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Original Article

Serological assessment of measles–rubella vaccination catch-up campaign among university students

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Abstract

Background: In Japan, 5000–300 000 persons succumbed to measles every year until 2001. The measles/rubella-combined (MR) vaccination at age 17–18 years (phase 4 MR vaccination: MR-IV) was launched in 2008 in Japan as a measles–rubella catch-up campaign. A serological assessment of this campaign has not been thoroughly performed.

Methods: Titers of anti-measles and anti-rubella immunoglobulin G antibodies, and past medical history including measles and rubella vaccination and infection were obtained from first-year university students in 2008 and 2009, and the immune status against measles and rubella was compared between students at the target MR-IV age (the target age group) and those 1 year older than the target age (non-target age group).

Results: A total of 186 students were in the target age group and 146 were in the non-target age group. The proportion of students with a history of measles and rubella infection was not significantly different between the two groups (8.8% vs. 6.3%, $P = 0.41$ and 11.0% vs. 9.9%, $P = 0.75$, respectively). A history of two or more measles and rubella vaccinations was significantly more frequent in the target age group (85.2% and 54.9%, respectively) than in the non-target age group (20.8% and 13.2%, respectively; both $P < 0.001$). Prevalence of seropositivity for measles and for rubella was also higher in the target age group (98.9% and 97.8%, respectively) than in the non-target age group (91.0% and 87.5%, respectively; both $P < 0.001$).

Conclusions: The MR-IV catch-up campaign helped achieve herd immunity and will contribute to the elimination of measles and rubella.

Key words antibody, catch-up campaign, maternal and child health handbook, measles–rubella vaccination, university students.

In the past the government of Japan mandated people to receive only a single-dose vaccination for measles and rubella, and partially due to this 5000–300 000 persons had succumbed to measles every year before 2001.[1,2] Mathematical models indicated that >95% of people in a community should be immunized to prevent an epidemic of measles, and the corresponding proportion is 85% for rubella.[3–5] The World Health Organization (WHO), therefore, recommends 95% immunization to eliminate measles,[6] but only 80.7% of Japanese people of all ages had received immunization for measles in 2001.[7] The government then launched a campaign with the theme "Give a measles vaccine as a first birthday gift!" in 2001.[8]

Nevertheless, Japan experienced measles outbreaks mainly among high school and college students in both 2006 and 2007. Especially in 2007, 1657 students (0.58%) suffered from measles nationwide.[9] Prevention of vaccine-preventable infectious diseases among youth then became an urgent matter. The greatest concerns were non-vaccination and vaccine failure. Indeed, a survey during the measles outbreak found that only 64.8% of patients had a history of measles vaccination.[10] Vaccine failure occurred in 7.4% of first-year students who had undergone the first vaccination at college

admission.[11]
Therefore, a two-dose policy with a measles/rubella-combined (MR) vaccine, requiring immunization at age 12–23 months (phase 1 MR vaccination: MR-I) and at age 5–6 years (just before school entry, phase 2 MR vaccination: MR-II) was enforced in 2006, not only to increase vaccine coverage but also to minimize vaccine failure.[12–16] In addition, a catch-up campaign with MR vaccinations at age 12–13 years (first-year junior high school students, phase 3 MR vaccination: MR-III) and at age 17–18 years (third-year high school students, phase 4 MR vaccination: MR-IV), has been carried out for 5 years since 2008 under the Preventive Vaccination Law.[6]
By these efforts, the annual number of measles cases decreased from an estimated 286 000 in 2001 to 11 005 in 2008, 741 in 2009, 457 in 2010, and 434 in 2011.[7,17–20] The number of measles outbreaks also rapidly decreased after peaking in 2007, and there has been no remarkable outbreak from 2009 on. According to the pediatric fixed-point survey of measles, the proportion of patients aged ≥10 years gradually increased, while that of patients aged 1–4 years gradually decreased until 2007.[21] The proportion of patients ≥10 years old, however, has dramatically decreased since 2008 when the catch-up campaign was introduced. The catch-up campaign seems successful in preventing measles and rubella epidemics among adolescents. The two-dose vaccination campaign has been known to reduce the incidence of measles early in the following year, as it did in England and Wales. We, therefore sought to evaluate the efficacy of the catch-up campaign in detail.[22]

Methods

Study design

This study was carried out as an analytical epidemiological study at a single institution. The 2008 and 2009 first-year students of Kyoto University Faculty of Medicine (School of Medicine, medical doctor course, and School of Human Health Sciences, co-medical professional course) and Faculty of Pharmaceutical Sciences (Division of Pharmacy, pharmacist course) were invited to participate in the study. Because the MR-IV launched in 2008 for 5 years was targeted at last year (third-year) high school students, first-year students in 2009 who entered the university right after graduating from high school were at the target MR-IV age. Meanwhile, all of the first-year students in 2008 were off the target MR-IV age. We therefore recruited the students who entered the university right after graduating from high school, both in 2009 and 2008, for the study.
Individual written informed consent was obtained from all participants. After merging data from different sources, all personal identifiers were removed from the database. This investigation was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (approval number, E-590).

Questionnaire survey

An informed consent form and a self-administered questionnaire with a reply envelope were handed out to the 2009 first-year students and mailed to the 2008 first-year students. The questionnaire included items on demographic characteristics and past medical history, including measles and rubella infection. Students were asked to complete the questionnaire and return it with the consent form and a photocopy of the immunization record from the Maternal and Child Health (MCH) Handbook. Unfortunately, however, the welfare committee of the School of Human Health Sciences did not allow us to collect photocopies of the MCH Handbook for the 2008 first-year co-medical students due to a lack of time for obtaining their consent.
The MCH Handbook is issued by the local government of one's residential area, and entries are completed by medical professionals mainly at pre- and postnatal periodic health checkups and on-demand perinatal medical office visits, according to the MCH law.

Biomarker assay

Titers of anti-measles and anti-rubella immunoglobulin (Ig) G antibodies were measured on enzyme immunoassay (EIA) and hemagglutination inhibition (HI) test, on 23, 24 and 27 June 2008, or 2 April 2009, respectively. Microbiology tests were examined by a clinical laboratory company outside Kyoto University, Kyoto Medical Science Laboratory. The cut-off levels of anti-measles and anti-rubella antibody titers were set at 6.0 IU/mL and 8 (dilution ratio of 1:8), respectively.[23] An HI titer 8–10 corresponds to an EIA level of 15 IU/mL.[24] During the research period, no incidence of measles or rubella was reported on campus.

Statistical analysis

Vaccine coverage, antibody titer levels and the prevalences of seropositivity for measles and rubella were compared between the two groups: the target age group and the non-target age group. The antivirus antibody titers were logarithmically transformed to be normalized for statistical tests. For comparison, Student's *t*-test was used for continuous variables after confirmation of normality, and Pearson's chi-squared test or Fisher's exact test was used for categorical variables. All tests of significance were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was done with STATA 10.0 (STATA, College Station, TX, USA).

Results

Student characteristics

A total of 379 eligible students (129 medical, 202 co-medical, and 48 pharmaceutical), were invited to participate, and 332 who consented (87.6% in total; 91.6% in the target age group and 83.0% in the non-target age group, $P = 0.011$) were enrolled in the study. Their characteristics are listed in Table 1. Among the enrollees, 186 students (56.0%) were in the target age group, 168 of whom (90.3%) had already received the MR-IV vaccination. The number of students in the non-target age group was 146 (44.0%).

Information on vaccination history is summarized in Table 2. A history of at least one measles vaccination was slightly more frequent among students in the target age group than in the non-target age group (98.9% vs. 95.4%, $P = 0.07$). A history of two or more measles vaccinations was significantly more frequent among students in the target age group than in the non-target age group (85.2% vs. 20.8%, $P < 0.001$). A history of at least one rubella vaccination in the target age group was significantly more frequent than in the non-target age group (98.9% vs. 77.5%, $P < 0.001$). A history of two or more rubella vaccinations in the target age group was significantly more frequent than in the non-target age group (54.9% vs. 13.2%, $P < 0.001$).

Anti-measles immune status

Anti-measles immune status is summarized in Table 2. The proportion of students with a history of measles infection was not significantly different between the target and non-target age groups (8.8% vs. 6.3%, $P = 0.41$). Measles antibody titers were significantly higher among the target age group than the non-target age group (geometric mean titer, 28.3 [–1 SD, 13.2; +1 SD, 60.6] vs. 16.8 [–1 SD, 6.9; +1 SD, 40.8]; $P < 0.001$). The prevalence of seropositivity against measles was also significantly higher among the target age group than the non-target age group (98.9% vs. 91.0%, $P = 0.001$).

Anti-rubella immune status

Anti-rubella immune status is summarized in Table 2. The proportion of students with a history of rubella infection was not significantly different between the two groups (11.0% vs. 9.9%, $P = 0.75$). Rubella antibody titers were significantly higher among the target age group than the non-target age group (geometric mean titer, 44.5 [–1 SD, 17.2; +1 SD, 115.0] vs. 30.8 [–1 SD, 9.7; +1 SD, 97.8]; $P = 0.002$). The prevalence of seropositivity against rubella was therefore significantly higher among the students in the target age group than in the non-target age group (97.8% vs. 87.5%, $P < 0.001$).

Discussion

The students at the target MR-IV age had higher vaccine coverage and were more frequently seropositive against measles and rubella than those 1 year older than them. Even though a history of two or more vaccinations for measles and rubella remained 85.2% and 54.9%, respectively, in the target age group, seropositivity against measles and rubella was 98.9% and 97.8%, respectively, achieving the WHO-recommended level for disease elimination at 95% and 85%.[3–5] The prevalence of seropositivity against measles increased by 7.9% after this catch-up campaign. This is similar to the increase in measles immunity in the target age groups observed in previous catch-up campaigns in England and Wales, the Americas, Australia, and Korea.[22,25–27] The Ministry of Health, Labor and Welfare of Japan also set a desired vaccination coverage of 95% for the two doses to eliminate measles by 2012. The MR-IV coverage of 90.3% in the present study and that of 77.3% in the nationwide survey, however, indicate that this level has not yet been reached.[28] Further efforts to increase vaccine coverage should be made by local governments, by, for instance, periodic monitoring of vaccine coverage and repeated invitations to vaccinate those who are unvaccinated, along with close cooperation with schools and the board of education of local governments.

The proportion of students with a history of at least one measles or rubella vaccination before the MR-IV period was higher in the non-target age group compared to the target age group. A considerable number of the 2008 first-year students might have received a MR vaccine in 2007 on their own, following the initiative according to the social requirements do so after the measles outbreak in 2006 and 2007, or in order to stay healthy for their entrance examinations.

In the non-target age group, the seroprevalence for measles did not reach the WHO-recommended level, and the two-dose measles and rubella vaccine coverage was far from the level demanded by the Japanese government. Thus, we still have a problem with insufficient immunization of youth who are not covered by the MR catch-up campaign. In particular, with regard to the future of health-care professionals, we need to provide an opportunity for further vaccination before clinical training.

In light of the fact that more than half of the Japanese population receives higher education, university health services are expected to play a key role in preventing outbreaks of adolescent infectious diseases.[29] Their easy access, during their routine activities, to the immune status of students from their history of infection and vaccination, would be the first step. One study showed that a questionnaire alone merely provides unreliable information regarding student immune status.[30] In contrast, the MCH Handbook can provide more objective and precise information on infection and immune history and, therefore, should be utilized more.

Some potential limitations of the current analysis must be acknowledged. First, only the specific anti-viral IgG antibody was measured for immune status. Immunoprophylaxis from infectious diseases involves the humoral, cellular and mucosal immune systems, and the anti-viral IgG antibody plays only a small role in humoral immunity. Anti-measles- and anti-rubella-specific antibodies, however, have corresponded well with clinical response to infection.[22,27,31–35] Furthermore, because measurement of the specific anti-viral IgG antibody is a relatively simple and economical method for ascertaining immune status compared to other laboratory examinations, the present results are easily applicable to clinical and public health settings.

Second, there are some uncertainties about the external validity of the study results due to potential selection bias. Further studies are warranted to investigate whether the present findings are applicable to other Japanese universities.

Third, the participation rate of the 2008 first-year students was significantly lower than that of the 2009 first-year students, which might distort the results. Because the included students were more selective and might have been more health-conscious in 2008 than in 2009, the better immune status of the target age students may have been underestimated.

Fourth, we could not collect photocopies of the MCH Handbook for co-medical course

students who entered in 2008, which could have caused misclassification of immunization status. Consequently, the vaccine coverage of co-medical students in the non-target age group could be underestimated.
From analyzing the data on the specific anti-viral IgG antibody titers and the vaccination and infection history among the 2008 and 2009 first-year university students, we conclude that the MR catch-up campaign helped achieve herd immunity and will contribute to the elimination of measles.

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Table 1 Subject characteristics

	Total *n* (%)	*n*	Target MR-IV age *n* (%)	*n*	Non-target age group *n* (%)	*n*	*P*
Male	137 (41.3)	332	82 (44.1)	186	55 (37.7)	146	0.24
Age (years), median (IQR)	18.6 (18.4–18.9)	331	18.5 (18.5–18.6)	185	18.8 (18.7–18.8)	146	<0.001
Available information							
Antiviral antibody titers	327 (98.5)	332	183 (98.4)	186	144 (98.6)	146	1.00
Questionnaire	319 (96.1)	332	181 (97.3)	186	138 (94.5)	146	0.26
Photocopy of MCH Handbook	242 (72.9)	332	179 (96.2)	186	63 (43.2)	146	<0.001
Actual vaccination in the MR-IV period	–	–	168 (90.3)	186	–	–	–

MCH, maternal and child health; MR-IV, phase 4 measles/rubella-combined vaccination at age 17–18 years.

Table 2 Immune status

	Target MR-IV age *n* (%)	*n*	Non-target age group *n* (%)	*n*	*P*
History of measles infection	16 (8.8)	182	8 (6.3)	127	0.41
History of at least one measles vaccination before MR-IV period	160 (87.9)	182	124 (95.4)	130	0.02
History of two or more measles vaccinations before MR-IV period	10 (5.5)	182	27 (20.8)	130	<0.001
History of at least one measles vaccination including MR-IV period	180 (98.9)	182	124 (95.4)	130	0.07
History of two or more measles vaccinations including MR-IV period	155 (85.2)	182	27 (20.8)	130	<0.001
Antibody titer for measles (IU/mL)	28.3 (13.2, 60.6)†	183	16.8 (6.9, 40.8)†	144	<0.001‡
Immunopositivity against measles	181 (98.9)	183	131 (91.0)	144	0.001
History of rubella infection	20 (11.0)	181	12 (9.9)	121	0.75
History of at least one rubella vaccination before MR-IV period	107 (58.8)	182	100 (77.5)	129	0.001
History of two or more rubella vaccinations before MR-IV period	9 (4.9)	182	17 (13.2)	129	0.01
History of at least one rubella vaccination including MR-IV period	180 (98.9)	182	100 (77.5)	129	<0.001
History of two or more rubella vaccinations including MR-IV period	100 (54.9)	182	17 (13.2)	129	<0.001
Antibody titer for rubella (IU/mL)	44.5 (17.2, 115.0)†	183	30.8 (9.7, 97.8)†	144	0.002‡
Immunopositivity against rubella	179 (97.8)	183	120 (87.5)	144	<0.001

†Geometric mean titer (–1 SD, +1 SD); ‡tested after logarithmic transformation. MR-IV, phase 4 measles/rubella-combined vaccination at age 17–18 years.