Persistence and Half-lives of Anti-measles and Anti-rubella Antibodies in Japanese Hospital Workers: A Longitudinal Study

Hideaki Kato^{1,2}, Masaaki Mori¹, Mari Oba³, Haruyo Kawahara¹ and Takeshi Kaneko¹

Abstract

Objective Antibody testing for endemic viruses in healthcare workers is used as an index of immunoprotection in Japan. However, it remains unclear how these antibody titers chronologically change and how they should be interpreted.

Methods We retrospectively collected two sets of antibody titers to measles and rubella, measured in 2013 and within the preceding 5 years, in adult hospital workers by an enzyme-linked immunoassay and calculated in international units. Subjects infected with, or vaccinated against, these viruses over this period were eliminated. Seropositivities and geometric mean titers were analyzed. Decay rates and half-lives of antibodies were calculated using a mixed-effect model according to the subjects' ages and antibody titers.

Results We analyzed 469 subjects for measles and 439 for rubella. Comparison with previous data revealed a mean measurement interval of 1,026 days between the previous and present tests, with seropositivity rates of 98.0% (previous) vs. 99.3% (present) for measles; 974 days and 90.7% vs. 94.9%, respectively, for rubella. For measles and rubella, 97.4% and 86.1%, respectively, of previously seropositive subjects remained positive in the present test. The geometric mean titers in the present and previous tests were 924.3 IU/mL and 853.2 IU/mL (measles) and 46.23 IU/mL and 40.78 IU/mL (rubella), respectively. In the mixed-effect model, measles and rubella antibody titers showed an increasing trend with age.

Conclusion Seropositivities against measles and rubella can remain high for more than 5 years. Among adult hospital workers in Japan, the antibody titers against measles and rubella have a sufficient lifetime persistence.

Key words: antibody, half-life, measles, rubella, persistence

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Introduction

In Japan, antibody testing in healthcare workers is widely used as an index of immunoprotection from epidemic infectious viral diseases—notably measles and rubella (1, 2). In the United States, routine testing for antibodies in healthcare workers is not considered to be necessary because a course of two vaccinations against each of these viruses is commonly given during childhood (2). In Japan, the history of vaccination programs is complicated (3). Measles vaccina-

tion was initiated in 1966 as a voluntary program to prevent nationwide outbreaks of measles, and routine single vaccination for children between 12 and 90 months of age was initiated in October 1978. Rubella vaccination was initiated in 1976, and routine vaccination was initiated in August 1977, but only for female junior high school students. In addition, a vaccination program in which a single dose of routine MMR (measles, mumps, and rubella) vaccine was provided to children between 12 and 72 months of age was initiated in April 1989, but it was terminated in April 1993 due to an increase in serious complications in the form of aseptic

¹Infection Control Department, Yokohama City University Medical Center, Japan, ²Department of Hematology and Clinical Immunology, Yokohama City University Graduate School of Medicine, Japan and ³Department of Biostatistics and Epidemiology, Yokohama City University, Japan
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Correspondence to Dr. Hideaki Kato, ekato@mac.com

meningitis. In 1994, routine rubella vaccination of children aged 12 to 90 months was restarted. However, this rubella vaccination was non-compulsory, and the coverage rate dropped sharply to 50-60% (3). It was not until April 2006 that routine administration of two doses of MR (measles-rubella) vaccine finally began in children older than 12 months of age. For the above reasons, reported antibody positivity rates among people now in their 30s and 40s are lower in men (73% to 86%) than in women (97% to 98%) (4); moreover, the majority of patients affected in the 2012 rubella outbreak were adult men born before 1979 (5, 6).

We estimated that none of the workers at our hospital who were older than 50 years of age at the time of this study (2013) had received measles and rubella vaccination. Men and women in their 20s to 40s were estimated to have had a single measles vaccination. Women aged in their 20s to 40s were estimated to have received one dose of rubella vaccine, and men in their 30s or 40s were considered to lack a rubella vaccination history. Workers in their early 20s were estimated to have received sufficient measles and rubella vaccination (i.e., two doses of each). Although the World Health Organization reported in 2015 that measles had been eliminated in Japan, an outbreak of measles occurred as recently as 2012 (7). Because the timing of vaccinations against measles and rubella has varied among generations, antibody titer tests are still considered to be important in the Japanese adult population. Japanese guidelines have suggested target protective antibody titers that healthcare workers must achieve against these viruses (8). It is accepted that antibody titers decrease exponentially with time in children without exposure to circulating virus (9-12). However, it remains unclear how antibody titers persist or decrease with age. It is also unclear whether antibody titers should be repeatedly measured. The aim of our study was to describe the temporal changes in measles and rubella antibody titers among adult hospital workers. We also estimated the decay rates and half-lives of measles and rubella antibodies in these workers.

Materials and Methods

Subjects

In July and August 2013, all workers at our hospital (Yokohama City University Medical Center; 726 beds and 1,839 workers) were requested to undergo serum testing for antibodies against measles and rubella, as detected by an enzyme-linked immunoassay (EIA) ("present test"). We also collected previous measles and rubella antibody titer data for our hospital workers for the preceding 5 years, as also detected by an EIA ("previous test"). If a subject had received three or more antibody tests during the previous 5 years, we collected their most recent past data. We were able to collect the results for 712 hospital workers who had undergone both present and previous antibody titer testing. Next, we

used a written questionnaire to confirm that these healthcare workers had had no history of infection by or vaccination against measles and rubella within the past 5 years. None of the healthcare workers answered that they had, to the best of their knowledge, been infected with either virus, however, some answered that they had been revaccinated between the present and previous antibody tests; these subjects were excluded from the analysis. Our final analysis included 469 subjects for measles and 439 for rubella. We obtained permission from the ethics committee of Yokohama City University Medical Center to obtain and analyze the data.

In the preceding 5 years, there had been no outbreaks of infection with either of the viruses at our hospital. In Yokohama City, which is home to 3.7 million people, there were 1,485 reported cases of measles and 12 of rubella in 2008; 43 and 4, respectively, in 2009; 32 and 3 in 2010; 12 and 15 in 2011; 4 and 113 in 2012; 2 and 624 in 2013; and 11 and 37 in 2014. These data were obtained courtesy of the Yokohama City Institute of Public Health (<http://www.city.yokohama.lg.jp/kenko/eiken/>; in Japanese). At our hospital, suspected cases of measles and rubella have been observed sporadically, which were not ruled out by either laboratory tests or clinical observations, and no secondary transmission has been reported.

Performing antibody tests

In the present and previous antibody tests, the blood samples obtained were submitted to an external laboratory (SRL, Tokyo, Japan). Antibody titers against measles and rubella were measured by EIAs using a Behring enzyme-linked immunosorbent assay (ELISA) Processor III (Siemens Healthcare Diagnostics Japan, Tokyo, Japan). EIAs for measles- and rubella-specific IgG were performed with commercial virus-specific IgG EIA kits [SEIKEN Measles IgG (II)-EIA and SEIKEN Rubella IgG (II)-EIA; Denka Seiken, Tokyo, Japan]. Optical density values were indexed in accordance with the manufacturer's instructions. The manufacturer demonstrated a correlation between the EIA titer and international units (IUs), namely $\text{IU (mIU/mL)} = 45 \times \text{EIA titer for measles}$ and $\text{IU} = 2.3 \times \text{EIA titer for rubella}$.

Statistical analysis

Antibody titers were summarized and compared on a log 10 scale and reported as back-transformed titers. EIA values of 4.0 or higher were considered to be positive. Negative values of less than 2.0 and equivocal values (values of 2.0 to 3.9) were considered to be negative in this study. To calculate the antibody decay rates and half-lives, values below the detection threshold for measles and rubella antibodies (value of <2.0 in the EIA) were assigned half the threshold value (1.0 in the EIA); those beyond the detection threshold (value of >128.0 in the EIA) were assigned double the threshold value (256.0 in the EIA). A two-tailed Mann-Whitney U-test was used for the comparison of continuous data. Fisher's exact test was used to analyze contingency between the groups. Correlations were evaluated with Spear-

Table 1. Demographic Profiles of Hospital Workers who Underwent Two Separate Antibody Titer Tests.

	Measles	Rubella
<i>n</i>	469	439
Male, <i>n</i> (%)	92 (19.6)	93 (21.2)
Job type, <i>n</i> (%)		
Physician	38 (8.1)	38 (8.7)
Nurse	307 (65.5)	305 (69.5)
Technician	47 (10.0)	44 (10.0)
Other	77 (16.4)	52 (11.8)
Present test, July to August 2013		
Age (years old, mean ± SD)	39.9 ± 10.0	40.1 ± 9.9
Geometric mean titer (EIA)	20.54 [19.05, 22.13]	20.10 [18.32, 22.08]
Geometric mean titer (IU/mL) §	924.3 [857.3, 995.9]	46.23 [42.14, 50.78]
Seropositive subjects, <i>n</i> (%)	453 (99.3)	406 (94.9)
Previous test		
Age (years old, mean ± SD)	37.3 ± 10.1	37.6 ± 10.0
Geometric mean titer (EIA)	18.96 [17.54, 20.46]	17.73 [15.92, 19.72]
Geometric mean titer (IU/mL) §	853.2 [789.3, 920.7]	40.78 [36.62, 45.36]
Seropositive subjects, <i>n</i> (%)	447 (98.0)	388 (90.7)

Measurement intervals are shown as means ± SD.

Geometric mean titers are shown as means and [95% CI].

§ Calculated on the basis of information supplied by the manufacturer.

Results

Seropositivity rates and geometric mean titers for subjects who had undergone previous and present testing

Demographic characteristics (gender, job type, age at time of previous and present tests); GMTs (expressed in both EIA units and IU/mL) and seropositivity rates for measles and rubella (EIA ≥4.0 as assigned by the manufacturer) in both past and present tests; and the mean measurement intervals (days) between the previous and present tests are shown in Table 1. The measurement intervals between the previous and present tests, as means for the group as a whole regardless of the measurement interval, were 1,026±576 days for measles and 974±528 days for rubella. Seropositivity rates were 99.3% in the present test and 98.0% in the previous test for measles, and 94.9% and 90.7% in the present and previous tests, respectively, for rubella. The GMTs were 20.54 in the EIA (924.3 IU/mL) in the present test and 18.96 (853.2 IU/mL) in the previous test for measles ($p=0.182$), and 20.10 (46.23 IU/mL) in the present test and 17.73 (40.78 IU/mL) in the previous test for rubella ($p<0.001$).

Correlation between gender or age and the antibody titer

As described above, in Japan, historical rates of vaccination of the population vary by gender and age. We analyzed the correlation between gender or age and the antibody titer. No significant differences in the GMT were found between men and women for measles (855 IU/mL vs. 940 IU/mL, respectively, $p=0.51$) or rubella (50.8 IU/mL vs. 45.1 IU/mL, $p=0.07$) in the present tests. Similarly, the GMTs did not significantly differ between men and women for measles (989 IU/mL vs. 851 IU/mL, $p=0.14$) or rubella (38.9 IU/mL vs. 41.4 IU/mL, $p=0.77$) in the previous tests. However, there was a positive correlation between age and the anti-measles antibody titer ($r=0.369$) and the anti-rubella antibody titer ($r=0.215$) in the present tests, and there was a negative correlation between age and the anti-measles antibody titer ($r=-0.108$) in the previous tests (Fig. 1).

Persistence of seroprevalence between the previous and present tests

Among the subjects examined, 457 (97.4%) and 378 (86.1%) subjects who were seropositive for measles and rubella, respectively, in the previous antibody test remained positive in the present test. None were seronegative in both the previous and the present tests for measles, and only three (0.7%) were seronegative for rubella in both the previous and present tests. Twelve subjects (2.5%) were seropositive for measles and 58 subjects (13.2%) were seropositive for rubella in only one of the two tests in the absence of re-vaccination or symptomatic infection (Table 2). The sero-

man's rank correlation coefficient, whereby $r<0.2$ indicated a meaningless correlation, $0.2\leq r<0.4$ indicated a weak correlation, $0.4\leq r<0.6$ indicated a moderate correlation, $0.6\leq r<0.8$ indicated a strong correlation, and $r\geq 0.8$ indicated a very strong correlation. Because the manufacturer of the EIA test supplied a demonstrated correlation, we used this correlation to calculate the geometric mean titers (GMTs), decay rates, and half-lives of the antibodies in IUs. In this study, the ± sign always indicates standard deviation. The rates of antibody decay were estimated using a mixed-effect model. This model had a fixed effect for age and a normally distributed random intercept. Measures were logarithmically transformed on a log10 scale before the analysis, resulting in a single exponential decay model of the untransformed data. Half-life estimates were obtained by transforming the decay rate and the boundaries of the 95% confidence intervals obtained from the fixed effect component of the model, as described previously (13). If a level increased over time, then the estimated half-life was considered to be infinity (∞). p values <0.05 were considered to be statistically significant. Statistical analyses were performed with the statistics software packages SPSS version 23 (IBM, Armonk, USA), GraphPad Prism 5 (GraphPad Software, San Diego, USA), and SAS version 9.3 (SAS Institute, Cary, USA).

Figure 1. Correlations of subject age and anti-measles and anti-rubella antibody titers in present and past tests. EIA: enzyme-linked immunoassay

Table 2. Antibody Serology for Measles and Rubella in Previous and Present Tests.

Seroprevalence in previous and present tests (no. of subjects, %)		Measles	Rubella
Positive > Positive		457 (97.4)	378 (86.1)
Seroconverted subjects	Negative > Positive	9 (1.9)	39 (8.9)
	Positive > Negative	3 (0.6)	19 (4.3)
Negative > Negative		0 (0)	3 (0.7)

prevalences for anti-measles and anti-rubella antibodies in the previous and present tests, plotted by gender and age, are shown in Fig. 2. For measles, more than 90% of the subjects were seropositive for anti-measles antibodies regardless of age or gender. For rubella, 66.7% of men in their 20s, 80.8% in their 30s, and 69.0% in their 40s remained seropositive for anti-rubella antibodies between the present and previous tests. Among women in their 60s, only 55.6% (n=5) remained seropositive for anti-rubella antibodies between the previous and present tests. The GMTs plotted by gender and age are shown in Fig. 3. The GMT for rubella in the subjects in their 20s to 40s was significantly lower than that of other age populations [15.11 (95% CI, 11.27-20.24) vs. 29.35 (95% CI, 16.43-52.42) in the EIA; $p=0.03$] in the previous test. However, in the present test, the GMT for rubella in men in their 20s to 40s were ele-

vated to 20.04 (95% CI, 15.47-25.96) in the EIA compared with that of men in their 50s and 60s [29.53 (95% CI, 16.38-53.23), $p=0.07$].

Statistical analysis of antibody half-lives

We used a mixed-effect model to calculate the decay rates according to an exponential decay model for measles and rubella antibody titers. The antibody titers commonly decrease exponentially unless a population group is exposed to wild-type epidemic viruses (12, 14); a simple exponential decay model can be used to represent this decrease (15). In the exponential decay model, circulating antibodies are at their highest soon after vaccination and subsequently decrease exponentially (16). We drew scatter graphs of the antibody titer against age for each virus in the previous and present tests; simple regression lines were then fitted to the

Figure 2. Seropositivities for anti-measles and anti-rubella antibodies at previous and present antibody tests plotted by gender and age at the time of the present antibody test. Columns indicate the seropositivity ratio in the previous and present antibody tests. EIA: enzyme-linked immunoassay

scatter graphs (Fig. 4). A visual inspection indicated that the linear model fit the data well. The antibody titers against measles and rubella showed increasing trends. The antibody titer decay rates (λ) in the present tests compared with the previous tests (log10-transformed) were: measles [mean (95% CI), -0.01018 (-0.004877, -0.01548) and rubella, -0.01192 (-0.004796, -0.01904). The antibody titers increased with age, and the half-lives of measles and rubella were infinite.

Discussion

The antibody titers for measles and rubella were well maintained for more than 5 years (mean measurement interval, 1,026 days for measles and 974 days for rubella), and the statistical half-lives of the titers in the population of adult hospital workers as a whole were estimated to be sufficient to cover the workers throughout their working life. Most adult subjects who were positive in a previous test for measles or rubella continued to be seropositive. Because it is difficult for some hospital workers to confirm their vaccination records at the time of recruitment, it is considered to be reasonable for workers to undergo measurement of the antibody titers against measles and rubella to determine immunoprotection, despite the existence of a documented vaccination record (8). Our present survey of hospital workers in July and August 2013 showed rates of seropositivity similar to those in previous studies of Japanese healthcare work-

ers (17, 18). The percentages of subjects who remained positive for antibodies against measles and rubella in two separate tests within 5 years were 97.4% and 86.1%, respectively. This result suggested that seropositivities for measles and rubella were well maintained in our study population.

The results of a mathematical analysis of a study of single MMR vaccination suggested that acquired measles antibody titers decrease chronologically and fall below the detectable threshold by 20 years after vaccination (19). In that report, the authors concluded that a single dose of MMR was not adequate for long-term immunoprotection unless the subjects were exposed to circulating measles virus. Another report showed a declining trend in seropositivity against measles over a period of as long as 25 years after a course of two measles vaccinations (20). In a follow-up study of single or two MMR vaccinations (21), the antibody titers to both measles and rubella decreased both 8 and 15 years after vaccination; the GMTs were 957 and 729 IU/mL for measles and 28 and 22 IU/mL for rubella at 8 and 15 years, respectively, after vaccination. These findings suggest that the antibody titers, once acquired through vaccination, decline as time passes, even when a course of two MMR vaccinations is given. One study from Taiwan attempted to determine the decay rates and half-lives of measles antibody. Lee et al. (22) found that the decay rate for vaccine-induced IgG against measles was 0.0253 in children (aged ≤ 6 years) who had received one dose of measles vaccine and 0.0114 for those who had received two doses (the half-lives were

Present test

Previous test

Figure 3. Geometric mean titers for anti-measles and anti-rubella antibodies, as assessed by enzyme-linked immunoassay (EIA) and plotted by gender and age at the time of tests.

Figure 4. Antibody titers against measles or rubella versus age in previous and present tests, and simple means. EIA, enzyme-linked immunoassay.

27 and 61 months, respectively). Their analysis was based on younger subjects, 12 to 72 months of age, after the completion of measles vaccination. It is accepted that the antibody titers decline shortly after the completion of vaccination (and for up to 15 years) (21), however, we consider these results to be insufficient for the prediction of long-term antibody persistence in adults older than 20 years of age. In contrast to the results of Lee et al., our results showed that the antibody titers increased with age. As a pos-

sible explanation, we consider that although the subjects who were older than 50 years of age (17.3% of 469 subjects analyzed for measles) had not received adequate measles vaccination, some of them may have been exposed to circulating wild measles and rubella viruses. It is also unclear why we found a positive correlation between age and the antibody titer for measles. However, the antibody titers for measles acquired by infection might be higher than those acquired by vaccination (23).

The GMT for rubella in our study population was significantly elevated from 17.73 in the EIA (40.78 IU/mL) in the previous test to 20.10 (46.23 IU/mL) in the present test ($p < 0.001$). Although it is difficult to explain why the GMT for rubella was elevated, a possible explanation for this increase is that the 2012 rubella epidemic in young men in Japan may have induced asymptomatic stimulation in our study population (5, 6). Our results showing the seropositivities for rubella by gender and age suggested that the antibody titers for rubella in men in their 20s to 40s were indeed variable, potentially due to a lack of appropriate vaccination; only 51 of 93 (54.8%) men in their 20s to 40s remained seropositive for rubella between the previous and present tests. The changes in the antibody titer within 5 years varied widely among individuals. When we focused on the data from those subjects whose antibody titers changed dramatically between the previous and present tests, we found that five workers in this group had high antibody titers (EIA ≥ 256) in the present test, despite low titers in the previous test (EIA ≤ 16), without revaccination or apparent infection with measles in the interim. Because the inter-test and intra-test variations in EIAs were less than 10% (data not shown) according to the manufacturer, we suspected that these subjects had incidentally encountered circulating viruses. Two of 22 workers in this group in the case of measles and three of 47 workers in this group in the case of rubella worked in the pediatric outpatient department or in admission care. However, the large remainder was not engaged in pediatric care. We were unable to determine the causes of these antibody titer changes in individual subjects, despite careful questioning and the exclusion of subjects who had apparently been infected or revaccinated. A long-term observational study has also shown that antibody titers to endemic viruses, including measles and rubella, have long half-lives (over 50 years), and that titers and their changes in value vary widely among individuals (13). An observational cohort study in pregnant Iranian women has shown that many factors affect individual antibody titers against measles and rubella (24). Some of these healthcare workers likely encountered infected patients incidentally, but had nevertheless remained asymptomatic. Measles symptoms can be modified in adults or in vaccinated or infected people (19). Incidental infection thus likely boosted the workers' antibody titers without their developing obvious symptoms. Another possibility is that incidental and asymptomatic infection with one virus can elicit the production of antibodies to other viruses through nonspecific B-cell activation (25). A limitation associated with the present study is that we were unable to obtain personal histories of measles or rubella vaccination or infection. Accurate histories could provide a more accurate statistical model for chronological changes in the antibody titers.

The Japanese Society for Infection Prevention and Control revised its guideline for healthcare workers in 2014 (8); the Society suggests that repeated antibody titer measurement is not required if subjects are confirmed to have high levels of

antibody against measles and rubella (≥ 16 and ≥ 8 , respectively, on EIA) in two separate antibody tests 4 or 5 years apart. Our results support this policy that repeated antibody titer measurement is unnecessary when subjects are confirmed in two tests to have adequate antibody titers against measles and rubella. The GMTs in our study group were 924.3 IU/mL against measles and 46.23 IU/mL against rubella in the present tests. An antibody titer of 1,000 IU/mL (EIA value, 22.2) has been reported to be sufficient to prevent measles infection, and 500 IU/mL (EIA value, 11.1) is reportedly sufficient to prevent the development of symptoms (26). A cut-off value of 10 IU/mL is widely used for immunoprotection against rubella (27). The mean age of the hospital workers in our study was 40 years (range, 22 to 65) at the time of the present tests. Our results therefore revealed that, in general, in adult hospital workers, antibodies against measles and rubella persisted at levels sufficient to protect against infection or symptom development. Our results support those of a meta-analysis by Anders et al. (28), who found that the rate of secondary failure of measles vaccination was less than 0.02%.

A potential limitation associated with this study is that we were unable to obtain accurate individual vaccination or infection histories for measles and rubella for all of the study subjects. Our model therefore cannot be used to explain individual changes in the antibody titer. Although our results suggested that antibody titers against measles and rubella are well maintained in the healthcare worker population as a whole, we still consider antibody titer testing to play an important role in monitoring healthcare workers in Japan. Indeed, our results suggested that the antibody titers against rubella in men in their 20s to 40s should be closely monitored.

This study was approved by the ethics committee of Yokohama City University Medical Center (D1307026).

The authors state that they have no Conflict of Interest (COI).

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