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Changes of Antibody Associated with Cell-Mediated Immunity in College Students During Two Years after Rubella Vaccination

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Abstract

Objective: This study measured cell-mediated immunity (CMI) and serum antibody levels against rubella to clarify antibody changes associated with CMI during 2 years after vaccination.

Methods: The study subjects were 64 college students in two groups: 38 subjects who (having exhibited hemagglutination-inhibition (HI) anti-rubella antibody titers of ≤ 1:16) had been vaccinated with a rubella vaccine 2 years previously (Group 1); and 26 subjects who (having exhibited HI titers ≥ 1:32) had not been vaccinated 2 years previously (Group 2). All students were tested for IgG antibody levels (by enzyme-linked immunosorbent assay) and CMI (by interferon-γ (IFN-γ release assay).

Results: The IgG antibody and IFN-γ values decreased significantly in Group 1 during the 2 years post-vaccination, while antibody titers in Group 2 did not decrease over this interval. The proportion of Group-1 individuals with HI antibody titers ≤ 1:16 increased to 27/38 (71.1%) at two years following vaccination, compared with 6/26 (23.1%) in Group 2. No correlation of IgG antibody titers was observed in Group 1 between one month and two years after vaccination. However, a strong correlation ($r=0.85$, $p<0.00001$) was detected in Group 2 between two years ago and the present. The correlation of IFN-γ values in Group 1 between one month and two years after vaccination was 0.614 ($p<0.00005$). When the subjects were classified by CMI status, the numbers of individuals who were intermediate and negative for IgG antibody at two years after vaccination were 1 and 0 of 13 subjects, 3 and 1 of 9 subjects, and 3 and 2 of 16 subjects in Group 1, respectively, while the antibody-positive status was maintained in all subjects in Group 2.

Conclusion: The IgG antibody and IFN-γ values decreased in distinct ways during the 2 years of the study; the persistence of the seropositivity was associated with CMI status.

Keywords: Cell-mediated immunity; Interferon-γ release assay; Antibody; Plasma cells; Reinfection

Introduction

Rubella virus is a member of the genus Rubivirus and belongs to the family *Togaviridae*. Although rubella is a relatively mild disease, rubella infection in pregnant mothers can lead to problems with congenital rubella syndrome (CRS) in the fetus. In Japan, the rubella vaccine was administered only to female junior high school students between 1977 and 1994, with the goal of preventing the occurrence of CRS in prospective offspring (rather than the goal of eliminating rubella epidemics). The Japanese NIH estimated that approximately 0.7 and 4.5 million female and male adults (respectively) of reproductive age remained susceptible as of 2003 [1], given the failure to perform catch-up vaccination in this cohort. Instead, measurement of rubella antibody titers has been recommended as a means for identifying vaccination candidates in Japan. Such a screen would be valuable as a part of antenatal screening; vaccination of susceptible individuals would prevent CRS at next pregnancy, and vaccination of susceptible medical and nursing students or new hospital workers would prevent nosocomial infection. Generally speaking, individuals who test positive for anti-rubella antibody (by hemagglutination-inhibition (HI) assay or enzyme-linked immunosorbent assay (ELISA)) are immune. However, there have been many reports regarding subjects who had previously tested antibody-positive but nonetheless contracted rubella, leading to CRS in offspring [2-9]. To decrease CRS risk, a research group supported by the Japanese government has (since 2004) recommended rubella vaccination not only for those who are negative by HI assay (antibody titers<1:8), but also for subjects with low titers (≤ 1:16). However, our previous study demonstrated that 42.6% of those with pre-vaccination HI antibody titers ≤ 1:16 again exhibited low titers (≤ 1:16) at two years after vaccination [10]. In addition, our previous study of cellular and humoral immunity in college students with low antibody titers [11] demonstrated that some subjects with positive but low antibody titers were negative in cell-mediated immunity (CMI) assays, which may explain why rubella reinfection can occur in seropositive individuals. Taillardet et al. showed that B cells that receive T-cell help generate antibody-secreting progeny cells that produce significantly more antibody than B cells that are activated by antigen in the absence of T-cell help [12].

The purpose of the present study was to further clarify associations between cellular and humoral immunity during the extended period of two years post-vaccination, a longer interval than the 6 to 8 weeks post-vaccination examined in our previous study [11]. The present

study primarily reports the data at two years post-vaccination, but some data from the previous study are incorporated here to permit assessment of changes in antibody and interferon-γ levels.

Subjects and Methods

The collection and use of human materials for the present study were approved by the Ethics Committee on Human Subjects of the Kawasaki Medical School (625-4), and in accordance with the ethical statements of the Declaration of Helsinki. Informed consent was obtained from each subject. The volunteers enrolled in this study comprised 64 healthy college students, each of whom was asked to present the school with written verification of their past history of vaccination.

Among the pool of 64 subjects, 38 individuals (Group 1) were newly enrolled from the 39 college students in the previous study [11], which examined rubella-specific cell-mediated and humoral immunity following vaccination in students with HI antibody titers <1:16. As part of the previous study, these subjects had been vaccinated two years ago with a monovalent, live, attenuated rubella vaccine against the Matsuura strain (Biken, Osaka, Japan; Lot R1701). The remaining 26 students (Group 2) enrolled for this study corresponded to individuals who had shown HI antibody titers ≥ 1:32 when screened two years ago at the college. Group-2 members were confirmed to be seronegative for IgM antibody against rubella virus at entry onto the present study. Samples from Groups 1 and 2 were assessed to determine the following parameters: general antibody levels using a hemagglutination-inhibition (HI) assay; IgM and IgG antibody levels by enzyme-linked immunosorbent assay (ELISA); and CMI against rubella virus using an interferon-γ release assay.

Antibodies against Rubella

Anti-rubella antibody levels were measured using the HI assay kit (Denka Seiken, Tokyo, Japan) according to the manufacturer's instructions. HI antibody titers <1:8 were defined as negative. The concentrations of IgG and IgM antibodies in sera were measured with an ELISA assay kit (Denka Seiken, Tokyo, Japan) according to the manufacturer's instructions.

Interferon-γ release assay

The antigen used for the interferon-γ release assay was the Bayler strain of rubella virus, provided as a suspension that contained 1.2 × 107 plaque-forming units per dose prior to inactivation by ultraviolet radiation (at 5,000 J/m^2). The inactivated virus (80 μL/dose) was added to heparinized whole blood (800 μL) from each individual subject and the mixture was cultivated at 37°C for approximately 32-36 h to elicit the secretion of interferon-γ from T-cells after recognition of the antigen. These co-cultivations were initiated within 2 h after the drawing of each blood samples. After incubation, the supernatants were collected, and interferon-γ concentrations were quantified by ELISA (Human INF gamma Platinum ELISA, e-Bioscience, San Diego, CA). For positive and negative control reactions, phytohemagglutinin (final concentration, 2.5 μg/mL in phosphate-buffered saline) and lysate after incubation without rubella virus, respectively, were added to the blood instead of antigen. The interferon-γ values were calculated by subtracting values in negative control wells from values in antigen-stimulated wells. The threshold (cut–off) was determined as mean + 2 standard deviations (SDs) for seronegative subjects without a past history of vaccination or natural infection in our preliminary experiment.

Statistical analysis

Anti-rubella IgG antibody titers and interferon-γ values over the 2 years of the study were compared using a two-tailed paired t test after logarithm-scale transformation. The correlation was performed using Spearman's rank correlation test. Comparisons of IgG antibody and interferon-γ levels after vaccination among groups of CMI-positive, intermediate, and negative individuals were evaluated using a two-tailed one-way ANOVA test with a post-hoc two-tailed unpaired t-test on data that had been subjected to logarithmic transformation. Differences with $p<0.05$ were considered significant. For the statistical analyses, an IgG antibody titer of <2.0 index units was expressed as 1.0 index unit.

Results

Characteristics of subjects

The subjects' characteristics, which are summarized in Table 1, included history of vaccination and HI antibody titers in Group 1 at two years after vaccination and those at two years later in Group 2. These records of Group 1 regarding history of rubella vaccination showed that 8 students had been vaccinated once two years ago, and 26 had been vaccinated twice previously; 4 had been vaccinated at least once, given that vaccination history before the last vaccination was unknown. The time of last vaccination was more than 2 years ago for all of the subjects. The records of Group 2 regarding history of the vaccination revealed that one student had not been vaccinated before; 17 had been vaccinated once, more than two years ago; 2 had been vaccinated twice, more than two years ago; the vaccination history was not known for the remaining 6 subjects.

Group 1								
History of vaccination	HI antibody titers at two years after vaccination							
	<1:8	1:8	1:16	1:32	1:64	1:128	1:256	total
One dose	0	1	3	2	1	1	0	8
Two doses	1	11	9	3	1	1	0	26
At least one dose	0	1	1	2	0	0	0	4
Total	1	13	13	7	2	2	0	38

Group 2								
History of vaccination	HI antibody titers two years later							
	<1:8	1:8	1:16	1:32	1:64	1:128	1:256	total
No vaccination	0	0	1	0	0	0	0	1
One dose	0	0	1	10	3	1	2	17
Two doses	0	0	0	1	1	0	0	2
Unknown	0	0	4	1	0	1	0	6
Total	0	0	6	12	4	2	2	26

Table 1: Characteristics of the subjects classified by HI antibody titer. Group-1 subjects were vaccinated 2 years ago because of pre-existing HI antibody titers ≤ 1:16. Group-2 subjects were not vaccinated 2 years ago because of pre-existing HI antibody titers ≥ 1:32.

Changes in antibody levels

At approximately one month after vaccination, 31/38 (81.6%) subjects in Group 1 (with pre-existing HI antibody titers ≤ 1:16) exhibited HI antibody titers ≥ 1:32, but titers remained ≥ 1:32 in 11/38 (28.9%) subjects at two years after vaccination, as shown in Table 2. In Group 2, in which individuals had HI antibody titers ≥ 1:32 two years previously, HI antibody titers remained ≥ 1:32 in 20/26 (76.9%) subjects after two years without vaccination (Table 2).

Pre-existing HI antibody		Two years after vaccination			
Group 1		<1:8	1:8	1:16	≥ 1:32
<1:8	8	1	1	1	5
1:8	14	0	10	3	1
1:16	16	0	2	9	5
Total	38	1 (2.6%)	13 (34.2%)	13 (34.2%)	11 (28.9%)
		two years later			
Group 2		<1:8	1:8	1:16	≥ 1:32
≥ 1:32	26	0	0	6 (23.1%)	20 (76.9%)

Table 2: Changes in HI antibody titers at one month and two years after vaccination in Group 1, and during that two-year interval without vaccination in Group 2.

The IgG antibody titers in Group 1 decreased in the two years after vaccination, with values (mean ± SD) falling from 22.32 ± 19.11 to 8.89 ± 8.16 index units ($p<0.001$). When the subjects were classified according to CMI status (negative, intermediate, or positive) at two years after vaccination, the IgG antibody values (mean ± SD) from one month after vaccination *vs.* two years after vaccination were 19.1 ± 22.8 *vs.* 6.9 ± 6.7 ($p>0.05$), 20.6 ± 13.5 *vs.* 7.3 ± 5.5 ($p=0.01$), and 27.5 ± 18.5 *vs.* 12.6 ± 10.7 index units ($p<0.05$), respectively, as shown in Figure 1. There were no significant differences in the antibody titers at 2 years after vaccination among the groups with CMI-positive, intermediate, or negative status in Group 1. Similarly, no significant change ($p>0.05$) in the antibody titers (mean ± SD) in Group 2 (with pre-existing HI antibody titers >1:32) was observed from two years ago to present (54.45 ± 63.43 *vs.* 59.11 ± 81.4 index units, respectively). When Group-2 subjects were classified based on CMI-negative, -intermediate, or -positive status, the IgG antibody values (mean ± SD) from two years ago *vs.* present were 63.0 ± 74.7 *vs.* 59.6 ± 79.8 ($p>0.05$), 43.1 ± 40.3 *vs.* 59.7 ± 86.1 ($p>0.05$), and 60.4 ± 72.5 *vs.* 58.1 ± 77.2 index units ($p>0.05$), respectively. Thus, there were not significant changes in the antibody titers during the 2 years among groups of CMI-positive, intermediate, and negative status in Group 2.

Fig. 1

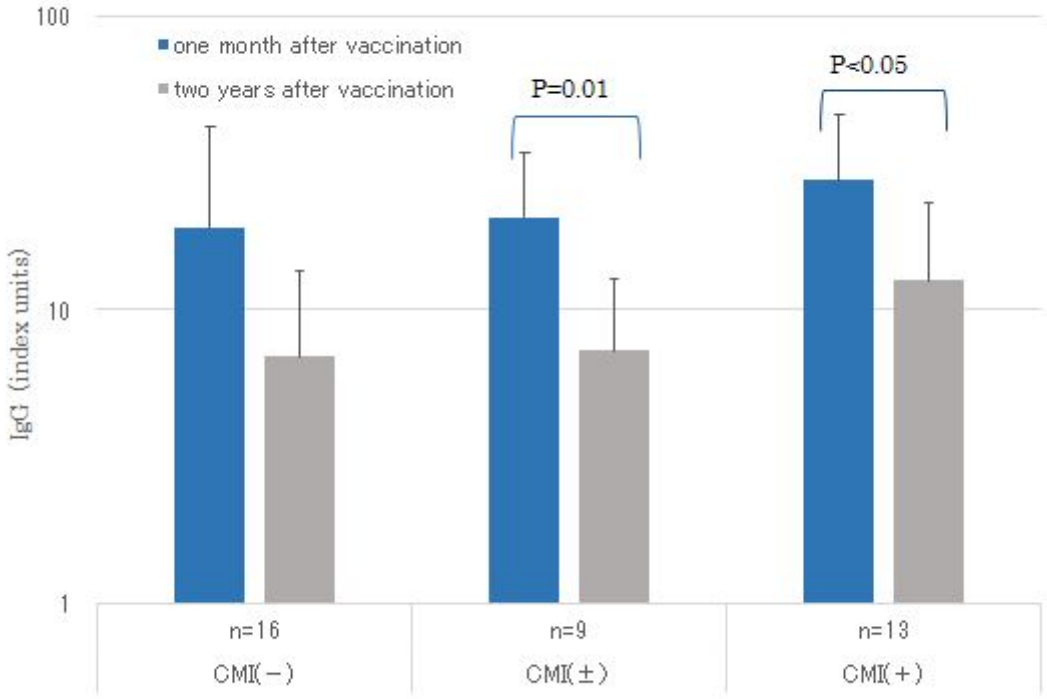

Figure 1: Changes in IgG antibody titers in subjects classified based on cell-mediated immunity (Data are presented as mean ± SD. Changes in anti-rubella IgG antibody (ELISA) values at one month and two years after vaccination were compared using a two-tailed paired t test after logarithm-scale transformation of the data. Comparison of the IgG antibody levels after vaccination among subjects with CMI-positive, intermediate, and negative status was performed by logarithmic transformation of the data, followed by a two-tailed ANOVA test with a post hoc two-tailed unpaired t-test).

The coefficient of correlation in IgG antibody titers in Group 1 was 0.385 ($p<0.02$) between pre-vaccination and one month after vaccination, but 0.147 ($p>0.05$) between pre-vaccination and two years after vaccination, and 0.139 ($p>0.05$) between one month and two years after vaccination, as shown in Figure 2. In contrast, in Group 2 the coefficient of correlation in IgG antibody titers between two years ago and present was 0.85 ($p<0.00001$).

Fig. 2

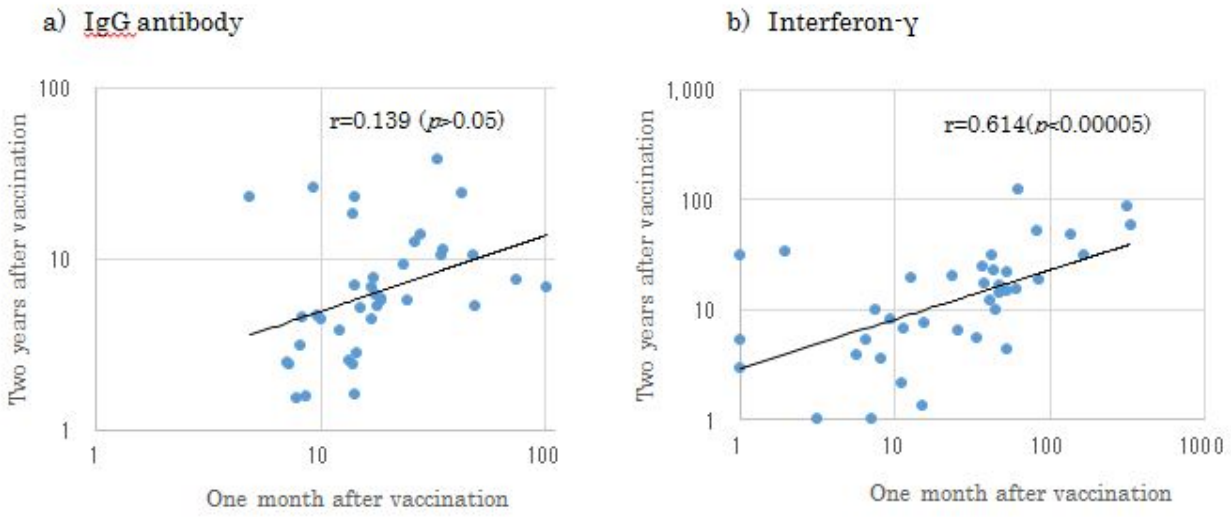

Figure 2: Coefficient of correlation in IgG antibody values and interferon-γ titers between one month and two years after vaccination in Group 1 (The correlation was performed using Spearman's rank correlation test).

Changes in interferon-γ production

Group-1 subjects exhibited CMI-positive status in 13/38 (34.2%), 22/38 (57.9%), and 13/38 (34.2%) individuals at pre-vaccination, one month after vaccination, and two years after vaccination, respectively, as shown in Table 3. The interferon-γ titers (mean ± SD) decreased from 51.13 ± 73.38 to 20.98 ± 24.79 ($p<0.005$) during the two years after vaccination. When Group-1 subjects were classified by CMI-negative, intermediate, and positive status at two years following vaccination, the interferon-γ values (mean ± SD) of one month *vs.* two years after vaccination were 13.3 ± 13.8 *vs.* 4.7 ± 2.7 ($p<0.05$), 47.8 ± 19.1 *vs.* 15.3 ± 3.0 ($p=0.001$), and 99.9 ± 109.9 *vs.* 45.0 ± 30.4 pg/mL ($p>0.05$), respectively (Fig. 3). The interferon-γ values of the CMI-positive group at two years after vaccination were significantly higher than those of the CMI-intermediate group ($p<0.005$) or those of the CMI-negative group ($p<0.0005$), as shown in Figure 3.

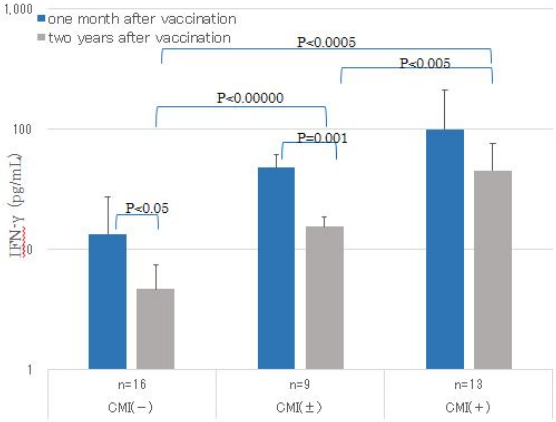

Figure 3: Changes of interferon-γ titers in the subjects classified based on cell-mediated immunity (Data are presented as mean ± SD. Changes in anti-rubella IgG antibody (ELISA) values one month and two years after vaccination were compared using a two-tailed paired t test after logarithm scale transformation. Comparison of interferon-γ levels after vaccination among groups of CMI positive, intermediate, and negative status was performed by logarithmic transformation of the data, followed by a two-tailed ANOVA test with a post-hoc two-tailed unpaired t-test).

The coefficient of correlation in interferon-γ titers in Group 1 was 0.848 ($p<0.00001$) between pre-vaccination and one month after vaccination, 0.504 ($p<0.002$) between pre-vaccination and two years after vaccination, and 0.614 ($p<0.00005$) between one month and two years after vaccination (Figure 2).

Group 1				
IgG antibody		Negative	Intermediate	Positive
CMI(-)	16	2 (12.5%)	3 (18.8%)	11 (68.8%)
CMI(±)	9	1 (11.1%)	3 (33.3%)	5 (55.6%)
CMI()	13	0 (0%)	1 (7.7%)	12 (92.3%)
	38	3	7	28

Table 3: Changes in IgG antibody titers associated with cell-mediated immunity at 2 years after vaccination in Group 1 (Group-1 subjects were vaccinated 2 years ago because of pre-existing HI antibody titers ≤ 1:16).

Association of antibody and interferon-γ

When the Group-1 subjects were classified by CMI status at two years after vaccination, the IgG antibody-positive status was maintained in 12/13 (92.3%) CMI-positive subjects, 5/9 (55.6%) CMI-intermediate subjects, and 11/16 (68.8%) CMI-negative subjects during the two years post-vaccination, as shown in Table 3. Of the 11 subjects who were CMI-negative and antibody-positive at two years, 7 (63.6%) had high antibody levels (≥ 1:32) at one month after vaccination. Additionally, when Group-1 subjects who were IgG antibody-negative at 2 years were classified by CMI status, none were CMI-positive, one was CMI-intermediate, and two were CMI-negative at two years after vaccination (Table 3). In contrast, Group-2 subjects who were originally antibody-positive remained antibody-positive two years later, regardless of CMI-positive or -negative status.

Discussion

Pre-existing virus–specific antibody represents the first line of defense against reinfection, but the best protection is likely to be elicited by a combination of strong humoral and cell-mediated immune responses. However, there have been few reports regarding the combination of humoral and cellular immunity against rubella [11,13-16]. The present study focused on the antibody changes associated with cellular immunity over a two-year interval following vaccination.

The interferon-γ release assay focuses on interferon-γ secretion by effector cells *via* T-cell memory, a process that is mediated almost entirely by CD4+ T-cells [17]. The interferon-γ levels in Group 1 (subjects who had been vaccinated because pre-existing HI antibody titers were ≤ 1:16) decreased significantly at 2 years after vaccination. In addition, the proportions of patients in this group with CMI-negative status at pre-vaccination, one month, and two years following vaccination were 42.1%, 28.9%, and 42.1%, respectively. Whereas, CMI negativity in Group 2 (subjects who exhibited pre-existing HI antibody titers ≥ 1:32 and therefore had not been vaccinated) was 26.9% at 2 years, but this value could not be compared to previous data, which was not collected. Nonetheless, CMI negativity was observed at a lower frequency in Group 2 than in Group 1. Even among Group-2 subjects with CMI-negative status, all showed HI antibody titers ≥ 1:16. The proportion of CMI-positive status among subjects with higher antibody levels (HI antibody titers ≥ 1:32) was higher than that in subjects with lower antibody levels (HI antibody titers ≤ 1:16). Thus, seropositive antibody status is thought to be maintained for a longer period in subjects with higher antibody levels, even in individual who are CMI-negative. In the present study, more than half of the subjects who were seropositive and CMI-negative had exhibited HI antibody levels ≥ 1:32 two years previously.

The antibody titers decreased significantly in Group 1, but did not decrease in Group 2. All of the previously seropositive subjects in Groups 1 and 2 remained seropositive at 2 years after vaccination. Kato et al. reported that 86% of previously seropositive hospital workers remained seropositive for over 3~5 years [18]. However, previous studies have shown that antibody responses in humans do not reach steady levels until approximately 2~4 years after infection or vaccination [19-21]. Therefore, the timing of the present study (2 years after vaccination) may have been too early to detect antibody levels in the steady period. However, the proportion of individuals with HI antibody titers ≤ 1:16 (the cut-off at which rubella vaccination is recommended in Japan) increased progressively over time in Group-1 subjects to 27/38 (71.1%) at two years following vaccination from 7/38 (18.4%) at one month after vaccination. Our previous study [10] also demonstrated that proportion of individuals with HI antibody titers ≤ 1:16 increased from 11.5% (14/122) at one month following vaccination to 42.6% (52/122) at two years after vaccination. These observations are consistent with data indicating that, in cases with high levels of pre-existing antibody, booster vaccination provides only a temporary increase in antibody production, with antibody levels often declining to pre-booster-vaccination levels within 2~3 years [22]. In addition, 21 (75%) of 28 subjects vaccinated twice in Group 1 exhibited HI antibody levels ≤ 1:16 at 2 years after the more recent vaccination, indicating that the second vaccination did not increase antibody titers to the levels that are recommended in Japan; this second vaccination is recommended worldwide. These data suggested that the recommended cut-off of HI antibody levels ≤ 1:16 for vaccination may not be a tight cut-off, given that many such subjects may need to be re-vaccinated every few years.

Correlation (r=0.504~0.848) of interferon-γ levels in Group 1 was observed among subjects prior to study start, at one month post-vaccination, and at 2 years post-vaccination. In contrast, unlike the interferon-γ correlation of the antibody titers was not found between 2 years post-vaccination *vs.* prior to study start or between 2 years and one month after vaccination; only a weak correlation ($r=0.385$, $p<0.02$) was found between prior to study start and one month after vaccination in Group 1. A much stronger correlation ($r=0.85$, $p<0.00001$) was detected in Group 2 between two years ago and the present. This study demonstrated that the changes in antibody titer, in response to the booster effect of vaccination, apparently differed from changes in interferon-γ levels. Immunity is often multifactorial; presumably other factors, beyond the booster effect of vaccination, influenced both humoral and cellular immune responses after vaccination.

Conversion from seropositive to seronegative antibody status in the 2 years after vaccination increased along with changes of CMI status from intermediate to negative. None, one, and two of the subjects with CMI-positive, intermediate, and negative statuses in Group 1 became antibody-negative at two years after vaccination, respectively. In contrast, seropositive status was retained in 10 of 11 subjects (91%)

that were CMI positive; compare that value to the 56~69% of CMI-intermediate and negative subjects who remained seropositive during this two-year interval (Table 3). Humoral immunity is derived primarily from memory B cells, plasma cells, and memory T cells. All of the seronegative subjects in this study were thought to have memory B cells, because IgM antibody was not detected after vaccination. Thus, the factors important to the distinct responses would have to consist of plasma cells and/or memory T cells. In the plasma cell imprinted lifespan model, there are T-cell independent and dependent antibody responses [23]. Availability of helper T cells can have a profound impact on antibody response and on the function of plasma cells. Short–lived plasma cells are T-cell dependent and exhibit a lifespan of 1~3 years [23]; thus changes in antibody levels during the first 2 years after vaccination, as seen in the present study, are likely to be associated with short-lived plasma cells.

Another factor associated with antibody response is the existence of genetic polymorphisms in the human leucocyte antigen (HLA) gene; a small number of specific HLA alleles are consistently associated with rubella-specific antibody titers [24,25]. Indeed, Kennedy et al. detected single nucleotide polymorphisms that are associated with variations in interferon-γ secretion and map near the genes encoding butyrophilin and cytokine receptors [26,27].

In conclusion, antiviral protective immunity depends on the interplay between T cells and B cells to efficiently protect against disease. Therefore, the recommendation of rubella vaccination for individuals with HI antibody titers ≤ 1:16 is thought to be loose; an approach that incorporates CMI responsivity will be needed to enhance longer-persisting immunity against reinfection. Measurement of CMI against major viral diseases, like CMI against tuberculosis, will play an important role for estimation of the efficacy of vaccines and decisions regarding vaccination candidates in the future.

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Disclosure

The authors declare no conflict of interest.

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