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Original Article

Seroprevalence of Measles- and Mumps-Specific Immunoglobulin G among Japanese Healthcare Students Increased during 2007–2012

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SUMMARY: We evaluated the seroprevalence of vaccine-preventable infectious diseases among Japanese healthcare students to create immunization guidelines. Between 2007 and 2012, a total of 1746 Japanese medical, nursing, and paramedical students were serologically screened for measles, mumps, rubella, varicella, and hepatitis B virus (HBV) antibodies at the time of admission. In 2007, the seroprevalence of measles and mumps was 52.7% and 65.6%, respectively. The seroprevalence of measles dramatically increased to 96.6% in 2009 and was then sustained at >90%. The seroprevalence of mumps gradually increased to >80.0% between 2010 and 2012. The seroprevalence of rubella remained at >90% except in 2008 (85.6%), and the seroprevalence of varicella was sustained at >92% throughout 2007–2012. The seroprevalence of HBV antibody remained at <7% during 2007–2012. Although the seroprevalence of vaccine-preventable infectious diseases among Japanese healthcare students increased during the 2007–2012 study period, a substantial number of students were susceptible to vaccine-preventable infectious diseases. Therefore, we propose targeted immunization of Japanese healthcare students using serological screening prior to clinical training.

INTRODUCTION

To prevent hospital-acquired infections, physicians, healthcare workers, and healthcare students require immunity against vaccine-preventable infectious diseases (1–3). The Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) of the US Centers for Disease Control and Prevention (CDC) have recommended immunization guidelines for healthcare personnel. These guidelines strongly recommend immunizations against hepatitis B virus (HBV), measles, mumps, rubella, and varicella for healthcare personnel (1,4). However, in contrast to those in the US, most Japanese medical institutions lack such guidelines. National surveys of clinical training hospitals, clinics, hospitals, nurses, and residents have shown that vaccinations are uncommon in Japan (5). Serological screening at university hospitals in Japan has shown that medical students and residents are susceptible to many vaccine-preventable diseases (6–9). Indeed, outbreaks of measles occurred in 2003 among Japanese medical students and in clinical training hospitals (10,11). Thus, immunization against vaccine-preventable infectious diseases is now required for healthcare students to protect them and their patients in Japanese hospitals offering clinical training.

There is a large gap between Japan and other developed countries regarding vaccine use to prevent serious infections (12,13). In Japan, a single-dose measles vaccination between 1 and 7.5 years of age was introduced as a routine immunization in 1978. In 2006, a new two-dose schedule of the measles–rubella vaccine was initiated with doses administered at 1 and 5–6 years of age, but this system did not prevent a measles epidemic in the summer of 2007 (14), which mainly affected young adults or high-school/university students. In 2008, the Japanese government implemented a 5-year measles–rubella vaccination catch-up campaign for cohorts aged between 13 and 18 years with the aim of eliminating measles by 2012 (14).

To evaluate the standard vaccination program against infectious diseases among healthcare students, we introduced serological screening and vaccination for measles, rubella, mumps, varicella, and HBV in 2007 for medical, nursing, and paramedical students at Gunma University at the time of admission. Paramedical students included laboratory medical technologists, physical therapists, and occupational therapists. We retrospectively investigated the positive ratios of measles-specific immunoglobulin G (IgG), rubella-specific IgG, mumps-specific IgG, varicella-specific IgG, and HBV antibody during 2007–2012 among healthcare students at Gunma University at the time of admission. To identify potential problems in Japan, we compared the data of Japanese healthcare students with those of other countries.

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Table 1. Number, gender, age and positive ratio of HBV antibody in medical students

	2007 $n = 273$	2008 $n = 292$	2009 $n = 302$	2010 $n = 295$	2011 $n = 290$	2012 $n = 294$
Gender						
Male/Female	82/191	107/185	104/198	81/214	105/185	110/181
Mean age, y ± S.D.	19.9 ± 2.3	19.9 ± 2.1	19.9 ± 2.2	19.9 ± 2.0	19.9 ± 2.1	19.9 ± 2.2
Positive ratio (%) of HBV antibody	4.0	5.1	6.6	4.7	4.1	3.7

Table 2. Positive ratio of measles-, rubella-, mumps- and varicella-specific IgG in Japanese healthcare students during 2007–2012

		2007	2008	2009	2010	2011	2012
Measles	Total (%)	52.7	76.8**	93.4**	92.9**	92.9**	96.6**
	Male (%)	46.6	79.4	89.9	86.4	89.6	98.2
	Female (%)	59.7*	72.3	95.5	95.3*	94.6	95.6
Rubella	Total (%)	95.2	86.5**	91.4	95.3	96.6	92.9
	Male (%)	93.9	88.8	85.6	88.9	96.2	91.3
	Female (%)	95.8	85.6	95.5*	97.7*	96.7	94.5
Mumps	Total (%)	65.6	74.3**	75.2**	82.4**	81.3**	82.0**
	Male (%)	52.4	72.9	75.0	80.2	79.2	80.5
	Female (%)	71.1*	75.1	76.3	83.2	82.1	82.9
Varicella	Total (%)	92.3	94.9	96.4	96.3	98.3	94.6
	Male (%)	92.7	94.4	97.1	95.1	98.1	92.9
	Female (%)	92.1	95.1	96.0	96.7	98.4	95.6

Categorical variables are presented as percentages. The positive ratio of measles-, rubella-, mumps- and varicella-specific IgG between genders or each year were compared of difference by using the Fisher's exact tests. Statistical significance was established for $P < 0.05$. *, $P < 0.05$; comparison between male and female. **, $P < 0.05$; comparison between 2007 and respective year.

MATERIALS AND METHODS

Between 2007 and 2012, serological screening of 1746 Japanese healthcare students (593 males and 1153 females) for measles, rubella, mumps, varicella, and HBV was performed at the time of admission to Gunma University. The 1746 subjects included 667 (38.2%) medical students, 543 (31.1%) nursing students, 275 (15.8%) laboratory medical technology students, 135 (7.7%) physical therapy students, and 124 (7.1%) occupational therapy students. The characteristics of subjects are summarized in Table 1. Students with a seronegative status were offered vaccination. Age, gender, and antibody titers were retrospectively analyzed. Blood samples were collected from the healthcare students at the time of admission. Titers of anti-measles, anti-rubella, anti-mumps, and anti-varicella antibodies were measured using an Enzygnost Enzyme-Linked Immunosorbent Assay kits (Enzygnost® Anti-Measles-Virus/IgG, Enzygnost® Anti-Rubella-Virus/IgG, Enzygnost® Anti-Mumps-Virus/IgG, Enzygnost® Anti-Varicella-Virus/IgG, respectively; Siemens Healthcare Diagnostics K.K., Tokyo, Japan). Antibody titers against the hepatitis B surface antigen (HBsAg) were measured using the ARCHITECT® AUSAB Anti-HBs assay (ABBOTT JAPAN CO., LTD, Tokyo, Japan). Analyses were performed according to the manufacturers' instructions. Positive test results were defined as measles-specific IgG ≥ 300 mIU/ml, rubella-specific IgG ≥ 8 IU/ml, mumps-specific IgG ≥ 500 (titer), varicella-specific IgG ≥ 100 mIU/ml, and HBsAg-specific IgG ≥ 10 mIU/ml. Antibody levels in the indeterminate range were considered seronegative.

Difference in the seroprevalence of measles, rubella, mumps and varicella between genders and each year of the study period were compared using the Fisher's exact test. Categorical variables are presented as percentages. A P-value <0.05 was considered statistically significant. This study was approved by the ethics committee of the Gunma University Graduate School of Medicine.

RESULTS

Table 2 shows the changes between 2007 and 2012 in measles-, rubella-, mumps-, and varicella-specific IgG-positive ratios among healthcare students at the time of admission. The positive ratio of measles-specific IgG was lowest (52.7%) in 2007. The proportion of students who were seropositive to measles dramatically increased to 93.4% in 2009 and was maintained at $>90\%$ between 2009 and 2012. Positive measles-specific IgG ratios were the same in female and male students except in 2007 and 2010.

During 2007–2012, the proportion of healthcare students who were seropositive to rubella was maintained at $>90\%$ except in 2008 (85.6%). The positive ratio of rubella-specific IgG was $>95\%$ in 2007, 2010, and 2011. Positive ratios of rubella-specific IgG were the same in female and male students except in 2009 and 2010.

The positive ratio of mumps-specific IgG was lowest

(65.6%) in 2007. The proportion of students who were seropositive to mumps gradually increased and was sustained at >80.0% between 2010 and 2012. The positive ratio of mumps-specific IgG was the same in female and male students except in 2007.

The proportion of healthcare students who were seropositive to varicella was stable (>92%) from 2007 to 2012. The positive ratio of varicella-specific IgG was >95% from 2009 to 2011, and it was the same among female and male students from 2007 to 2012.

The proportion of students who were seropositive to HBV was notably low as shown in Table 1. The positive HBV antibody ratio was lowest (3.7%) in 2012 and highest (6.6%) in 2009.

DISCUSSION

The present study provided important information regarding serological immunity against vaccine-preventable infectious diseases among healthcare students in Japan. Our results revealed that a significant number of healthcare students in our region remained susceptible to vaccine-preventable infectious diseases. We found a high seroprevalence of measles, rubella, and varicella, a lower seroprevalence of mumps, and a notably low seroprevalence of HBV.

There is a large gap between Japan and other developed countries regarding vaccine use to prevent serious infections (12,13). A single-dose measles vaccination between 1 and 7.5 years of age was introduced as a routine immunization in Japan in 1978. In 2006, a two-dose schedule for the measles-rubella vaccination was initiated with doses administered at 1 and 5–6 years of age, but this system did not prevent a measles epidemic in the summer of 2007 (14), which mainly affected young adults or high-school/university students. In 2008, the Japanese government implemented a 5-year measles-rubella vaccination catch-up campaign for cohorts aged between 13 and 18 years to eliminate measles by 2012 (14). Therefore, most new students admitted to Gunma University from 2009 to 2012 were assumed to be vaccinated by the measles vaccination catch-up campaign. The lowest positive ratio (53.0%) of measles-specific IgG among the healthcare students was detected in 2007. This is comparable with data from the United Arab Emirates (UAE), which reported a rate of 54% during 2011–2012 (3), but it was lower than that reported in Australia (73.8%) from 2002 to 2005 (15). The seropositive ratio of measles-specific IgG dramatically increased to >92% from 2009 to 2012, and this was comparable with data from Europe (2,16–18). These findings can be explained by the measles epidemic in 2007 and the effect of the measles vaccination catch-up campaign implemented by the Japanese government in 2008. Thus, our findings suggested that the measles vaccination catch-up campaign was successful and may lead to the elimination of measles in Japan.

The seroprevalence of rubella-specific IgG among Japanese healthcare students was high throughout the 2007–2012 study period. It remained at >92% from 2009 to 2012, which is comparable with data from Europe (2,16–18) and the UAE (3). Although both measles and rubella vaccinations are routinely administered in Japan, the seroprevalence of rubella-specific IgG was high during 2007–2008; in contrast, the seroprevalence of measles-specific IgG was low during the same period. Greater acceptance of rubella immunization by women in view of the potential risk of congenital rubella syndrome has been reported to create a difference in seroprevalence of rubella between men and women (2); however, in our study, a difference in seroprevalence of rubella was only observed during 2009–2010. In Japan, a routine rubella immunization program for junior high school students was introduced in 1995. Therefore, most students admitted to Gunma University from 2007 to 2012 were seropositive to rubella. A superior seroprevalence of rubella-specific IgG rather than that of measles-specific IgG in Gunma University students from 2007 to 2008 could be explained from this background.

The seroprevalence of mumps-specific IgG was low (65.6%) among the students in 2007. Nearly identical levels of mumps-specific immunity were reported in Germany (2) and Australia (15). In Japan, the measles, mumps, and rubella (MMR) combination vaccine was introduced in 1989 and subsequently terminated in 1993. Since 2006, a routine measles-rubella vaccine was introduced; however, the mumps vaccine continues to be excluded from routine vaccinations. These facts explain the low seroprevalence of mumps-specific IgG among Gunma University students. Although vaccination against mumps is voluntary in Japan, the seroprevalence of mumps-specific IgG gradually increased to >80% between 2010 and 2012. Similar values have been reported in the UAE (3), Switzerland (16), and Greece (18). In Slovenia, seropositivity to mumps was higher than our findings among Japanese students (17). In these countries, an MMR combination vaccine was introduced (3,16–18), which suggests that implementation of the MMR combination vaccine may improve immunity against mumps in Japan.

High immunity against varicella (>92.3%) was observed among the Japanese healthcare students in this study. Nearly identical levels of varicella-specific immunity were reported in Europe (2,16–18), Australia (15), and the UAE (3). Varicella vaccine was initially licensed in Japan in 1987 for high-risk children but was extended just after licensure to include normal children based on the needs of parents and physicians. Because varicella vaccination is not compulsory in Japan, only approximately 40% of Japanese children received the vaccine in 2008. This low level of coverage was not sufficient to alter the circulation of wild-type varicella zoster virus; thus, the epidemiology of natural varicella has not changed since the vaccine was introduced (19). In the case of varicella infection, over 90% of unvaccinated persons get infected, and over 80% get infected by 10 years of age in Japan (20). Most studies have found high seropositivity to varicella among adults. These findings could be explained by the fact that varicella infections occur in childhood (16,21,22). Thus, a high seroprevalence against varicella among Gunma University students was maintained during the 2007–2012 study period, although vaccination against varicella remains voluntary in Japan.

Varicella and mumps vaccinations are voluntary; thus, both had low coverage rates. Therefore, it was assumed that sufficient stimulation for the generation of

adequate antibody titers against both viruses may have been achieved through natural infection; in particular, immunity to varicella was strongly influenced by natural infection (23–25). The mumps vaccine was included in the MMR vaccine program for 5 years (1989–1993), likely affecting subjects who were immunized during that period. Latner et al. reported that mumps vaccination or natural infection may not generate robust B-cell memory (26). This would explain why the seroprevalence of mumps was lower than that of varicella even though both mumps and varicella vaccinations were voluntary, and the vaccination rates of both vaccines were similar (27).

Seropositivity to HBV was notably low among the Japanese students. This could be explained by the fact that the HBV vaccination is administered to those at risk of contracting HBV in Japan, and HBV is a blood-transmissible pathogen. Students who were seronegative to HBV were offered vaccinations in Gunma University. Therefore, the majority of students were seropositive to HBV prior to coming into contact with patients. Previous reports have shown higher seroprevalence rates against HBV (48%–91%) among medical students (2,3,15–18). In the countries mentioned in those reports, HBV vaccination has been introduced for infants (2,3,15–18); however, in Japan, HBV vaccination is administered to those at the risk of contracting HBV. Among Gunma University students, the positive ratio of antibody to hepatitis B surface antigen (anti-HBs) ranged from 3.7% to 6.6% during 2007–2012. The HBs antibody-positive students may have been inoculated with hepatitis B vaccine before admission to Gunma University, although the vaccination histories of these students were unclear. On the other hand, in 2012, among the blood donors of Japanese Red Cross Society, the positive ratio of antibody to hepatitis B core antigen (anti-HBc) was 0.5% (28). Positive HBc antibody among those donating blood to the Japanese Red Cross Society indicated that the donor might have had a history of HBV infection. These facts could explain why the positive ratio of HBs antibody among Gunma University students was higher than the positive ratio of HBc antibody among those donating blood to Japanese Red Cross Society.

Although seroprevalence of vaccine-preventable infectious diseases was increased among medical students during 2007–2012, a significant number of students in our region remained susceptible to HBV, and several were susceptible to measles, mumps, rubella, or varicella. To prevent transmission of vaccine-preventable infectious diseases among healthcare students and patients in clinical training hospitals, targeted immunization programs using serological screening is recommended prior to clinical training involving direct contact with patients.

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Conflict of interest None to declare.

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