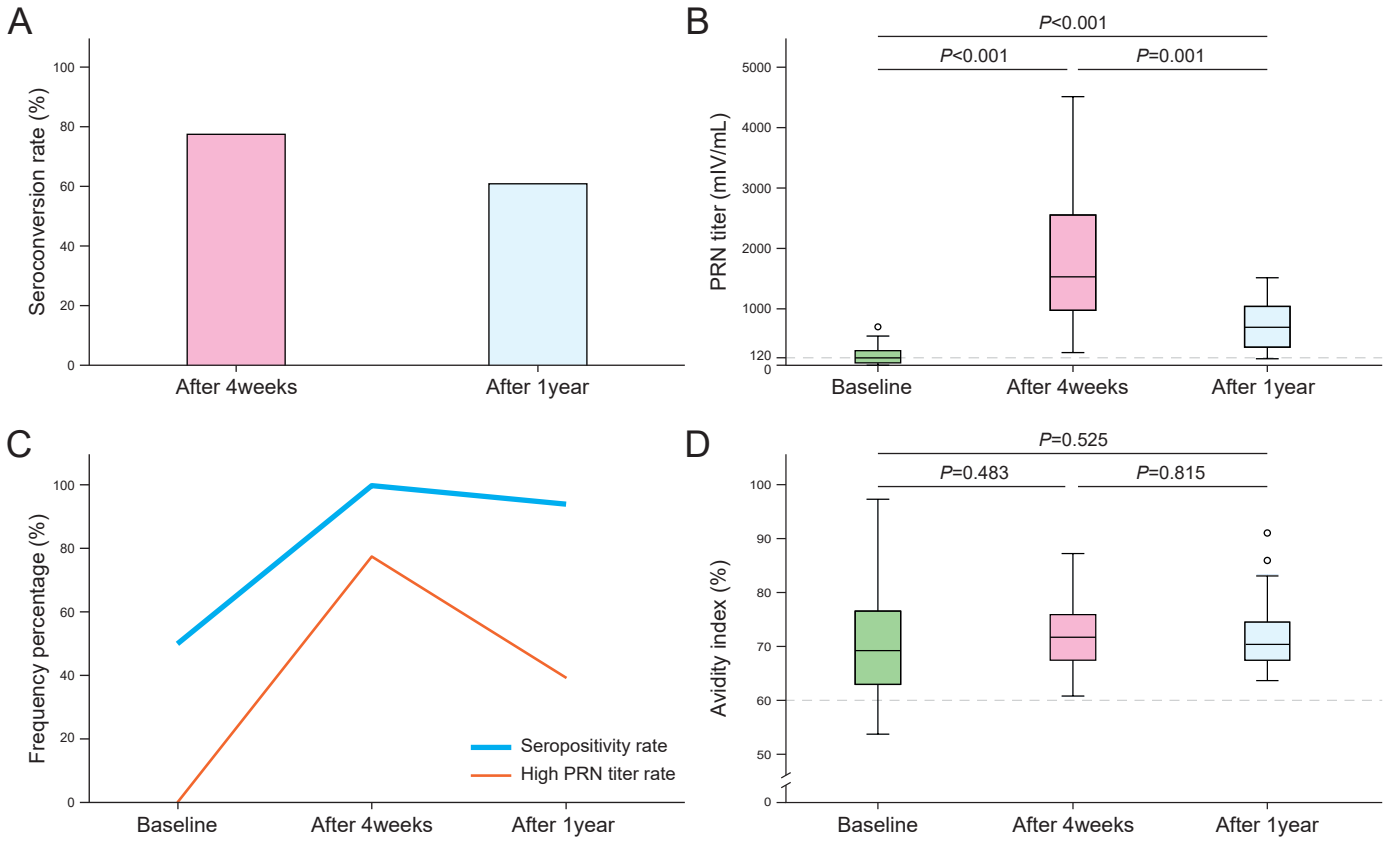

Fig. 3. Humoral immune response in young healthcare workers (born after March 1985) who had negative or equivocal IgG results by ELISA after administration of a third dose of measles-containing vaccine. A, Seroconversion (4-fold increase in neutralizing antibody titer) rates. B, PRN titer. C, Seropositive rate of neutralizing antibody and high PNR titer (> 900 mIU/mL) rate. D, Avidity IgG antibody index before (baseline) and after (4 weeks and 1 year) vaccination. IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; PRN, plaque reduction neutralization.

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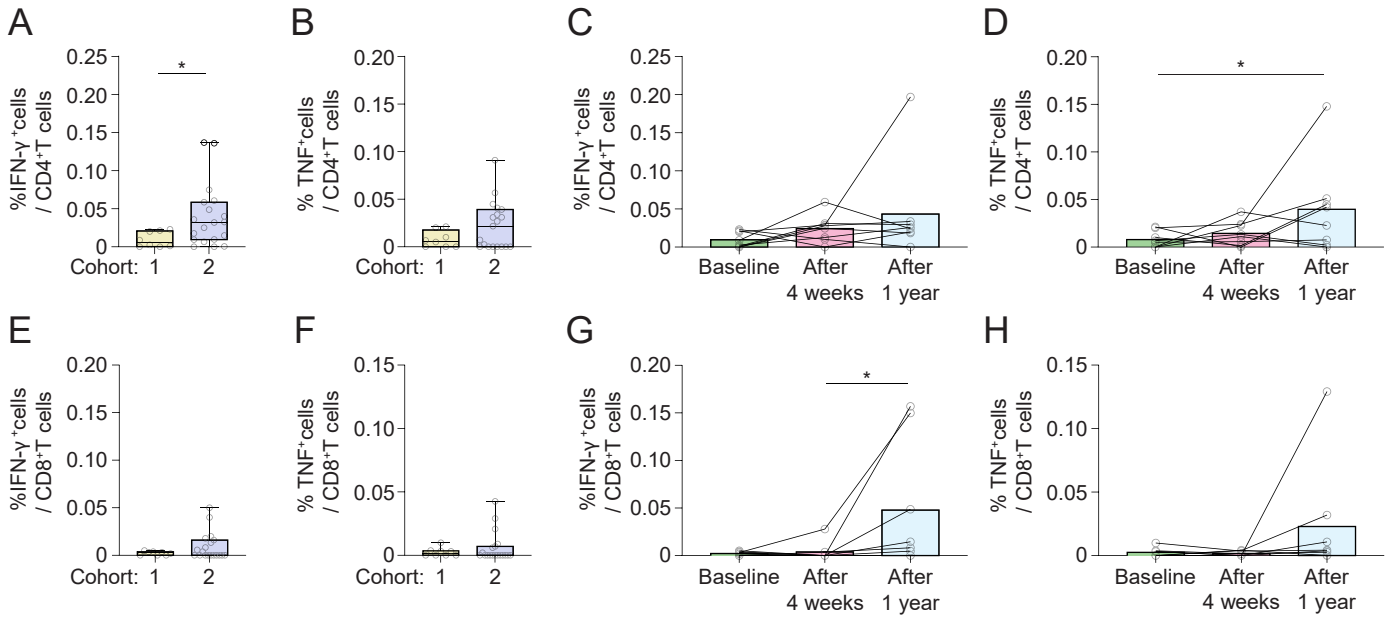

Fig. 4. Frequency of measles virus-specific, cytokine-producing T cells was analyzed using PBMC samples from HCWs with (cohort 2; n = 19) or without (cohort 1; n = 8) anti-measles IgG based on intracellular cytokine staining (ICS). In ICS, PBMCs were *ex vivo* stimulated with uninfected or measles virus-infected Vero cell lysate (1:50 for each lysate) for 18 h and stained for IFN-γ and TNF. A and B, The baseline frequency of IFN-γ$^+$ (A) and TNF$^+$ (B) cells among CD4$^+$ T cells in cohorts 1 and 2. C and D, The frequency of IFN-γ$^+$ (C) and TNF$^+$ (D) cells among CD4$^+$ T cells from cohort 1 was analyzed before (baseline) and after (4 weeks and 1 year) the third dose of MCV (n = 8). E and F, The baseline frequency of IFN-γ$^+$ (E) and TNF$^+$ (F) cells among CD8$^+$ T cells in cohorts 1 and 2. G and H, The frequency of IFN-γ$^+$ (G) and TNF$^+$ (H) cells among CD8$^+$ T cells from cohort 1 was analyzed before (baseline) and after (4 weeks and 1 year) the third dose of MCV (n = 8). Data are presented as the mean ± SD. Statistical analysis was performed using the unpaired non-parametric Mann-Whitney *t* test (A, B, E, and F) or the Wilcoxon signed-rank *t* test (C, D, G, and H). MCV, measles containing vaccine; Uninfected, uninfected Vero cell lysate; MeV, measles virus infected Vero cell lysate. $^*P < 0.05$.

cell function. Our results from a thorough functional assessment of T cells suggest that a third dose of MCV may help to clear the virus from the body. In general, a third dose of MCV is not recommended for HCWs who do not show anti-measles IgG after two doses [27,28]. However, a third dose may be required under specific circumstances, such as in hospitals. Considering the immunogenicity of a third dose of MCV, as demonstrated in our detailed experiments, we suggest that a third dose can be used as an effective intervention to limit the nosocomial spread of measles and prevent measles transmission in HCWs without anti-measles IgG when measles outbreaks occur in hospitals.

The safety of the first or second dose of the measles vaccine has been well-established in several studies. In Italy, a surveillance program for monitoring AEs of MCV in children demonstrated that serious AEs occurred in 26 cases (6.3 cases per 100,000 doses) during 8 years of observation, with only 10 AEs classified as having a consistent causal association with immunization [29]. All consistent serious cases were completely resolved at the subsequent follow-up. Additionally, a prospective cohort study conducted in Israel during a measles outbreak in Europe found low rates of systemic AEs and no serious AEs following one or two doses of MCV in adults who were not completely vaccinated [30]. In the present study, we demonstrated that the safety profiles of a third dose of MCV were similar to those of the first and second doses. A third dose of MCV was well tolerated, and no serious AEs were reported. Although systemic symptoms, such as lymphadenopathy, diarrhea, headache, and arthralgia, were reported among young adults who received a third dose of MCV, the episodes were mild and occurred at low rates. The safety data for a third dose of MCV can also be found in studies that evaluated the effect of a third dose of MCV to control mumps outbreaks [31–33].

In this study, the IgG results obtained using ELISA were inconsistent with the neutralizing antibodies determined using the PRN test. No samples had positive ELISA results at baseline; however, the PRN test was positive for neutralizing antibodies in 50% of the samples. This variation may be explained by differences in the target antigens in the two assays. The target antigen in ELISA is composed of purified and inactivated measles virus. In contrast, the PRN assay measures neutralizing antibodies against measles virus surface glycoproteins, primarily hemagglutinin [34,35]. Therefore, the PRN test is more sensitive than ELISA for detecting measles antibodies. As shown in our study, false-negative ELISA results were more likely to be observed in samples with low neutralizing antibody titers [36].

All participants in our study without anti-measles IgG had a high avidity index 4 weeks after the third dose of MCV. IgG that develops after vaccination has low avidity for 6–8 weeks, and it takes more than 3 months to develop IgG with high avidity after vaccination [37]. However, high-avidity IgG was detected in young HCWs shortly after the administration of the third dose of MCV. This finding indicates that immunity waned after two doses of the measles vaccine.

This study had some limitations. First, we recruited only a small number of participants who met the inclusion criteria to evaluate the effects of a third dose of MCV. Therefore, further studies with a larger number of subjects are required to provide more potent evidence for the immunogenicity of the third dose. Second, we did not collect data on the measles vaccination status of HCWs who participated in the seroprevalence survey because not all vaccination records were registered in the national immunization registry system created in 2002. However, HCWs aged 20–24 years who had to submit a certificate for two doses of measles vaccination at elementary school entry were considered to be vaccinated with two doses [16]. Therefore, we presumed that the effect of the third dose of MCV occurred in HCWs aged 20–24 years. Third, the cellular immunity of HCWs treated with the third dose of MCV was not statistically significant, owing to the small sample size. However, measles virus-specific T-cell effector functions (both IFN γ and TNF) tended to increase 1 year after the third dose of MCV in subjects without anti-measles IgG after two doses.

In conclusion, this study presents important evidence for the use of a booster shot in vaccinated HCWs with waning immunity by

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providing data on the safety and immunogenicity of a third dose of MCV. Although routine administration of a third dose of MCV is not necessary to maintain measles immunity, it can be used to prevent measles transmission among HCWs who lack anti-measles IgG after two previous doses when measles outbreaks occur in hospitals.

Declaration of Competing Interest

We have no conflict of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.08.002.

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