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Original Article

Influence of Vaccination Dose and Clinico-Demographical Factors on Antibody Titers against Measles, Rubella, Mumps, and Varicella-Zoster Viruses among University Students in Japan

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SUMMARY: To evaluate the influence of vaccination dose and clinico-demographical factors on immune status against measles, rubella, mumps, and varicella viruses among university students, we conducted a case-control study by analyzing serum antibody titers according to past immunization and infection, and perinatal histories, using a multivariate regression model. A total of 1370 medical, paramedical, and pharmaceutical students were included in the analysis. Two or more doses of measles and rubella vaccination yielded notably greater odds ratios for immuno-positivity (9.1; 95% confidence interval (CI), 2.8–28.9 and 12.2; 95% CI, 0.71–210.3, respectively), compared with 1-dose vaccination, even though the superiority did not reach statistical significance for rubella. Students having younger/older siblings were more likely to be immuno-positive for mumps (2.5; 95% CI, 1.3–4.9 and 2.7; 95% CI, 1.4–5.5, respectively). On the other hand, post-term birth or macrosomia was associated with seronegative rubella virus antibodies. We concluded that a 2-dose vaccination strategy could successfully prevent measles and rubella outbreaks by increasing immunity.

INTRODUCTION

The Japanese government established a 2-dose policy for a measles/rubella-combined (MR) vaccine in 2006: the first dose must be administered at the age of 1 year (MR-I) and the second at the age of 5–6 years (MR-II, just before starting school) (1). Nevertheless, Japan experienced measles outbreaks primarily among high school and college students in both 2006 and 2007. Therefore, a catch-up campaign of MR vaccinations at ages 12–13 years (MR-III, first-year junior high school students) and 17–18 years (MR-IV, third-year high school students) has been implemented for the past 5 years since 2008, under the amended Preventive Vaccination Law, which authorized the 2-dose policy (2). However, the influence of vaccination doses on antibody titers against corresponding viruses among college students has not been completely investigated.

Antibody responses to vaccination are influenced by various endogenous factors, including genetic background, sex, and age, and exogenous factors, such as exposure to stressors, diet, and infectious disease status (3). However, few studies have evaluated the impact of perinatal history on the immune reaction to vaccination (4). In Japan, the Maternal and Child Health (MCH) Handbook is issued by the local government in one's place of residence and implemented by medical professionals primarily during pre- and post-natal periodic health checkups and on-demand at perinatal medical office visits, in accordance with the MCH Law. The MCH Handbook can provide reliable information regarding childhood immunization and infection and perinatal clinical histories (5–8).

To evaluate the influence of vaccination doses and clinico-demographical factors, including perinatal history on immune status against measles, rubella, mumps, and varicella among university students, we performed a case-control study by analyzing the antibody titers of individual students in accordance with the MCH Handbook and additionally administering questionnaires to students attending a single institution.

MATERIALS AND METHODS

All students in 2008 and first-year students in 2009 of the Kyoto University Faculty of Medicine (School of Medicine: medical doctor course, and School of Human Health Sciences: nurse, clinical laboratory technologist, occupational therapist, and physical therapist courses) and Faculty of Pharmaceutical Sciences (Division of Pharmacy: pharmacist course) were enrolled in the present study. An informed consent form and a self-administered questionnaire with a reply envelope were handed to the first-year students in 2009 and mailed to all the students in 2008. The students were asked to complete the questionnaire with the help of their parents and return the consent form and a photocopy of their immunization records from the MCH Handbook. However, the welfare committee of the School of Human Health Sciences did not permit us to collect photocopies of the MCH Handbook records because of insufficient time to adequately inform all the students in 2008 of its usage. The self-administered questionnaire or the MCH Handbook included the dates of measles,

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rubella, mumps, and varicella vaccinations, measles–mumps–rubella (MMR) triple vaccination, history of infection with those viruses, history of infectious diseases requiring hospitalization, history of neonatal asphyxia, gestational week at birth, birth weight, birthday, birthplace, and the existence of older and younger siblings.

Immunoglobulin (Ig) G titers of anti-measles, rubella, mumps, and varicella-zoster virus antibodies were measured by enzyme immunoassay (EIA), hemagglutination inhibition (HI) test, EIA, and immune adherence hemagglutination (IAHA) test, respectively, on June 23, 24, and 27, 2008 and April 2, 2009 at Ikagaku Co., Ltd., Kyoto, Japan. During the research period, there were no incidences of measles, rubella, mumps, or varicella among the university students. In consideration of clinical efficacy, cut-off levels of anti-measles, rubella, mumps, and varicella-zoster virus antibody titers for immuno-positivity were set at 6.0 U/mL, 8 (dilution ratio of 1:8), 8.0 U/mL and 4 (dilution ratio of 1:4), respectively (9,10). An HI titer of 8–10 corresponded to 15 U/mL in the EIA (11). Although fluorescent antibody to varicella membrane antigen is the most extensively validated assay and correlates best with protection against this pathogen, the IAHA assay is a very practical and reasonably sensitive test (12,13).

Antiviral antibody titers are presented as median values and interquartile ranges (IQRs). When the antibody titers were statistically compared between groups, the titers were logarithmically transformed for data normalization, and Student's *t*-test was applied. Logistic regression analysis was used to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for immuno-positivity. Multivariate regression analysis was performed to control for potential confounding factors. When calculating the ORs for vaccination history, we set 1-dose vaccination as a reference for measles and rubella and no vaccination for mumps and varicella because vaccination was mandatory for measles and rubella, but optional for mumps and varicella. Histories of neonatal asphyxia and MMR vaccination were not included in the multivariate models because of the large amount of missing data. Since immuno-positivity and negativity were completely separated by 2 or more doses of rubella vaccination and an unknown history of varicella infection, we used penalized maximum likelihood logistic regression for the analyses involving those variables (14). Analyses were performed using Stata 10.0 software (Stata Corporation, College Station, Tex., USA). All tests of significance were 2-tailed and P values <0.05 were considered statistically significant.

Written informed consents were obtained from all study participants. After linking the data from different sources, all personal identifiers were removed from the database. This investigation was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

RESULTS

Of a total of 1370 students (744 medical, 508 paramedical, and 118 pharmaceutical) who were invited to participate in this study, 1031 (75.3%) submitted informed written consent and were enrolled. The proportions of male and preclinical (1st- or 2nd-year at the immunological evaluation) students were 63.5% and 70.1%, respectively (Table 1). Of the participating students, 889 (93%) and 672 (70%) had received measles and rubella vaccines, respectively, while 88 (9.2%) and 169 (18%) had experienced a measles and rubella infection, respectively. Here, 4.9% and 8.8% of those vaccinated experienced measles and rubella, respectively. On the other hand, only 552 (58%) and 247 (26%) of the students, respectively, had received a mumps and varicella vaccination, whereas 307 (32%) and 653 (68%) had a history of mumps and varicella infections, respectively. Two or more vaccination doses for measles and rubella were administered to 255 (27%) and 162 (17%) of the students, respectively. However, there were relatively few students who received multiple doses of mumps and varicella vaccines (14 [1.5%] and 3 [0.32%], respectively).

Table 1. Characteristics of participants

No. of students	1031
Male	655 (63.5)
Enrollment year and grade	
2009 1st year	265 (25.7)
2008 1st year	218 (21.1)
2nd year	239 (23.2)
3rd year	64 (6.2)
4th year	90 (8.7)
5th year	84 (8.1)
6th year	70 (6.8)
Major	
Medical doctor course	578 (56.1)
Paramedical personnel course	349 (33.9)
Pharmacist course	104 (10.1)
Available data source	
Virus antibody measurements	876 (85.0)
Questionnaire	703 (68.2)
Photocopies of MCH Handbook	677 (65.7)

Values are expressed in numbers (percentage).

Immunogenic factors are summarized in Table 2 (A–D). For measles viruses, the median antibody titers were 39.3 (IQR, 18.4–91.8), 16.5 (IQR, 10.0–29.4), and 25.8 (IQR, 16.0–40.4) for those with a natural infection, 1-dose vaccination, and 2 or more dose vaccination, respectively. Antibody titers were greater in individuals vaccinated during catch-up period than in those vaccinated in childhood (median, 27.1; IQR, 16.1–42.7 vs. median, 16.2; IQR, 9.7–26.8; $P < 0.001$). For rubella viruses, the median antibody titers were 64 (IQR, 64–128), 32 (IQR, 16–64), and 32 (IQR, 32–64) for those with a natural infection, 1-dose vaccination, and 2 or more dose vaccination, respectively. Antibody titers were greater in individuals vaccinated during the catch-up period than in those vaccinated in the childhood (median, 64; IQR, 32–64 vs. median, 32; IQR, 16–64; $P < 0.001$). For mumps virus, the median antibody titers were 10.1 (IQR, 6.4–16.0), 5.7 (IQR, 3.3–9.1), and 5.5 (IQR, 3.6–12.8) for those with a natural infection, 1-dose vaccination, and 2 or more dose vaccination, respectively. Antibody titers were similar in individuals vaccinated during catch-up period and in those vacci-

Table 2-A Factors associated with immune status for measles viruses

	Antibody titer (median, IQR‡)	Immune-positives (n = 811)	Immune-negatives (n = 65)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Vaccination					
None	36.5 (14.4–80.9)	50	5	1.2 (0.44–3.0)	0.64 (0.15–2.8)
1 dose	16.5 (10.0–29.4)	422	49	Reference	Reference
≥2 doses	25.8 (16.0–40.4)	233	3	8.9 (2.7–28.7)	9.1 (2.8–28.9)
Measles-mumps-rubella triple vaccine usage					
No	23.1 (13.7–38.3)	136	3	Reference	—
Yes	17.1 (9.8–27.6)	160	15	0.24 (0.07–0.83)	—
Past infection of measles					
No	18.6 (10.8–30.9)	614	53	Reference	Reference
Yes	39.3 (18.4–91.8)	71	2	3.1 (0.73–12.8)	13.9 (0.78–248.6)
Unknown	25.6 (13.8–35.7)	24	2	1.0 (0.24–4.5)	1.8 (0.32–10.6)
History of infectious diseases requiring hospitalization					
No	20.6 (11.5–36.4)	467	33	Reference	Reference
Yes	19.5 (13.0–34.4)	75	6	0.88 (0.36–2.2)	0.77 (0.28–2.1)
History of neonatal asphyxia					
No	20.2 (12.9–35.5)	186	8	Reference	—
Yes	18.4 (8.0–44.0)	10	2	0.22 (0.04–1.1)	—
Gestational week/birth weight					
Normal week and weight	19.8 (11.7–35.2)	487	33	Reference	Reference
Preterm/low birth weight	26.9 (10.8–60.8)	27	3	0.63 (0.18–2.2)	0.55 (0.13–2.4)
Post term birth/macrosomia	22.9 (10.8–30.3)	24	3	0.56 (0.16–1.9)	0.65 (0.18–2.4)
Age					
<20 years	20.4 (11.1–36.7)	505	38	Reference	Reference
≥20 years	18.4 (10.8–31.6)	305	27	0.85 (0.51–1.4)	1.3 (0.62–2.6)
Born in metropolitan cities†					
No	19.8 (11.7–35.9)	151	10	Reference	Reference
Yes	20.2 (11.6–35.4)	349	26	1.1 (0.53–2.4)	0.93 (0.43–2.0)
Having siblings					
No	25.4 (13.0–44.9)	66	3	Reference	Reference
Having younger siblings	20.8 (12.8–35.5)	248	8	3.2 (1.5–7.2)	1.6 (0.43–2.0)
Having elder siblings	19.2 (10.3–31.4)	168	23	0.31 (0.16–0.60)	0.37 (0.11–1.2)
Having younger and elder siblings	19.5 (11.7–35.2)	63	5	0.89 (0.34–2.4)	0.72 (0.16–3.2)

Sample sizes vary among presented variables due to missing data.
*Adjusted for vaccination, measles-mumps-rubella triple vaccine usage, past infection of measles, history of infectious diseases requiring hospitalization, history of neonatal asphyxia, gestational week/birth weight, age, born in metropolitan cities, and having siblings.
†Cities with ≥500 thousand inhabitants.
‡IQR, interquartile range; 25- and 75-percentile level. CI, confidence interval.

nated in childhood (median, 5.0; IQR, 3.3–7.9, vs. median, 5.8; IQR, 3.3–9.7; P = 0.66). For varicella-zoster virus, the median antibody titers were 32 (IQR, 16–64), 16 (IQR, 8–32), and 32 (IQR, 32–32) for those with a natural infection, 1-dose vaccination, and 2 or more dose vaccination, respectively. Antibody titers were also similar in individuals vaccinated during catch-up period and in those vaccinated in childhood (median, 24; IQR, 8–32 vs. median, 16; IQR, 8–32; P = 0.02).

Two or more doses of measles and rubella vaccination yielded considerably greater ORs for immuno-positivity: 9.1 (95% CI, 2.8–28.9) and 12.2 (95% CI, 0.71–210.3), respectively, even though the superiority of the rubella antibody did not reach statistical significance. Prior infections were significantly associated with immuno-positivity for rubella, mumps, and varicella (ORs, 16.6; 95% CI, 4.3–64.1, 4.3; 95% CI, 2.6–7.1, and 24.5; 95% CI, 4.2–141.9, respectively). Students having younger/older siblings exhibited more frequent immuno-positivity states for mumps (OR, 2.5; 95% CI, 1.3–4.9 and 2.7; 95% CI, 1.4–5.5, respectively). On the other hand, post-term birth or macrosomia were inversely associated with rubella immunity (OR, 0.24; 95% CI, 0.06–0.94).

DISCUSSION

We explored the factors involved in immuno-positive titers of measles, rubella, mumps, and varicella-zoster virus antibodies among university students. Previous immunization or infection was found to cause a remarkably positive immune status. Of note, 2-dose vaccination substantially enhanced immunity to measles and rubella. WHO recommends a 2-dose strategy in MMR vaccinations since occasional individuals, who had received only 1-dose vaccination, continued to develop infections that resulted in a number of outbreaks in colleges and schools in the 1980s (15–18). Results of the current analysis support this recommendation for at least measles and rubella.

We cannot demonstrate the effectiveness of immunization against mumps and varicella irrespective of the

Table 2-B Factors associated with immune status for rubella viruses

	Antibody titer (median, IQR‡)	Immune-positives (n = 789)	Immune-negatives (n = 86)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Vaccination					
None	32 (4–128)	141	55	0.10 (0.06–0.17)	0.06 (0.03–0.13)
1 dose	32 (16–64)	398	13	Reference	Reference
≥2 doses	32 (32–64)	151	0	43.5 (2.7–704.8)	12.2 (0.71–210.3)
Measles-mumps-rubella triple vaccine usage					
No	32 (32–64)	132	7	Reference	—
Yes	32 (16–64)	172	3	1.7 (0.54–5.6)	—
Past infection of rubella					
No	32 (16–64)	505	56	Reference	Reference
Yes	64 (64–128)	110	4	4.0 (1.4–11.3)	16.6 (4.3–64.1)
Unknown	32 (16–64)	67	5	0.95 (0.45–2.0)	1.5 (0.58–3.8)
History of infectious diseases requiring hospitalization					
No	32 (16–64)	459	40	Reference	Reference
Yes	32 (16–64)	76	5	1.5 (0.64–3.7)	1.1 (0.39–3.1)
History of neonatal asphyxia					
No	32 (16–64)	179	15	Reference	—
Yes	32 (16–64)	10	2	0.36 (0.09–1.4)	—
Gestational week/birth weight					
Normal week and weight	32 (16–64)	484	36	Reference	Reference
Preterm/low birth weight	64 (32–64)	27	3	0.61 (0.21–1.8)	0.36 (0.09–1.5)
Post term birth/macrosomia	32 (16–64)	22	4	0.36 (0.14–0.93)	0.24 (0.06–0.94)
Age					
<20 years	32 (16–64)	497	46	Reference	Reference
≥20 years	32 (16–64)	291	40	0.58 (0.39–0.88)	0.92 (0.45–1.9)
Born in metropolitan cities†					
No	32 (16–64)	348	27	Reference	Reference
Yes	32 (16–64)	147	13	0.82 (0.45–1.5)	1.0 (0.39–3.1)
Having siblings					
No	32 (16–64)	59	10	Reference	Reference
Having younger siblings	32 (16–64)	240	16	1.3 (0.76–2.3)	1.1 (0.42–3.0)
Having elder siblings	32 (16–64)	173	17	0.78 (0.45–1.4)	1.4 (0.51 3.8)
Having younger and elder siblings	64 (16–128)	65	3	2.0 (0.69–5.6)	2.2 (0.57–8.4)

Footnotes are in Table 2-A.

dose. Some students could have acquired immunity to mumps and varicella through childhood infections. In fact, a number of students (32% and 68%, respectively) developed mumps and varicella infections. Thus, 2-dose vaccination during early childhood should also be adopted for mumps and varicella, considering the burden of these diseases and the risk of primary or secondary vaccine failures. Several previous studies support our view (19,20).

To our knowledge, no previous study has focused on reductions in antibody responses by post-term birth or macrosomia, even though premature infants were reported to have lower antibody titers than term infants for several vaccines (4). Moreover, we found no previous studies that showed any relationship between the existence of siblings and antibody titers. The observed high titers of mumps virus antibody in our student cohort with younger/older siblings may be attributable to increased opportunities of clinical/subclinical infections from their siblings.

In colleges, there are numerous personal encounters; thus, students are particularly vulnerable to outbreaks of infectious diseases. Because more than half of the population in developed countries receives higher education, university healthcare services are expected to play a key role in the prevention of outbreaks of infectious diseases (21). Among the routine activities of university healthcare workers, the first step should be to quickly grasp the immune status of students from histories of vaccinations and infections. In particular, review of histories of 2-dose vaccination should be the most effective tool for risk assessment.

Some potential limitations of the current analysis must be acknowledged. First, only the specific antiviral antibody was measured for immunological laboratory evaluation. However, the specific antiviral antibody has been shown to be a general indicator of clinical response to infections (10,22–27). Second, we could not establish a solid consensus based on our findings because of the limited number of participants and the imbalanced distribution of outcomes and predictors. For example, only 1.7% of students were immuno-negative for varicella. Likewise, only 9.2% of students had a history of measles infection. Third, a recall bias of parents responding to the self-administered questionnaire may have distorted the results of the current analysis. Some studies have shown that the questionnaire alone is insufficient to provide reliable information on student immune status (28). Therefore, we used the MCH Handbook to obtain objective infection and immunization

Table 2-C Factors associated with immune status for mumps viruses

	Antibody titer (median, IQR‡)	Immune-positives (n = 358)	Immune-negatives (n = 518)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Vaccination					
None	8.4 (4.9–13.4)	169	151	Reference	Reference
1 dose	5.7 (3.3–9.1)	135	289	0.44 (0.33–0.58)	0.66 (0.42–1.0)
≥2 doses	5.5 (3.6–12.8)	4	6	—	—
Measles-mumps-rubella triple vaccine usage					
No	5.8 (3.5–10.3)	49	90	Reference	—
Yes	6.1 (3.6–10.7)	66	109	1.1 (0.70–1.8)	—
Past infection of mumps					
No	5.3 (3.1–8.9)	134	334	Reference	Reference
Yes	10.1 (6.4–16.0)	153	88	4.3 (3.1–6.0)	4.3 (2.6–7.1)
Unknown	6.3 (3.7–11.6)	21	29	1.8 (0.99–3.3)	1.7 (0.85–3.4)
History of infectious diseases requiring hospitalization					
No	6.6 (3.9–12.0)	211	289	Reference	Reference
Yes	5.9 (3.2–10.6)	33	48	0.94 (0.58–1.5)	0.87 (0.50–1.5)
History of neonatal asphyxia					
No	7.4 (4.1–12.6)	92	102	Reference	—
Yes	6.9 (4.2–8.4)	3	9	0.37 (0.10–1.4)	—
Gestational week/birth weight					
Normal week and weight	6.4 (3.8–11.9)	213	307	Reference	Reference
Preterm/low birth weight	4.9 (3.7–15.3)	13	17	1.1 (0.52–2.3)	1.3 (0.56–3.3)
Post term birth/macrosomia	6.5 (3.7–10.6)	13	14	1.3 (0.61–2.9)	1.4 (0.56–3.3)
Age					
<20 years	6.7 (3.9–12.0)	227	316	Reference	Reference
≥20 years	6.3 (3.7–10.7)	130	202	0.90 (0.68–1.2)	1.1 (0.75–1.7)
Born in metropolitan cities†					
No	6.4 (3.8–11.3)	151	224	Reference	Reference
Yes	6.8 (3.7–13.2)	73	88	1.2 (0.85–1.8)	1.5 (0.999–2.3)
Having siblings					
No	5.2 (3.1–7.9)	17	52	Reference	Reference
Having younger siblings	7.0 (4.2–12.3)	110	146	1.1 (0.78–1.5)	2.5 (1.3–4.9)
Having elder siblings	6.8 (4.1–12.5)	89	102	1.3 (0.95–1.9)	2.7 (1.4–5.5)
Having younger and elder siblings	6.2 (3.2–10.6)	28	40	0.97 (0.58–1.6)	2.0 (0.87–4.6)

Footnotes are in Table 2-A.

histories.

Despite several limitations, the findings of the current analysis still provide healthcare workers with an insight into the control of outbreaks of epidemic-prone infectious diseases because the influence of immunization doses and other clinico-demographical factors on antibody levels among university students has not been thoroughly discussed. Therefore, we conclude that the number of vaccination doses was more important than clinico-demographical factors to promote an antibody response against measles and rubella and further propose that a 2-dose vaccination strategy could successfully prevent measles and rubella outbreaks by increasing immunity.

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Table 2-D Factors associated with immune status for varicella-zoster viruses

	Antibody titer (median, IQR‡)	Immune-positives (n = 859)	Immune-negatives (n = 15)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Vaccination					
None	32 (16–64)	543	7	Reference	Reference
1 dose	16 (8–32)	200	7	0.37 (0.13–1.1)	1.4 (0.47–4.5)
≥2 doses	32 (32–32)	2	0	—	—
Past infection of varicella					
No	16 (8–32)	206	13	Reference	Reference
Yes	32 (16–64)	500	1	31.64 (4.1–242.7)	24.5 (4.2–141.9)
Unknown	32 (16–64)	37	0	4.9 (0.29–84.3)	7.7 (0.43–139.8)
History of infectious diseases requiring hospitalization					
No	32 (16–64)	487	12	Reference	Reference
Yes	32 (16–64)	79	2	0.97 (0.21–4.4)	0.76 (0.18–3.3)
History of neonatal asphyxia					
No	32 (16–64)	188	6	Reference	—
Yes	32 (16–48)	12	0	0.86 (0.05–16.2)	—
Gestational week/birth weight					
Normal week and weight	32 (16–64)	507	12	Reference	Reference
Preterm/low birth weight	32 (16–64)	29	1	0.71 (0.09–5.6)	0.41 (0.06–2.8)
Post term birth/macrosomia	32 (16–64)	26	1	0.63 (0.08–5.0)	0.35 (0.05–2.3)
Age					
<20 years	32 (16–64)	534	9	Reference	Reference
≥20 years	32 (16–64)	324	6	0.91 (0.32–2.6)	0.59 (0.20–1.8)
Born in metropolitan cities†					
No	32 (16–64)	364	10	Reference	Reference
Yes	32 (16–64)	157	4	1.1 (0.33–3.5)	1.1 (0.35–3.6)
Having siblings					
No	32 (16–64)	68	1	Reference	Reference
Having younger siblings	32 (16–64)	249	6	1.0 (0.36–3.0)	0.59 (0.09–3.5)
Having elder siblings	32 (16–64)	187	4	1.2 (0.38–4.0)	0.64 (0.10–4.3)
Having younger and elder siblings	32 (16–64)	65	3	0.47 (0.13–1.7)	0.28 (0.04–2.1)

Footnotes are in Table 2-A.

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