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Antibody Response to Live Attenuated Vaccines in Adults in Japan

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Abstract: The purpose of this study was to examine the efficacy rendered with a single dose of live attenuated measles, rubella, mumps, and varicella containing vaccine.

We inoculated healthcare workers (HCWs) with a single dose of vaccine to a disease lacking in antibody titer for those not meeting the criteria of our hospital (measles: <16.0 (IgG enzyme immunoassay (EIA)), rubella: $\leq 1:32$ (hemagglutination-inhibition), mumps: <4.0 (IgG EIA), and varicella: <4.0 (IgG EIA)). At 28–60 days after vaccination, the antibody titer was tested again.

We included 48 HCWs. A total of 32, 15, 31, and 10 individuals were inoculated with a single dose of measles-containing, rubella-containing, mumps, or varicella vaccine, respectively, and showed significant antibody elevation (9.2 ± 12.3 to 27.6 ± 215.6 , $p < 0.001$; 8 ± 1.2 to 32 ± 65.5 , $p < 0.001$; 3.0 ± 1.0 to 13.1 ± 8.6 , $p < 0.05$; and 2.6 ± 1.3 to 11.8 ± 8.1 , $p < 0.001$, respectively). Major side effects were not observed.

In a limited population, a single dose of live attenuated vaccine showed elevation of antibody titer without any severe adverse reactions. However, whether the post-vaccination response rate criteria of our university was fulfilled could not be determined owing to limited sample size.

Keywords: Measles; Rubella; Mumps; Varicella; Antibody titer; Vaccination; Occupational health

1 Introduction

In recent years, measles, rubella, mumps, and varicella vaccines have been frequently used for adults as a component of occupational health especially for healthcare workers (HCWs). Although the efficacy of these vaccines for children has been proven with respect to disease reduction [1-3], the studies for adults have not been sufficient to confirm their validity as vaccine effectiveness in adults has been primarily assessed using antibody titer mostly in small groups. Therefore, it is necessary to accumulate pre- and post-vaccination antibody titer data from vaccine recipients to establish evidence of effective vaccination in adults for these four vaccines.

The Japanese population experienced a massive outbreak of measles in 2007 [4]. Subsequently, a vaccination campaign, mainly for teenagers, was implemented. As a result, the elimination of measles in Japan has been verified by the World Health Organization Western Pacific Region (WPRO) in 2015 [5]. However, imported measles cases mostly from southeast Asia have been reported [6], demonstrating that Japanese adults still do not exhibit sufficient immunity to measles. Rubella outbreaks have also occurred in 2013, primarily in males in their 30s and 40s [7]. The Japanese public health authority is currently educating this generation about vaccination, with the goal of eliminating rubella by 2020, the year of the Tokyo Olympic Games. Varicella vaccination became routine on October 2014, although the mumps vaccine has not yet been used routinely. Accordingly, in Japan, the acquisition of immunity against mumps and varicella remains relatively unaffected.

In this situation, HCWs in Japan face high risks of accidentally coming into contact with patients carrying

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measles, rubella, mumps, and varicella, as has been previously reported [8]. Furthermore, medical institutions whose staff have developed measles have reportedly suffered medical-economic related damages because of the associated admission suspensions or operation restrictions [9]. Taken together, it is therefore necessary for HCWs to exhibit sufficient immunity against measles, rubella, mumps, and varicella to not be infected by these contagious diseases and, at the same time, to not become a source of infection to other patients and staff.

In Nara Medical University, staff without sufficient antibody titers are strongly encouraged to receive vaccination against measles, rubella, mumps, and varicella viruses. In this study, we obtained consent from 48 healthy HCWs to measure antibody titers at the time of pre-vaccination and post-vaccination to assess the effectiveness of vaccine inoculation.

2 Materials and methods

Among the staff, interns, and nursing students from Nara Medical University Hospital, a total of 48 individuals classified by the Health Management Center as not meeting the criteria of antibody titers against measles, rubella, mumps, and varicella attended our Center for Infectious Diseases for vaccination between October 2011 and March 2013. The criteria for determining the deficiency of antibody titer in our hospital are shown in Table 1. The 48 subjects included 26 men and 22 women. The median age was 26 years old with a range from 18 to 39 years old. Except for one male who only exhibited a deficiency of measles antibody titer who was an outpatient of our hospital suffering from well controlled type 1 diabetes, no other underlying disease was noted in the subject group. Among the 48 subjects, 18 lacked only one kind of antibody titer, including 7 lacking only measles, 2 lacking

rubella, 2 without varicella, and 7 without mumps. Each was inoculated once with the appropriate live vaccine.

In addition, 21 individuals lacked two kinds of antibody titer, among which 4 lacked measles and rubella, 1 lacked measles and varicella, 11 were without measles and mumps, 1 lacked rubella and varicella, 2 were missing rubella and mumps, and 2 were without varicella and mumps. Individuals lacking measles and rubella antibody titers were inoculated with the measles-rubella mixed vaccine (MR vaccine) and all others were inoculated with two kinds of vaccines simultaneously according to their respective antibody titer deficiencies.

Furthermore, 8 people lacked of three kinds of antibody titers. Of these, 5 lacked measles, rubella, and mumps, and 3 lacked measles, varicella, and mumps. Other combinations were not identified. The first group was inoculated simultaneously with the MR and mumps vaccines whereas the second group was inoculated simultaneously with the three corresponding vaccines. Only 1 individual was deficient in all four kinds of antibody titers and they were simultaneously inoculated with the MR, varicella, and mumps vaccines (Table 2). Therefore, altogether 32 HCWs were inoculated with measles-containing vaccines, with the breakdown consisting of 10 MR vaccines and 22 measles vaccines; 15 HCWs were provided with rubella containing vaccines, which included 10 MR vaccines and 5 rubella vaccines; and 10 and 31 HCWs were administered varicella or mumps vaccines, respectively (Figure 1).

Individuals receiving vaccinations were asked to wait within the reach of doctors for at least 10 minutes after the inoculation, at which time it was confirmed that no side effect reaction occurred in that short period of time. In addition, they were instructed to consult with the Center for Infectious Diseases of Nara Medical University in the case of e.g., fever over 38°C, abnormal feelings, or localized pain. Subjects were also instructed to contact the Center for Infectious Diseases in the case of other questions.

Among the vaccines used for inoculation, the live attenuated measles and rubella combined vaccine (Schwartz FF-8 and TO-336 strains) manufactured by Takeda Pharmaceutical Company Limited was used as the MR vaccine; the dried live attenuated measles vaccine (Schwarz FF-8 strain) manufactured by Takeda Pharmaceutical Company Limited was used as the measles vaccine; the live attenuated rubella virus vaccine “Kitasatodaiichisankyo” (Takahashi strain) manufactured by Kitasato Daiichi Sankyo Vaccine Co., Ltd. was used as the rubella vaccine; the varicella vaccine live attenuated “BIKEN” (Oka strain) manufactured by The Research

Table 1: Judging criteria of antibody titer against measles, rubella, mumps, and varicella for healthcare workers in our hospital.

	Measuring method	Insufficient	Sufficient
Measles	IgG (EIA)	<16.0	≥16.0
Rubella	HI	≤1:16	≥1:32
Varicella	IgG (EIA)	<4.0	≥4.0
Mumps	IgG (EIA)	<4.0	≥4.0

EIA: enzyme immunoassay; HI: hemagglutination inhibition test

	Number of HCWs with insufficient antibody titer
Measles	32
Rubella	15
Varicella	10
Mumps	31

Inoculated vaccine	Number of HCWs
MR vaccine	10
Measles vaccine	22

Inoculated vaccine	Number of HCWs
MR vaccine	10
Rubella vaccine	5

All inoculated Varicella vaccine

All inoculated Mumps vaccine

Figure 1: Number of people who did not have enough antibody titer to measles, rubella, mumps, or varicella are shown on the left half of the figure. HCWs who were short of measles and rubella antibody were inoculated with measles-containing and rubella-containing vaccine, respectively. The breakdowns of measles-containing vaccine and rubella-containing vaccine are shown on the top right half of the figure.

HCWs: health care workers MR vaccine: measles-rubella combined vaccine

Foundation for Microbial Diseases of Osaka University was used as the varicella vaccine; and the dried live attenuated mumps vaccine (Torii strain) manufactured by Takeda Pharmaceutical Company Limited was used as the mumps vaccine.

A total of 32 measles-containing vaccines, 15 rubella-containing vaccines, 31 mumps vaccines, and 10 varicella vaccines were inoculated. Antibody tests following vaccine inoculations were only carried out on patient behalf in accordance with their wishes after explaining the usefulness of the test after vaccination. In addition, the antibody test subsequent to vaccination was performed during the period from 28 to 60 days after the vaccination. The duration of vaccination and antibody titer measurement was 29.4 ± 8.13 days for the measles-containing vaccine, 31.0 ± 8.94 days for the rubella-containing vaccine, 28.6 ± 6.22 days for the mumps vaccine, and 30.6 ± 3.47 days for the varicella vaccine. The antibody titers of measles, mumps, and varicella were measured using IgG (enzyme immunoassay (EIA) method) and that of rubella was measured using the hemagglutination-inhibition (HI) method. All four kinds of antibody titers were examined with serum samples obtained from each HCW. The obtained serum samples were frozen at -70°C and tested within a couple of days.

Moreover, we evaluated whether there was significant difference in acquisition rate of sufficient antibody titer after vaccination between the two groups using the antibody titer criteria of our university (Table 1) as a basis. First group was consisted of HCWs who are completely seronegative before vaccination. The second group was

HCWs with positive and insufficient antibody titer before vaccination.

For measles, varicella, and mumps, the paired t-test was used to measure the changes of antibody titers before and after inoculation. On the other hand, for rubella, the Wilcoxon signed-rank test was used for the same purpose. We performed statistical processing by Fischer's exact test to determine whether there was significant difference in acquisition rate of sufficient antibody titer after vaccination between the two groups stated above. It was determined that a significant difference existed when the p value was under 0.05 in either case.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Results

The antibody titers of the 32 individuals inoculated with measles-containing vaccines were compared before and after inoculation. This demonstrated that the replacement titer before the inoculation was 9.2 ± 12.3 and an increase to 27.6 ± 215.6 was confirmed after the inoculation ($p < 0.001$).

Table 2: Characteristics of 48 HCWs without sufficient antibody titer and administered vaccines.

Measles	Rubella	Varicella	Mumps	Number of people	Inoculated Vaccine(s)
HCWs* lacking of one kind of antibody titer					
-	+	+	+	7	Measles
+	-	+	+	2	Rubella
+	+	-	+	2	Varicella
+	+	+	-	7	Mumps
HCWs lacking of two kind of antibody titer					
-	-	+	+	4	MR
-	+	-	+	1	Measles+ Varicella
-	+	+	-	11	Measles+ Mumps
+	-	-	+	1	Rubella+ Varicella
+	-	+	-	2	Rubella+ Mumps
+	+	-	-	2	Varicella+ Mumps
HCWs lacking of three kind of antibody titer					
-	-	+	-	5	MR+ Mumps
-	+	-	-	3	Measles+ Varicella+ Mumps
HCWs lacking of four kind of antibody titer					
-	-	-	-	1	MR+ Varicella+ Mumps

HCWs: health care workers; MR: measles-rubella combined vaccine

“-”: inadequate antibody titer; “+”: antibody titer satisfying the criteria of our university.

Among the 15 subjects inoculated with rubella-containing vaccines, their average antibody titer of 8 ± 1.2 before the inoculation changed to 32 ± 65.6 after inoculation ($p < 0.001$). For the 10 individuals inoculated with varicella vaccine, their antibody titer of 3.0 ± 1.0 before the inoculation changed to 13.1 ± 8.6 after inoculation ($p < 0.05$). Finally, for the 31 subjects inoculated with mumps vaccine, their antibody titer of 2.6 ± 1.3 before the inoculation changed to 11.8 ± 8.1 after inoculation ($p < 0.001$). Thus, all the four types of vaccines achieved statistically sufficient increase of antibody titer after a single inoculation.

In addition, after only a single vaccination, 26 individuals (81.3%) inoculated with measles-containing vaccines, 19 (60.0%) inoculated with rubella-containing vaccines, 8 (80.0%) inoculated with varicella vaccine, and 28 (90.3%) inoculated with mumps vaccine succeeded in generating sufficient increases of antibody titer to meet each criterion of our hospital (Figure 2).

We compared the rate of acquisition of sufficient titer between the two groups of HCWs; one group included HCWs whose antibody titer was completely negative and the other group included HCWs whose antibody titer was

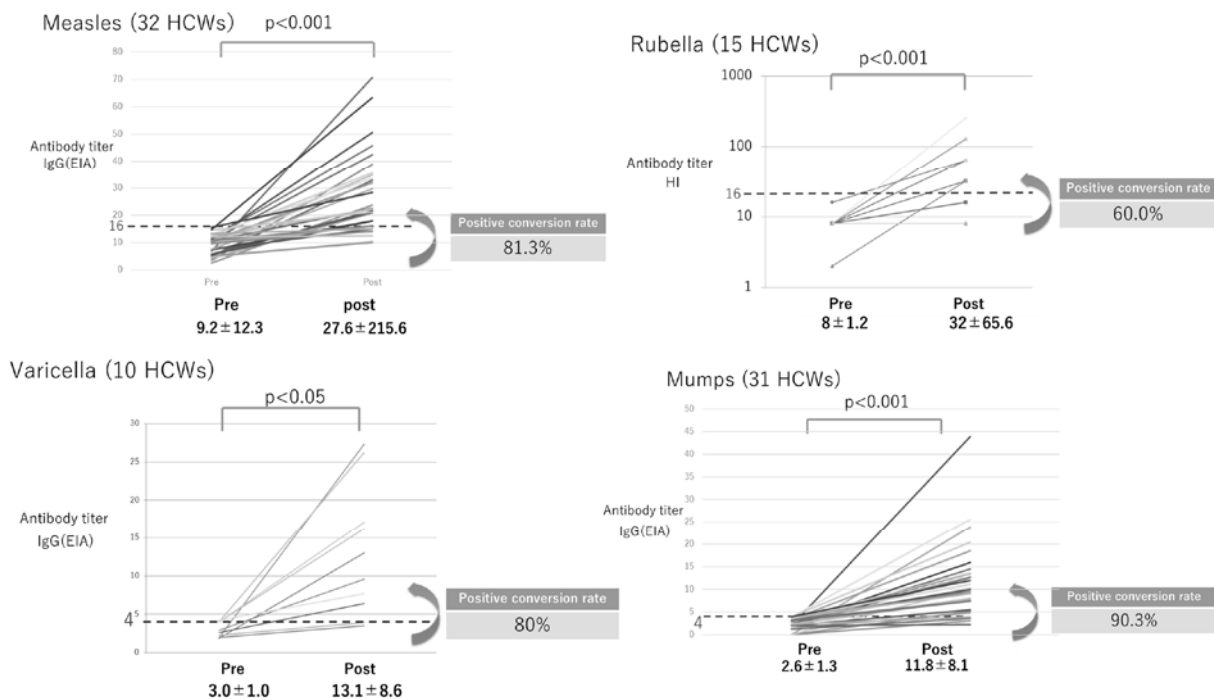


Figure 2: Change of antibody titers against measles, rubella, mumps, and varicella before and after single dose vaccine inoculation is shown. All of the four types of vaccines achieved an increase of antibody titer after a single inoculation. EIA: enzyme immunoassay; HCWs: health care workers; HI: hemagglutination inhibition test.

positive but insufficient. We were able to compare the two groups only among rubella-containing vaccine-inoculated HCWs and mumps-inoculated HCWs because there were no HCWs whose antibody titers were completely negative in the measles and varicella groups. After inoculation with the rubella-containing vaccine, 3 in 5 HCWs whose titer was completely negative acquired sufficient antibody titer after vaccination, as did 6 in 10 HCWs whose prior antibody titer was positive but insufficient to meet the antibody titer fitting the criteria of our university. After inoculation of the mumps vaccine, 6 in 9 HCWs whose titer was completely negative met the criteria of our university after inoculation of the mumps vaccine. Furthermore, 21 in 22 HCWs whose titer was positive but not suitable to meet the criteria acquired sufficient antibody titer after vaccination. No significant difference in criteria achievement proportion was observed between the two rubella or mumps inoculation groups ($p = 0.70$, $p = 0.06$, respectively).

Side effects following vaccination were also investigated. However, systemic secondary reactions involving fever over 37.5°C were not observed, and only mild local reactions were noted.

4 Discussion

HCWs have been reported to be more likely to be exposed to measles and rubella than the general public, and the same can also be inferred for varicella and mumps. Furthermore, if medical personnel become infected with such viral diseases, they might also become the source of infection. Therefore, not only should HCWs prevent their occupational infection, it is also important for them to acquire immunity to avoid becoming the source of infection themselves.

In the case of previous inoculation, it is relatively simple to increase antibody titer upon second vaccination compared to the first inoculation; this phenomenon is termed the “booster effect.” Therefore, it is necessary to estimate the prior vaccination rate of the group participating in this study to determine whether the single-dose vaccination administered herein was sufficient to increase antibody titer. The ratios of individuals having received at least one prior measles vaccination and rubella vaccination within Japan have been aggregated at the National Institute of Infectious Diseases (NIID), with the vaccination rate being compiled by age [10,11]. Since the ages of all the medical personnel participating in this study are clear, it is possible to calculate the approximate vaccina-

tion rate of this group based on the NIID data. Thus, it was predicted that 96.8% of the 34 individuals accepting a measles-containing vaccine had received more than a single vaccination overall. For the 16 people who received a rubella-containing vaccine having exhibited a rubella antibody titer lower than the criteria, it was predicted that 96.5% had at least one prior vaccination. Therefore, we can conclude that one dose of inoculation of measles-containing and rubella-containing vaccine may be effective in Japanese healthy adults if the 48 HCWs in this study represent the general population of Japan with respect to vaccination response rate. However, the sample size of this study is too small to suppose that these 48 HCWs represent the entire Japanese population. Therefore, a larger study is required. Furthermore, since our study does not include adults over 40 years old, it is still unknown whether the same effect would be found among older age groups.

On the other hand, the varicella vaccination rate of children in 2009 was about 40% [12], and it is considered that the vaccination rate is likely lower for higher age groups. In addition, since the varicella vaccination rate exhibits regional differences, it was difficult to estimate the vaccination rate of the group accepting inoculation in this study. Thus, although a single varicella vaccination rendered significant increases of antibody titer to the study cohort, it remains unclear whether this might be generally applicable to all adults. Furthermore, the vaccination rate using the mumps vaccine is still undetermined. Therefore, it is also difficult to infer the impact of the subject vaccination history against mumps to this study. Finally, a previous history of disease would also be likely to stimulate the booster effect following inoculation in this study, as would prior vaccination. As subject disease history was not investigated in this study, it is difficult to estimate the influence of previous disease history on the observed increase of antibody titer. Together, these three points represent the major limitations of this study.

Although significant average increases of antibody titers were observed following vaccination in this study, some individuals were not able to attain the criteria adopted by the hospital following inoculation. From the viewpoint of society as a whole, developing herd immunity can decrease the number of individuals affected with a given disease and eventually eliminate the disease itself. However, in the hospital, individuals who do not have sufficient immunity to the disease cannot be permitted because even one HCW infected with measles, rubella, mumps, or varicella might cause an outbreak involving hospital patients. We considered that the antibody titer prior to inoculation of the vaccines might affect the rate of acquisition of sufficient titer after vaccination. To analyze

the validity of this hypothesis, we compared the rate of acquisition of sufficient response rate between the two groups of HCWs whose antibody titer was completely negative and one group whose antibody titer was positive but insufficient. Our study included no completely seronegative HCWs for measles and varicella; therefore, we were not able to assess the hypothesis for measles-containing and mumps vaccines. As a result, we found that there is no relation in criteria achieving proportion after rubella-containing vaccine inoculation between the two groups. A similar comparison was performed for mumps inoculation, which also demonstrated no significant difference in the proportion of individuals achieving criteria between the two groups. However, it was noted that the insufficient titer group tended to achieve our criteria after single dose mumps vaccination somewhat more frequently than the completely seronegative group ($p = 0.06$). Therefore, in the use of larger HCW groups might lead statistically significant differences for the mumps vaccine.

5 Conclusion

Inoculating one dose of measles-containing, rubella-containing, mumps, or varicella vaccine to 48 HCWs in Nara Medical University provided statistical elevation of antibody titer with no reported serious adverse reactions. However, the hypothesis that pre-vaccination antibody titer affects the achieving rate of the antibody titer criteria of our university could not be sufficiently addressed. Larger studies are required to confirm the universality of this result.

Conflict of interest statement: Authors state no conflict of interest.

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