### Prevaccination Antibody Screening and Immunization Program for Healthcare Personnel against Measles, Mumps, Rubella, and Varicella in a Japanese Tertiary Care Hospital

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Susceptible healthcare personnel (HCP) are at high risk for acquiring and transmitting measles, mumps, rubella, and varicella (MMRV). Presumptive evidence of immunity to MMRV is recommended for HCP. The aim of this investigation was to examine the seroprevalence of MMRV in Japanese HCP and the association with history or vaccination in terms of occupational safety. To improve infection control at our hospital, we also assessed their immune status by implementing prevaccination antibody screening and an immunization program with postvaccination serological testing. We implemented seroprevalence surveys on MMRV antibodies among 243 newly and 2,664 previously hired HCP in a Japanese tertiary care hospital. Self-administered questionnaires about history of MMRV and vaccination with or without written documentation were completed for newly hired HCP. Prevaccination and postvaccination serological tests were performed using virus-specific IgG enzyme-linked immunosorbent assays. Indeed, only a few HCP accurately remembered or had written records of their disease or vaccination history. After our immunization program was implemented, the seropositivity rate reached levels as high as ~98% for measles, rubella, and varicella, and increased to ~80% for mumps. Our program was cost-effective, and no severe adverse reactions were reported. The prevaccination antibody screening for HCP would be helpful, given the lack of written vaccination records or documented disease history, and is also useful for the prevention of adverse reactions associated with unnecessary vaccination. It is important for infection control practitioners to comprehend the immune status of HCP against MMRV, and then provide an appropriate immunization program for susceptible HCP.

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### Introduction

Susceptible healthcare personnel (HCP) are at high risk for acquiring and transmitting measles, mumps, rubella, and varicella. Outbreaks of these vaccine preventable diseases have been described in the healthcare setting as well as in the community, Therefore, immunization for HCP against measles, mumps, rubella, and varicella is important for infection prevention and control. In Japan, the guideline provided by the Japanese Society for Infection Prevention and Control recommends that HCP without history of these infectious diseases have documentation of vaccination with two doses of measles, mumps, rubella, and varicella (Japanese Society for Infection Prevention and Control 2009). In the U.K., the Public Health England recommends that satisfactory evidence of immunity be documentation of having received two doses of measles, mumps, rubella (MMR) or having had positive serological testing results for measles and rubella, and HCP with a negative or uncertain history of chickenpox or herpes zoster receive serological testing and seronegative HCP be vaccinated against varicella (Public Health England 2013). In the U.S., the Advisory Committee on Immunization Practices (ACIP) recommends that HCP have the following presumptive evidence of immunity to these infectious diseases: 1) written documentation of vaccination with two doses for measles,

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mumps and varicella, and one dose for rubella; 2) laboratory evidence of immunity (i.e., positive serology), 3) laboratory confirmation of disease for mumps, measles and rubella; or 4) physician diagnosed varicella (Centers for Disease Control and Prevention 2011).

In 2007 and 2008, Japan experienced large measles outbreaks (Centers for Disease Control and Prevention 2008), and then a catch-up measles-rubella (MR) vaccination program was implemented, targeting two age cohorts (those aged 12 years and those aged 17 years) each year during 2008-2013 (Centers for Disease Control and Prevention 2013). In 2013, however, a nationwide rubella epidemic occurred in Japan, and the majority of cases were reported among adult males (Centers for Disease Control and Prevention 2013). In 2006, the MR combined vaccine was introduced with a 2-dose schedule, but Japanese born before 1990 have not received 2-dose of MR vaccines as routine immunization. Moreover, the occurrence of mumps and varicella is endemic (National Institute of Infectious Diseases 2013), and the vaccine coverage remains low in our country because vaccination for mumps and varicella has been provided as voluntary immunizations. In other countries MMR vaccine has been successfully introduced in a two dose schedule for children (McLean et al. 2013; World Health Organization 2014). Therefore, immunity to measles, mumps, rubella, and varicella among Japanese adult HCP would not be reliable unless they present presumptive evidence of immunity to those infectious diseases as ACIP recommends.

In this investigation, we examined the seroprevalence of measles, mumps, rubella, and varicella and the association with history of these infectious diseases or vaccination among newly hired HCP in a Japanese tertiary care hospital. We also conducted an updated seroprevalence survey of those vaccine-preventable diseases among previously hired HCP and analyzed the immune status by providing an immunization program with postvaccination serologic testing for susceptible HCP.

#### **Materials and Methods**

### Seroprevalence survey on measles, mumps, rubella, and varicella antibodies among newly hired healthcare personnel

Of 590 newly hired HCP, 243 HCP (41.2%) participated in the seroprevalence survey and received serologic testing at Tohoku University Hospital between April 2012 and March 2013. The number of HCP was 82 males and 161 females with the following age distribution: 109 aged 20-29 years, 97 aged 30-39 years, 26 aged 40-49 years, 7 aged 50-59 years, and 4 aged 60-69 years. By occupation, there were 75 physicians, 7 dentists, 11 pharmacists, 72 nurses, 26 technicians, 34 administrative staff, and 18 other staff. All of the 243 newly hired HCP completed self-administered questionnaires about their history of these infectious diseases and vaccination with or without written documentation. Serologic testing for measles, mumps, rubella, and varicella was performed using commercially available enzyme linked fluorescent assay (ELFA) kits (VIDAS Measles-IgG, Mumps-IgG, RUB-IgG, and varicella-zoster IgG, SYSMEX bioMérieux Co., Ltd., Tokyo, Japan). The seronegative cutoff was < 0.7 for

measles, < 0.50 for mumps, < 15 IU/mL for rubella, and < 0.9 for varicella, and the seropositive cutoff was  $\geq$  0.7 for measles,  $\geq$  0.5 for mumps,  $\geq$  15 IU/mL for rubella, and  $\geq$  0.9 for varicella. Positive predictive value (PPV) of the self-administered questionnaire was calculated by defining as the seropositive probability of those who answered yes to questions about the history of disease or vaccination as previously described (Trevisan et al. 2007).

### Seroprevalence survey on measles, mumps, rubella, and varicella antibodies among previously hired healthcare personnel

Tohoku University Hospital is a 1,262-bed tertiary care facility. HCP have been required to submit serologic testing results at our hospital since 2006 and the susceptible HCP have been recommended to receive vaccination, however, the policy was not mandatory but voluntary. Prevaccination antibody screening for measles, mumps, rubella, and varicella was conducted among 2,664 (97.5%) of 2,733 current HCP in October 2012. Serological testing for measles, mumps, rubella, and varicella was performed using commercial virusspecific IgG enzyme-linked immunosorbent assay (EIA) kits (Measles IgG-EIA "SEIKEN", Mumps IgG-EIA "SEIKEN", Rubella IgG-EIA "SEIKEN", and Varicella-zoster IgG -EIA "SEIKEN", Denka Seiken Co., Ltd., Tokyo, Japan). EIA values of 4.0 or greater were considered positive and values of less than 4.0 were considered negative as previously described (Hatakeyama et al. 2004). We used different serologic tests among newly and previously hired HCP; interpretative criteria for each test were in accordance with the manufacturer's instructions. For susceptible HCP who had a negative antibody titer by EIA, immunizations were recommended with live-attenuated measles, mumps, rubella, and/or varicella vaccines between January and March 2013. Vaccine adverse events were evaluated. Postvaccination antibody testing was conducted by using EIA for HCP who were vaccinated in June 2013. Costs for prevaccination antibody screening, immunization program, and postvaccination antibody testing were assessed. Because serologic testing costs for HCP differ by each facility, the costs were converted into medical service fee for Japanese standard serologic testing methods. This investigation was conducted to improve infection control at our hospital and ensure occupational safety. Serologic testing and immunization program for HCP at our hospital were approved by the Infection Control Committee of Tohoku University Hospital.

### Results

# Susceptibility to measles, mumps, rubella, and varicella in newly hired healthcare personnel

Of 243 newly hired HCP, 31 (12.8%), 19 (7.8%), 33 (13.6%), and 13 (5.3%) were considered to be seronegative for measles, mumps, rubella, and varicella, respectively. Differences in serosusceptibility to measles, mumps, rubella, and varicella between memory and documentation among newly hired HCP are shown in Table 1. Of HCP who answered that they had previous history of disease, 12.2% (6/49), 14.7% (14/95), 18.2% (10/55), and 19.6% (30/153) had written documentation for history of measles, mumps, rubella, and varicella, respectively. Only one HCP who had documentation about history of these infectious diseases was seronegative for varicella. Of HCP who answered that they were previously vaccinated, 57.7% (64/111), 52.5% (42/80), 54.3% (51/94), and 52.8% (28/53)

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	Measles	Mumps	Rubella	Varicella
Previous history of diseas	e (%)			
Memory	6/49 (12.2)	4/95 (4.2)	3/55 (5.5)	5/153 (3.3)
Documentation	0/6 (0)	0/14 (0)	0/10 (0)	1/30 (3.3)
Previous history of vaccir	nation (%)			
Memory	16/111 (14.4)	9/80 (11.3)	14/94 (14.9)	4/53 (7.5)
Documentation	9/64 (14.1)	5/42 (11.9)	11/51 (21.6)	4/28 (14.3)

Table 1. Differences in serosusceptibility to measles, mumps, rubella, and varicella between memory and documentation among newly hired healthcare personnel.

The numerator is serosusceptible HCP. The denominator is all HCP who have memory or documentation.

Table 2. Serological testing results before/after vaccination for measles, mumps, rubella, and varicella among previously hired healthcare personnel.

	Prevaccination		Postvaccination					
	No. of seropositive HCP/ No. of HCP tested	Rate of seropositivity (%)	No. of HCP vaccinated	No. of HCP seroconverted/ No. of HCP tested	Rate of seroconversion (%)	No. of seropositive HCP/ No. of HCP tested	Actual rate of seropositivity (%)	Estimated rate of seropositivity <sup>a</sup> (%)
Measles	2,545/2,664	95.5	110	87/88	98.9	2,632/2,664	98.8	99.6
Mumps	1,528/2,664	57.4	1,005	601/837	71.8	2,129/2,664	79.9	84.4
Rubella	2,444/2,664	91.7	202	160/168	95.2	2,604/2,664	97.7	99.0
Varicella	2,595/2,664	97.4	55	38/48	79.2	2,633/2,664	98.8	99.0

<sup>a</sup>The estimated rate was calculated according to our seroconversion rate in this study.

had written documentation of vaccination for measles, mumps, rubella, and varicella, respectively. Of them, 14.1% (9/64), 11.9% (5/42), 21.6% (11/51), and 14.3% (4/28) were seronegative for these infectious diseases, respectively. PPV of self-reported history both of disease/ vaccination for measles, mumps, rubella, and varicella was 87.8%/85.6%, 95.8%/88.7%, 94.5%/85.1%, and 96.7%/ 92.5%, respectively.

## Susceptibility to measles, mumps, rubella, and varicella in previously hired healthcare personnel

Table 2 shows serological testing results before/after vaccination for measles, mumps, rubella, and varicella among previously hired HCP. Prevaccination antibody screening for previously hired HCP revealed that 4.5% (119/2,664), 42.6% (1,136/2,664), 8.3% (220/2,664), 2.6% (69/2,664) were susceptible to measles, mumps, rubella, and varicella. Post-serological testing after immunizations showed that 98.9%, 71.8%, 95.2%, and 79.2% of susceptible HCP who received immunization and subsequent serological testing were found to be immune to measles, mumps, rubella, and varicella, respectively. Finally, the actual rate of seropositivity to measles, mumps, rubella, and varicella was 98.8% (2,632/2,664), 79.9% (2,129/2,664), 97.7% (2,604/2,664), 98.8% (2,633/2,664), respectively. In addition, based on our seroconversion rate, the seropositivity rate was estimated as more than 99% for measles, rubella, and varicella, and more than 80% for mumps. The prevaccination antibody screening, immunization program, and postvaccination antibody testing cost \$128,256, \$34,841, and \$22,322, respectively (Table 3). Of the four infectious diseases, serological testing and vaccination for mumps cost \$107,775 mostly for HCP who were confirmed to be immune to the infectious disease. Nine HCP who received vaccination reported mild vaccine adverse events, including fever, rash, and local swelling and redness at the injection site (Table 4). No serious adverse events were reported after the immunization program.

### Discussion

In this study, few of the newly hired HCP in our hospital remembered or had written records of their disease history or vaccination history; and even among those who had written records, some had negative serologic tests. Our findings of PPV for a history of disease or vaccination suggest that immunity against measles, mumps, rubella, and varicella among HCP cannot be guaranteed on the basis of self-enumeration alone. In a previous study of paramedical students in Italy, the self-reported history of vaccination and disease did not necessarily represent the immunity against these infectious diseases (Trevisan et al. 2007). Therefore, each person's written records and own memories of their disease history and vaccination history may not be suitable for use in the screening of individuals targeted for vaccination. The finding of disparities between the subjects' written records and own memories of their disease history and

Table 3. Costs of antibody testing and vaccination for measles, mumps, rubella, and varicella among previously healthcare personnel.

	Prevaccination antibody screening		Vaccination		Postvaccination antibody testing	
	No. of HCP tested	Cost (USD)	No. of HCP vaccinated	Cost (USD)	No. of HCP tested	Cost (USD)
Measles	2,664	21,696	110	2,722	88	717
Mumps	2,664	63,167	1,005	24,762	837	19,846
Rubella	2,664	21,696	202	4,998	168	1,368
Varicella	2,664	21,696	55	2,359	48	391
Total (USD <sup>a</sup> )		128,256		34,841		22,322

<sup>a</sup>1 USD  $\Rightarrow$  97 JPY (annual average exchange rate for 2013).

Table 4	Vaccine adverse events a	mong previously h	nired healthcare personnel.
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	Healthcare personnel	Type of vaccine	Onset time after vaccination (day)	Adverse events
1	40s F	Measles	1	Local swelling and redness at the injection site
2	20s F	Measles	2	Local swelling and redness at the injection site
3	40s M	Rubella	4	Fever and rash
4	50s M	Rubella	5	Fever and rash
5	30s M	Rubella	0	Fever and rash
6	40s M	Rubella	12	Fever and rash
7	50s M	Rubella/Mumps	10	Fever and rash
8	20s M	Mumps	21	Swelling of the parotid gland
9	50s M	Rubella	3	Fever and rash

vaccination history, and the results of tests for antibodies against each virus may have been due to a failure to acquire immunity after vaccination, to a time-dependent decrease in the antibody level, or to the subject's faulty memory. In countries like Japan, where no structure has been established for the recording and storage of vaccination history, prevaccination antibody screening for measles, mumps, rubella, varicella, or the submission of laboratory evidence of immunity, is required at the time of entrance to work in medical institutions, although written documentation of immunization may be a better measure of immunity than serological positive results. HCP targeted for vaccination should be determined on the basis of the results thereof, and effective vaccination programs for susceptible HCP should be conducted. In such circumstances, providing vaccination with one dose of measles, mumps, rubella, and varicella for HCP who have serological positive results can be deemed equal to the written proof of immunization with two doses.

It is important for infection control practitioners to ascertain the immune status of HCP against measles, mumps, rubella, and varicella, and then provide an appropriate vaccination program for susceptible HCP. In the same way as newly hired HCP, immunity against measles, mumps, rubella, varicella is not reliable in previously hired HCP, especially those who were born before 1990, therefore, in this study, we carried out a prevaccination antibody screening on all previously hired HCP, and conducted a vaccination program for antibody-negative subjects. The prevaccination antibody screening in our study conducted between 2012 and 2013 revealed that the seroprevalence of measles, rubella and varicella was virtually the same as previous Japanese studies in the early first decade of the 2000s (Asari et al. 2003; Hatakeyama et al. 2004); and after vaccination, the antibody prevalence for measles, rubella and varicella among previously hired HCP reached levels as high as approximately 98%. However, in this study, the prevaccination seroprevalence of mumps was as low as 60% or lower, whereas the antibody prevalence for mumps in previously hired HCP increased successfully to about 80% after vaccination. In our hospital, additional vaccination is considered for HCP who test negative with antimumps antibodies. Seropositivity rate for measles, mumps, rubella, and varicella varies by each country (Fedeli et al. 2002; Almuneef et al. 2006; Celikbas et al. 2006; Trevisan et al. 2007; Weber et al. 2010) and would be influenced by the prevalence of these infectious diseases, the policy of immunization program, and the type of serological antibody testing. In the community setting, herd immunity is expected to be acquired when the prevalence of positive serologic results for measles, rubella and mumps is higher than the critical prevalence, ranging from 89-91% for measles, 84-90% for mumps, and 81-91% for rubella (Plans 2013). Given the transmission risk for both HCP and patients, the immunity level should be higher in the healthcare setting, and vaccination is recommended for all susceptible HCP unless they have contraindication. Immunized HCP can continue to work in all areas of the hospital and care for immunocompromised hosts after immunization without risk to the immunocompromised patient. It is also important to assure that trainees and students are immune to measles, mumps, rubella, and varicella because they have an appropriate opportunity for vaccination before becoming healthcare professionals. After a rubella epidemic occurred in Japan in 2013, the Ministry of Health, Labour and Welfare issued a statement which recommended vaccination against rubella; and as a result, in July, rubella vaccination was also carried out in our HCP who tested weakly positive for the relevant antibodies (antibody titers in EIA: 4.0-8.0). No case of measles, mumps, rubella, or varicella among HCP at our hospital has been reported in 2013.

In this study, the cost of antibody tests per person was less than the cost of a single vaccination. When vaccinating HCP without performing antibody tests beforehand, most Japanese HCP born before 1990 are assumed to not have received two inoculations; and therefore, according to the ACIP's standard criteria (Centers for Disease Control and Prevention 2011), written documentation of vaccination with two doses for measles, mumps, and varicella, or with one dose for rubella, are required in such cases. In such circumstances, our prevaccination antibody screening and subsequent immunization program for susceptible HCP may be useful and cost-effective. Prevaccination antibody screening is also considered if it is cost-effective (Centers for Disease Control and Prevention 2011).

Reported cases of secondary reactions to the vaccines administered to the recipients in this study were few in number, and there were no severe secondary reaction. Most of the secondary reactions which are common to measles, mumps, rubella, and varicella live attenuated vaccines are mild reactions such as fever and rash or local swelling, pain, and redness at the injection site; however, there have also been reports of rare cases of shock, anaphylaxis, acute thrombocytopenic purpura and severe secondary reactions specific to individual vaccines (Centers for Disease Control and Prevention 1996). Unnecessary vaccination and vaccine adverse events can be avoided by conducting a prevaccination antibody screening. National policies (e.g. mandatory or recommended) for immunization of HCP were implemented in various ways (Centers for Disease Control and Prevention 2011; Maltezou et al. 2011), and vaccination programs need to be conducted in consideration of concerns regarding the side effects of live vaccines, as well as each country's cultural background in regard to vaccination.

In conclusion, prevaccination antibody screening would be useful in Japan, from the perspective of the subjects' written records and own memories of their disease history and vaccination history, the prevention of secondary reactions associated with unnecessary vaccination, and cost-effectiveness. Through this study, we have been able to determine the exact situation regarding the immunity of HCP against measles, mumps, rubella and varicella, and have been able to construct a database for the recording and storage of evidence of immunity. This has made it possible to conduct a rapid survey of contacts even when accidental exposure occurs in hospital settings. In addition, in the year 2013, the expenses related to the prevaccination antibody screening of all newly hired HCP, as well as the vaccination of susceptible HCP, have started to be provided free of charge by our hospital. We need to continue educating and promoting awareness regarding measures against measles, mumps, rubella and varicella in all HCP, and to conduct efforts in immunization programs for HCP susceptible to these vaccine-preventable diseases.

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### **Conflict of Interest**

The authors declare no conflict of interest.

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