DOCTORAL THESIS

Factors Predicting Rubella Vaccination and Antibody in Pregnant Women in Japan:

A Report from Pregnant Women Health Initiative

（日本の妊婦における風疹ワクチン接種と抗体保有を予測する因子）

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Factors Predicting Rubella Vaccination and Antibody in Pregnant Women in Japan: A Report from Pregnant Women Health Initiative

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Abstract: This study aimed to identify the factors predicting rubella vaccination status based on self-reported data and the presence of sufficient rubella antibody titers in pregnant women in Japan. We used the results of the nationwide questionnaire survey conducted at obstetric facilities in the Pregnant Women Health Initiative Project (PWHI), with 23 participating hospitals recruiting pregnant women from June 2018–November 2019. We extracted age, the number of deliveries, educational level, household income, pre-pregnancy smoking, and knowledge of rubella from questionnaires and medical records. We analyzed the association of rubella vaccination status and antibodies with each of these factors. We found that the number of previous deliveries, educational level, annual household income, smoking before pregnancy, and knowledge of rubella were factors predicting self-reported rubella vaccination status, while age and the number of previous deliveries were identified as factors predicting the presence of sufficient rubella antibody titers (32 folds or higher). Women considering pregnancy should be immunized against rubella to prevent congenital rubella syndrome in the future. Furthermore, social policies are needed to strongly encourage vaccination, especially for all citizens who were not given the opportunity or missed the chance to be vaccinated against rubella.

Keywords: rubella; rubella vaccine; rubella antibody; pregnant women; Japan; vaccination status; pregnant women health initiative

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1. Introduction

Rubella is a viral disease characterized by fever, rash, and lymphadenopathy. When a pregnant woman susceptible to rubella is infected with the rubella virus before approximately 20 weeks of pregnancy, her baby may develop congenital rubella syndrome (CRS) [1,2]. In Japan, a rubella outbreak occurred from 2012–2013; consequently, 45 babies were born with CRS [3–7]. Thus, the Ministry of Health, Labour, and Welfare issued the "Guidelines for the Prevention of Specific Infections: Rubella" to eliminate CRS prevalence in newborns as soon as possible and rubella by fiscal 2020 [8,9]. However, another rubella outbreak occurred from 2018–2019, and five infants were born with CRS [4,5]. Although the ministry aimed to constrain the prevalence of rubella before the Tokyo Olympic Paralympic Games, scheduled to be held in 2020, cases of CRS were registered in 2020 and 2021 [3]. The rubella outbreaks, repeating every few years, are associated with changes in the Japanese rubella vaccination program (Figure 1). In Japan, routine vaccination against rubella began in August 1977 [10]. With an emphasis on preventing infection in pregnant women, girls

in junior high school were vaccinated en masse at school. In April 1995, the vaccination target was changed to infants of both sexes to prevent outbreaks of rubella in the society as a whole, and as a time-limited measure, vaccinations were administered to boys and girls in junior high school from April 1995 to September 2003. Furthermore, in June 2006, the previous one-dose vaccination regime was changed to a two-dose vaccination regime for one-year-old children (first period) and children in the year before entering elementary school (second period) [11]. Due to these program changes, men over 42 years of age currently had no opportunity to be vaccinated against rubella before adulthood, and some women of reproductive age have also missed vaccination opportunities [11,12]. These people became the hosts of the current rubella epidemic in Japan. Since 2020, the number of people infected with rubella has been decreasing [3]. This is presumably attributable to the restriction on human activities due to the coronavirus disease 2019 (COVID-19) pandemic. When human activities resume in the future, rubella outbreaks are expected to recur.

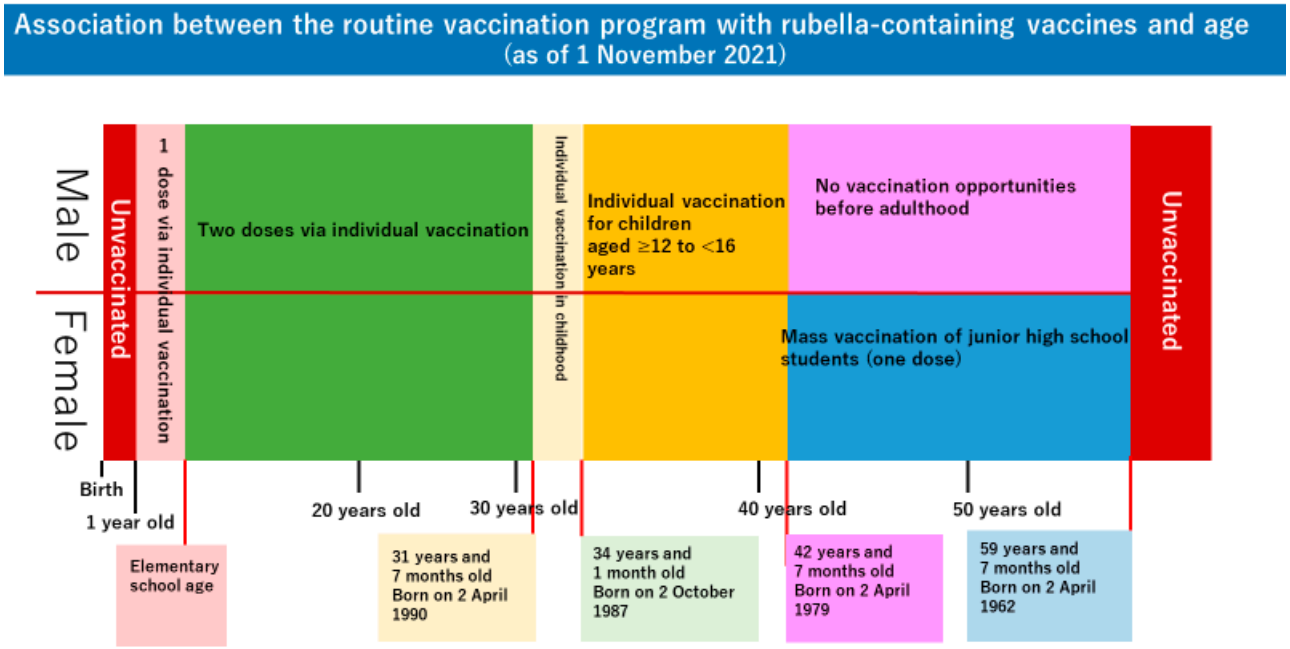

Figure 1. Association between the routine vaccination program with rubella-containing vaccines and age (as of 1 November 2021).

Pregnant women in Japan undergo screening for infectious diseases, including rubella, in the first trimester and receive necessary follow-up during pregnancy and after delivery based on screening results. To investigate the effects of this screening for infectious diseases on long-term maintenance and enhancement of maternal and child health, the Pregnant Women Health Initiative Project (PWHI) was launched. The PWHI is a study designed by Miyagi et al. and funded by the Health Labour Sciences Research Grant in 2018. This project conducts questionnaire surveys on hepatitis B, hepatitis C, rubella, human T-cell leukemia virus type 1 (HTLV-1), syphilis, and cervical cancer (human papillomavirus: HPV), for which pregnant women are screened in the first trimester. This study examines pregnant women for awareness and knowledge of rubella, vaccination, antibody seroprevalence, and socio-statistical or economic characteristics.

The following questions will allow effective implementation of preventive measures against rubella in Japan in the future: "Do pregnant women in Japan understand the extent of the rubella outbreak and take actions to protect their fetuses from CRS?" and "What characteristic makes pregnant women more likely to receive rubella vaccines and be seropositive for rubella antibodies?" We published the results of an interim analysis of data collected on rubella at a limited number of hospitals in Yokohama City [13]. In the present study, using the results of the nationwide questionnaire survey conducted at obstetric

facilities in the PWHI, we investigated rubella vaccination and seroprevalence of rubella antibodies in pregnant women and aimed to identify factors predicting these features.

2. Materials and Methods

The PWHI was launched in April 2018, and 23 participating hospitals recruited pregnant women from June 2018–November 2019. Although these hospitals are dispersed across Japan, the most considerable number (11 hospitals) is located in Kanagawa Prefecture, where the PWHI was developed. Pregnant women (excluding those aged less than 20 years) scheduled for delivery at the participating hospitals received a written explanation of the objectives of the study and a leaflet containing the study participant number and QR (quick response) code from obstetricians at the participating hospitals. The women who wished to participate submitted the consent form with the study participant number to the obstetricians at the participating hospitals. Later, the participants sent an email to the study administration office at the address indicated by the QR code to complete the registration. After registration, the study administration office sent an email containing the link to the online questionnaire survey to the participants. At the survey site, they entered their study participant number and answered the questions. The questionnaire survey was conducted with SurveyMonkey®, a paid online survey tool with enhanced security. In the questionnaire survey, each participant was asked about the highest educational level, annual household income, lifestyle before pregnancy, physical conditions, results of screening for six infectious diseases (hepatitis B, hepatitis C, syphilis, rubella, HTLV-1, and HPV), vaccination status of the participant and her partner, and the knowledge of each infectious disease. The study collaborators provided data on the screening results of the participants, including age, the number of previous deliveries, and rubella antibody titers. The report rubella antibody titers (hemagglutination inhibition) were selected from the following options: "16 folds or lower" and "32 folds or higher". From these data, those associated with rubella were extracted and analyzed. Regarding rubella vaccination status, the participants were asked, "Have you ever received rubella vaccination (including measles-rubella vaccines)?" and answered from the following options: "yes", "no", and "unknown". To investigate factors predicting (self-reported) rubella vaccination status, participants who answered "unknown" were excluded, and the remaining participants were divided into the "yes" group and the "no" group. The characteristics of each group were compared. The following characteristics were extracted from the questionnaire survey responses and the data provided by the study collaborators: age, the number of previous deliveries, highest educational level, annual household income, smoking before pregnancy, rubella antibody titers, and knowledge of rubella ("Do you know about the outbreak of rubella in 2012–2013 in Japan?" and "Do you think rubella can affect your baby's health directly?"). Subsequently, to investigate factors predicting the presence of sufficient rubella antibody titers, the same population was divided into two groups according to rubella antibody titers: the $\leq$16-fold group and the $\geq$32-fold group. The characteristics of each group were compared. In Japan, HI titers are widely used to evaluate rubella antibody titers. The most common international titer is the IgG international unit (IU/mL), and a titer of 10 IU/mL or higher is considered to be most protective against rubella [14]. The number of HI titers converted to IgG varies slightly across testing companies but is generally considered to be 15 IU/mL (12.340–18.476) [15]. The Clinical Guidelines for Obstetrical Practice in Japan recommend rubella vaccination for women who wish to conceive with HI titers $\leq$ 16 [16]. Therefore, in this study, we divided women into two groups: those with HI titers $\leq$ 16 and those with HI titers $\geq$ 32. In addition, rubella vaccination was recommended after delivery for pregnant women with HI titers $\leq$ 16.

2.1. Statistical Analysis

Binary logistic regression analysis was performed to examine whether there were differences in the rubella vaccine status based on socioeconomic and clinical characteristics of the participants (e.g., age, number of previous deliveries, or educational level) and whether those differences remained after adjusting for each background variable. The same analysis was performed for the rubella antibody status. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. The level of significance was set to $p < 0.05$ (two-tailed). JMP Pro 15.0.0 (SAS Institute Japan, Tokyo, Japan) for Windows was used for statistical analysis.

2.2. Ethical Considerations

The protocol of this study was approved by each participating institution's ethics review board at the Yokohama City University, aligning with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

3. Results

A total of 3003 pregnant women completed the questionnaire survey. Figure 1 shows the flowchart of the selection of study participants. Table 1 shows the study participants' characteristics and responses to the questionnaire. The most common age group was in the 30s, and primiparous participants accounted for 47.0%. The proportion of pregnant women with a rubella antibody titer of 16 folds or lower was 29.8%. Those who reported having received rubella vaccines accounted for 68.1%, while those who reported that their partners had received them accounted for 48.6%.

Table 1. Study participants' characteristics and responses to the questionnaire (N = 3003).

Characteristics and Responses to the Questionnaire	*n*	Rate, %
Age group		
20–29	707	23.9
30–39	1938	64.5
40–49	348	11.6
Number of deliveries		
0	1410	47.0
1	1141	38.0
2	368	12.3
≥3	84	2.8
Educational level		
≤High school graduate	573	19.1
Junior college graduate	1016	33.8
≥University graduate	1399	46.6
No answer	15	0.5
Characteristics and Responses to the Questionnaire	***n***	**Rate, %**
Household income (ten thousand yen)		
<500	921	30.7
≥500, <700	827	27.5
≥700	1088	36.2
No answer	167	5.6

Table 1. *Cont.*

Characteristics and Responses to the Questionnaire	*n*	Rate, %
Did you smoke before pregnancy?		
No	2590	86.2
Yes	408	13.6
No answer	5	0.2
Rubella antibody titer (HI)		
≥32	2102	70.2
≤16	893	29.8
Do you know about the outbreak of rubella in 2012–2013 in Japan?		
Yes	1900	63.3
No	1068	35.6
Unknown	35	1.2
Do you think rubella can affect your baby's health directly?		
Yes	1082	36.0
No	1921	64.0
Have you ever had the rubella vaccination?		
Yes	2046	68.1
No	327	10.9
Unknown	630	21.0
Has your partner ever had the rubella vaccination?		
Yes	1459	48.6
No	335	11.2
Unknown	1209	40.3

Table 2 shows the results of the comparison of characteristics between participants who reported to have received rubella vaccines and those who reported having been unvaccinated. Of the 3003 participants who completed the questionnaire survey, 790 answered a few questions regarding vaccination, educational level, annual household income, and so on by conveying that "they do not know or want to answer" or did not answer those questions. After these participants were excluded, 2213 participants were analyzed (Figure 2). Although younger participants were more likely to report being vaccinated, no significant difference was observed between age groups. Participants with fewer previous deliveries were more likely to report being vaccinated. The adjusted ORs were 0.53 (95% CI: 0.38–0.68, $p < 0.0001$) for participants with one previous delivery and 0.35 (95% CI: 0.24–0.50, $p < 0.0001$) for those with two or more previous deliveries, compared to those with no previous delivery. Participants with a higher educational level were more likely to report being vaccinated (adjusted OR = 1.89, $p = 0.0003$ for those with a junior college degree; adjusted OR = 2.02, $p < 0.0001$ for those with a university or higher degree compared to those with a high school diploma), and those with an annual household income of seven million yen or more were more likely to report being vaccinated than those with an annual household income of fewer than five million yen (adjusted OR = 1.42, $p = 0.0366$). Participants who had not smoked before pregnancy were more likely to report being vaccinated (adjusted OR = 1.90, $p = 0.0002$). Rubella antibody titers were not associated with vaccination status. Participants who correctly answered the questions regarding the knowledge of rubella ("Do you know about the outbreak of rubella in 2012–2013 in Japan?" and "Do you think rubella can affect your baby's health directly?") were more likely to report being

vaccinated (adjusted OR = 1.63, $p = 0.0002$; adjusted OR = 1.33, $p = 0.0458$, respectively, for the questions).

Table 2. Factors predicting rubella vaccination among pregnant women ($N = 2213$).

	Have You Ever Had the Rubella Aaccination?		OR (95% CI)	*p* Value **	Adjusted * OR (95% CI)	*p* Value **
	Yes	No				
Age group						
20–29	460	66	1.20 (0.78–1.83)	0.4078	1.49 (0.96–2.34)	0.0773
30–39	1228	193	1.09 (0.75–1.59)	0.6390	1.28 (0.87–1.89)	0.2095
40–49	227	39	1.00		1.00	
Number of deliveries						
0	980	111	1.00		1.00	
1	687	124	0.63 (0.48–0.83)	0.0009	0.58 (0.38–0.68)	<0.0001
≥2	248	63	0.45 (0.32–0.63)	<0.0001	0.35 (0.24–0.50)	<0.0001
Educational level						
≤High school graduate	275	83	1.00		1.00	
Junior college graduate	653	98	2.01 (1.45–2.78)	<0.0001	1.89 (1.34–2.67)	0.0003
≥University graduate	987	117	2.55 (1.86–3.48)	<0.0001	2.02 (1.42–2.88)	<0.0001
Household income (ten thousand yen)						
<500	549	113	1.00		1.00	
≥500, <700	574	88	1.34 (0.99–1.81)	0.0561	1.28 (0.93–1.76)	0.1302
≥700	792	97	1.68 (1.25–2.25)	0.0005	1.42 (1.02–1.96)	0.0366
Did you smoke before pregnancy?						
No	1717	236	2.28 (1.66–3.12)	<0.0001	1.90 (1.35–2.67)	0.0002
Yes	198	62	1.00		1.00	
Rubella antibody titer (HI titer)						
≥32×	1324	198	1.13 (0.87–1.47)	0.3505	1.15 (0.88–1.51)	0.3100
≤16×	591	100	1.00		1.00	
Do you know about the outbreak of rubella in 2012–2013 in Japan?						
Yes	1327	171	1.68 (1.31–2.15)	<0.0001	1.63 (1.26–2.11)	0.0002
No	588	127	1.00		1.00	
Do you think rubella can affect your baby's health directly?						
Yes	1151	210	1.58 (1.22–2.06)	0.0007	1.33 (1.01–1.75)	0.0458
No	764	88	1.00		1.00	

* Model includes all variables for which values are shown in the column. ** The red colored numbers indicate $p < 0.05$.

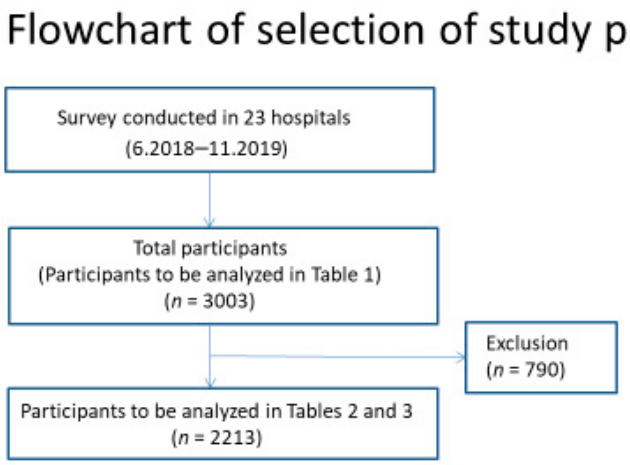

Figure 2. Flowchart of selection of study participants. Of the 3003 participants who completed the questionnaire survey, 790 did not answer questions regarding vaccination, educational level, annual household income, and so on or responded with "I do not know or want to answer." After excluding these participants, 2213 participants were analyzed as shown in Tables 2 and 3.

Table 3. Factors predicting rubella antibody titer among pregnant women (*N* = 2213).

	Rubella Antibody Titer (HI Titer)		**OR (95% CI)**	***p* Value ****	**Adjusted * OR (95% CI)**	***p* Value ****
	≥32×	**≤16×**				
Age group						
20–29	351	175	0.55 (0.39–0.77)	0.0006	0.60 (0.42–0.86)	0.0048
30–39	962	459	0.57 (0.42–0.78)	0.0005	0.55 (0.40–0.76)	0.0003
40–49	209	57	1.00		1.00	
Number of deliveries						
0	676	415	1.00		1.00	
1	611	200	1.88 (1.53–2.29)	<0.0001	1.85 (1.50–2.27)	<0.0001
≥2	235	76	1.90 (1.43–2.53)	<0.0001	1.91 (1.42–2.56)	<0.0001
Educational level						
≤High school graduate	222	136	1.00		1.00	
Junior college graduate	516	235	1.35 (1.03–1.75)	0.0273	1.13 (0.86–1.49)	0.3743
≥University graduate	784	320	1.50 (1.17–1.03)	0.0014	1.23 (0.93–1.63)	0.1402
Household income (ten thousand yen)						
<500	426	236	1.00		1.00	
≥500, <700	454	208	1.21 (0.96–1.52)	0.1033	1.03 (0.81–1.31)	0.8144
≥700	642	247	1.44 (1.16–1.79)	0.0010	1.13 (0.89–1.43)	0.3261
Did you smoke before pregnancy?						
No	1354	599	1.24 (0.94–1.62)	0.1239	1.04 (0.78–1.39)	0.7771
Yes	168	92	1.00			

Table 3. *Cont.*

	Rubella Antibody Titer (HI Titer)		OR (95% CI)	*p* Value **	Adjusted * OR (95% CI)	*p* Value **
	≥32×	≤16×				
Have you ever had the rubella vaccination?						
Yes	1324	591	1.13 (0.87–1.47)	0.3505	1.16 (0.88–1.52)	0.2889
No	198	100	1.00		1.00	
Do you know about the outbreak of rubella in 2012–2013 in Japan?						
Yes	1054	444	1.25 (1.04–1.51)	0.0200	1.13 (0.93–1.37)	0.2335
No	468	247	1.00		1.00	
Do you think rubella can affect your baby's health directly?						
Yes	610	242	1.24 (1.03–1.50)	0.0236	1.17 (0.96–1.42)	0.1218
No	912	449	1.00		1.00	

* Model includes all variables for which values are shown in the column. ** The red colored numbers indicate $p < 0.05$.

Table 3 shows the results of the comparison of characteristics between the ≥32-fold and ≤16-fold groups according to rubella antibody titers. Participants in their 40s were more likely to have a rubella antibody titer of 32 folds or higher. The adjusted ORs were 0.60 for those in their 20s ($p = 0.0048$) and 0.55 for those in their 30s ($p = 0.0003$), compared to those in their 40s. Multiparous participants were more likely to have a rubella antibody titer of 32 folds or higher than primiparous participants. The adjusted ORs were 1.85 for those with one previous delivery ($p < 0.0001$) and 1.91 for those with two or more previous deliveries ($p < 0.0001$), compared to primiparous participants. No association was observed with the educational level, annual household income, smoking before pregnancy, self-reported rubella vaccination status, or knowledge of rubella.

4. Discussion

The questionnaire survey of pregnant women revealed two things. First, the factors predicting self-reported rubella vaccination status included the number of previous deliveries, educational level, annual household income, smoking before pregnancy, and the knowledge of rubella. Second, the factors predicting the presence of sufficient rubella antibody titers included age and the number of previous deliveries.

To protect pregnant women and their fetuses from rubella infection, vaccination before pregnancy is essential. We initially believed we could determine the rubella vaccination rate in pregnant women by asking about their vaccination status in a questionnaire survey. We wanted to identify factors predicting the vaccination status of pregnant women and use these factors to raise awareness of rubella vaccination. The results of this questionnaire survey showed that pregnant women with a higher educational level or a higher annual household income were more likely to report being vaccinated. Those who had not smoked before pregnancy and those who had knowledge of rubella were also more likely to report being vaccinated. Based on these results, we inferred that social background, lifestyle, and knowledge of the disease affected the vaccination status. If our assumption is correct, educational and raising awareness activities may effectively increase the vaccination rate. However, we could not explain why the vaccination rate was lower as the number of previous deliveries increased. Since postpartum vaccination is recommended for women with low rubella antibody titers in Japan, the vaccination rate should increase with more

previous deliveries. However, the results contradicted this assumption. This may be because the results of this questionnaire survey might not accurately reflect the rubella vaccination rate. In this questionnaire survey, healthcare professionals were not required to check maternal and child health handbooks directly or ask pregnant women to submit their records of vaccination to determine their vaccination status. In Japan, vaccination certificates are not provided, making it difficult to know the vaccination history. Consequently, we examined "self-reported" rubella vaccination status and found that many participants (21.0%) answered that they did not know their vaccination status. While the rubella vaccination program has been changed in Japan, women in their 40s should have been vaccinated through mass vaccination at school when they were junior high school students [11]. However, this questionnaire survey showed that 39 of the 346 participants in their 40s (11.3%) reported not being vaccinated. We also excluded women in their 40s from our analysis because of the possibility of a larger recall bias. However, the results remained unchanged. This indicates that some participants completed the questionnaire survey without confirming they were vaccinated. The lack of association between self-reported rubella vaccination status and rubella antibody titers in this questionnaire survey also supports the possibility that self-reported rubella vaccination status is inaccurate. Trevisan et al. reported that self-reported vaccination history did not accurately predict immunity in five vaccine-preventable infectious diseases [17]. We consider that "self-reported" rubella vaccination status does not reflect actual rubella vaccination status but rather reflects the welfare of pregnant women in their own and their fetuses' health. The reason why self-reported vaccination rates decrease as the number of deliveries increases is unknown. However, we suspect that women pay less attention to their bodies when they have more children and, as a result, may not check their vaccination history before pregnancy. Therefore, with a higher number of deliveries, pregnant women's awareness of their vaccination history may become ambiguous, causing them to respond "not vaccinated" or "unknown" even when they are vaccinated.

The factors predicting the presence of sufficient rubella antibody titers included age and the number of previous deliveries. In Japan, the rubella vaccination program has been changed several times since the first introduction of rubella vaccines. As of 1 August 2018, the vaccination rate is high in women aged 39 years and 4 months or older (less than 56 years and 4 months) because they received a dose of the vaccine through mass vaccination when they were junior high school students. The vaccination rate in women aged 30 years and 10 months to 39 years and 4 months is considered low despite available opportunities for vaccination because the program was in transition. Women aged 28 years and 10 months to 30 years and 10 months had an opportunity to receive only one dose of the vaccine in their childhood. Women aged less than 28 years and 10 months had opportunities to receive two doses of the vaccine in their childhood [5]. Rubella antibody titers may reflect the vaccination status of these age groups. We consider that the results showed high antibody seroprevalence, especially in participants in their 40s, in whom the vaccination rate is reported to be high (although they had received only one dose). As described above, postpartum rubella vaccination is recommended for pregnant women with a rubella antibody titer of 16 folds or lower in Japan [16]. Women who have experienced pregnancy and delivery are expected to have their rubella antibody titers measured in screening during a previous pregnancy and to have been vaccinated during the postpartum period if their antibody titers are low. Thus, we consider that many pregnant women with at least one previous delivery had a rubella antibody titer of 32 folds or higher. Both age and the number of previous deliveries were expected to reflect the actual vaccination rate. Although antibody titers do not accurately indicate vaccination status, rubella antibody titers can be a factor in predicting vaccination status in a situation where the vaccination rate based on a questionnaire survey is less reliable. Unfortunately, the "undetectable rubella antibody titer (<8 folds)" and the "low antibody titer (8–16 folds)" were not distinguished for analyses in this questionnaire survey. To facilitate the entry of data by the study collaborators, the format was designed to group participants with an antibody titer of 16 folds or lower into

one group. If we had analyzed antibody titers by dividing participants with an undetectable antibody titer and those with a low antibody titer, the antibody titers might have more accurately reflected rubella vaccination status.

The association between rubella antibodies in pregnant and prepregnant women and epidemiological factors has been reported in each country and region. Facciola et al. reported in a survey of pregnant women in Sicily, Italy, that rubella antibodies statistically correlate with age and educational levels [18]. Jonas et al. reported in a survey of women of reproductive age in Namibia that rubella antibody seroprevalence was higher in urban residents than in rural residents [19]. AlShamlan et al. reported in a survey of pregnant women in Saudi Arabia that rubella antibody seroprevalence decreases with increasing age [20]. Liu et al. reported in a survey of women preparing for pregnancy in rural China that women in regions with the low gross domestic product (GDP) per capita were more likely to be susceptible to rubella than women in regions with high GDP per capita [21]. Although factors affecting rubella antibodies vary among these reports, all reports concluded that susceptibility to rubella is affected by the environment where women live and their age. In Japan, no study has investigated rubella antibodies and multiple epidemiological factors in pregnant women. Regarding rubella antibody seronegativity in pregnant women by birth year, Hanaoka et al. and Okuda et al. reported that rubella antibody seronegativity is low in some age groups because the rubella vaccination program has been changed over time in Japan [22,23]. The results of the present study showed that rubella antibody titers in pregnant women in Japan were associated with age groups (probably affected by the changes in the rubella vaccination program) and the number of previous deliveries. Although our findings are partially consistent with those reported overseas, antibody titers did not differ among pregnant women with different educational levels or household incomes in Japan. Although the Japanese rubella vaccination program changes have caused confusion and a temporary decrease in the vaccination rate, the program can be regarded as having provided vaccines significantly to the target population.

In some people, rubella antibodies do not sufficiently increase or gradually decrease after rubella vaccination. In this questionnaire survey, 38% of primiparous women had a rubella antibody titer of 16 folds or lower. One of the future challenges of rubella preventive measures in Japan appears to be how to make women accurately understand their vaccination and immune status for rubella before their first pregnancy and how to vaccinate them before pregnancy if necessary. As reflected in the 'self-reported' vaccination status, it is possible that, in current Japan, the interest of pregnant women in their own and their fetuses' health is affected by their social backgrounds and knowledge of the disease. Raising awareness and educational activities on rubella should be extensively implemented to encourage more women to practice preventive behaviors before pregnancy. Furthermore, it is important to eliminate rubella from women considering pregnancy and their families and from the entire society. The World Health Organization (WHO) currently recommends two vaccination doses for both boys and girls at an early age to eliminate rubella. By following this recommendation, some areas have successfully eliminated rubella [24,25]. Japan has also now adopted the program recommended by WHO. However, when rubella vaccination was first initiated, only adolescent girls were eligible. As a result, boys were not vaccinated. Furthermore, when the program was switched to vaccinating young boys and girls, vaccination coverage among women in the eligible years declined. These people became the hosts of the current rubella epidemic in Japan. Thus, a program was initiated in 2019 to provide opportunities to take a rubella antibody test and be vaccinated for men aged 41–58 years [11,26,27]. Some local governments subsidize rubella antibody tests and vaccines for women who are considering pregnancy [28–30]. A government policy promoting these programs and eliminating low rubella antibody prevalence could lead to the elimination of rubella from Japan.

The present study has some limitations. First, many surveyed items are based on self-reported questionnaire data. Specifically, the vaccination status was not verified by healthcare professionals, as described above. Second, the participating institutions

are not evenly distributed regarding location. Although they are located across Japan, the most significant number is located in Kanagawa Prefecture, where the PWHI was developed. While all participating institutions are general hospitals that accept high-risk pregnant women, low-risk pregnant women in Japan often select small maternity hospitals. The vaccination rate and antibody seroprevalence may vary among regions and selected obstetric facilities. Third, the survey response rate could not be calculated. We surveyed 23 hospitals in Japan but do not know the number of people recruited overall. The study participant selection may be biased toward those who are health literate and have been vaccinated, thus affecting generalization. Next studies should have a way to collect information on the people approached and then participating to be able to calculate a response rate.

Based on the questionnaire survey of pregnant women, the present study identified the number of previous deliveries, educational level, annual household income, smoking before pregnancy, and knowledge of rubella as factors predicting self-reported rubella vaccination status, while age and the number of previous deliveries were identified as factors predicting the presence of sufficient rubella antibody titers. To immunize more women against rubella before pregnancy, the entire Japanese population needs to understand rubella, including women considering pregnancy. To this end, raising awareness and educational activities on rubella are essential.

5. Conclusions

The present study identified factors predicting rubella vaccination status based on self-reported data and the presence of sufficient rubella antibody titers in pregnant women in Japan. Although the prevalence of rubella decreased during 2020–2021 because of the COVID-19 pandemic, the Japanese rubella preventive measures are fragile with a possibility of a resurgence with increased human activities. The effect of herd immunity is also questionable. To prevent CRS in the future, women considering pregnancy should be immunized against rubella. Furthermore, social policies are necessary to strongly encourage vaccination, particularly for the citizens who had not received the opportunity or missed the chance to be vaccinated against rubella.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author, K.K., upon reasonable request.

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References

1. What Is Rubella? Available online: https://www.niid.go.jp/niid/ja/kansennohanashi/430-rubella-intro.html (accessed on 28 September 2021).
2. Lambert, N.; Strebe, P.; Orenstein, W.; Icenogle, J.; Poland, G.A. Rubella. *Lancet* **2015**, *385*, 2297–2307. [CrossRef]
3. Epidemiological Information on Rubella: As of 30 June 2021. Available online: https://www.niid.go.jp/niid/images/epi/rubella/2021/rubella210630.pdf (accessed on 28 September 2021).
4. Oishi, K.; Satoh, H.; Tanaka-Taya, K. Re-emerging Rubella Epidemic and Public Health Measures in Japan. *Yakugaku Zasshi-J. Pharm. Soc. Jpn.* **2020**, *140*, 901–904. [CrossRef] [PubMed]
5. Ujiie, M. Rubella Resurgence in Japan 2018–2019. *J. Travel Med.* **2019**, *26*, taz047. [CrossRef] [PubMed]
6. Nationwide Rubella Epidemic—Japan. 2013. Available online: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6223a1.htm (accessed on 7 April 2022).
7. Jindai, K.; Funaki, T.; Nishijima, T.; Takakura, S.; Noda, H.; Miyake, K. Towards rubella elimination in Japan. *Lancet Infect. Dis.* **2018**, *18*, 713–714. [CrossRef]
8. Guidelines for the Prevention of Specific Infectious Diseases Related to Rubella. Available online: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000041928.pdf (accessed on 28 September 2021).
9. Hori, A.; Wada, K.; Smith, D.R. A Socio-Demographic Examination of Adults Responding to Governmental Vaccination Recommendations during the Japanese Rubella Outbreak of 2013. *PLoS ONE* **2015**, *10*, e0129900. [CrossRef] [PubMed]
10. Ueda, K. Epidemiology of rubella and congenital rubella syndrome in Japan before 1989. *Vaccine* **2016**, *34*, 1971–1974. [CrossRef] [PubMed]
11. Changes in the Routine Vaccination System for Rubella. Available online: https://www.niid.go.jp/niid/ja/allarticles/surveillance/2468-iasr/related-articles/related-articles-474/9037-474r02.html (accessed on 28 September 2021).
12. Rubella Vaccination Coverage. Available online: http://idsc.nih.go.jp/iasr/24/277/dj2771.html (accessed on 10 April 2022).
13. Iwata, A.; Kurasawa, K.; Kubota, K.; Sugo, Y.; Odagami, M.; Aoki, S.; Okuda, M.; Yamanaka, T.; Miyagi, E. Factors Predicting Rubella Vaccination among Pregnant Women in Japan: An Interim Report from the Pregnant Women Health Initiative. *Jpn. J. Infect. Dis.* **2021**, *74*, 337–343. [CrossRef] [PubMed]
14. Trevisan, A.; Mason, P.; Nicolli, A.; Maso, S.; Bertoncello, C. Rubella Serosurvey Among Future Healthcare Workers. *Front. Public Health* **2021**, *9*, 741178. [CrossRef] [PubMed]
15. Correlation between HI and EIA Titers and Conversion of Antibody Titers. Available online: https://www.niid.go.jp/niid/images/idsc/disease/rubella/RubellaHI-EIAtiter_Ver7.pdf (accessed on 7 April 2022).
16. Guidelines for Obstetrical Practice in Japan 2020. Available online: https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf (accessed on 28 September 2021).
17. Trevisan, A.; Frasson, C.; Morandin, M.; Beggio, M.; Bruno, A.; DaVanzo, E.; Di Marco, L.; Simioni, L.; Amato, G. Immunity against infectious diseases: Predictive value of self-reported history of vaccination and disease. *Infect. Control. Hosp. Epidemiol.* **2007**, *28*, 564–569. [CrossRef] [PubMed]
18. Facciola, A.; Squeri, R.; Genovese, C.; Alessi, V.; La Fauci, V. Perception of rubella risk in pregnancy: An epidemiological survey on a sample of pregnant women. *Ann. Ig. Med. Prev. E Comunita* **2019**, *31*, 65–71.
19. Jonas, A.; Cardemil, C.V.; Beukes, A.; Anderson, R.; Rota, P.A.; Bankamp, B.; Gary, H.E.; Sawadogo, S.; Patel, S.V.; Zeko, S.; et al. Rubella immunity among pregnant women aged 15–44 years, Namibia, 2010. *Int. J. Infect. Dis.* **2016**, *49*, 196–201. [CrossRef] [PubMed]
20. AlShamlan, N.A.; AlOmar, R.S.; AlOtaibi, A.S.; Almukhadhib, O.Y.; AlShamlan, A.A.; Alreedy, A.H.; Zabeeri, N.A.; Darwish, M.A.; Al Shammri, M.A. Seroprevalence of rubella virus among pregnant women: A 4-year registered-based study from family medicine and obstetric clinics in Saudi Arabia. *Int. J. Clin. Pract.* **2021**, *75*, e14156. [CrossRef] [PubMed]
21. Liu, F.; Zhang, S.; Liu, J.; Wang, Q.; Shen, H.; Zhang, Y.; Liu, M. Sociodemographic and economic characteristics of susceptibility to rubella among women preparing for pregnancy in rural China. *Int. J. Infect. Dis.* **2017**, *62*, 112–118. [CrossRef] [PubMed]
22. Hanaoka, M.; Yamaguchi, K.; Yamaguchi, S. Impact of vaccination policy on changes in rubella virus antibody in Japanese pregnant women. *J. Public Health* **2020**, *30*, 823–828. [CrossRef]
23. Okuda, M.; Yamanaka, M.; Takahashi, T.; Ishikawa, H.; Endoh, M.; Hirahara, F. Positive rates for rubella antibody in pregnant women and benefit of post-partum vaccination in a Japanese perinatal center. *J. Obstet. Gynaecol. Res.* **2008**, *34*, 168–173. [CrossRef] [PubMed]
24. Rubella Vaccines: WHO Position Paper—July 2020. Available online: https://apps.who.int/iris/handle/10665/332952 (accessed on 7 April 2022).
25. Orenstein, W.A.; Cairns, L.; Hinman, A.; Nkowane, B.; Olive, J.M.; Reingold, A.L. Measles and Rubella Global Strategic Plan 2012-2020 midterm review report: Background and summary. *Vaccine* **2018**, *36*, A35–A42. [CrossRef] [PubMed]
26. Hori, A.; Yoshii, S.; Isaka, Y.; Wada, K. Factors associated with participation in an ongoing national catch-up campaign against rubella: A cross-sectional internet survey among 1680 adult men in Japan. *BMC Public Health* **2021**, *21*, 292. [CrossRef] [PubMed]
27. Norizuki, M.; Hori, A.; Wada, K. Factors associated with adults' actions to confirm their own rubella immune status in Japan's drive toward rubella elimination: Cross-sectional online survey of non-healthcare workers in their 20s to 40s. *Environ. Health Prev. Med.* **2021**, *26*, 77. [CrossRef] [PubMed]

28. Mori, Y. Summary of the special symposium 'Towards Elimination of Rubella'. *Vaccine* **2020**, *38*, 6344–6345. [CrossRef] [PubMed]
29. Urabe, C.T.; Tanaka, G.; Oshima, T.; Maruyama, A.; Misaki, T.; Okabe, N.; Aihara, K. Comparing catch-up vaccination programs based on analysis of 2012-13 rubella outbreak in Kawasaki City, Japan. *PLoS ONE* **2020**, *15*, e0237312. [CrossRef] [PubMed]
30. Operation to Eliminate Rubella in Kanagawa Prefecture. Available online: http://www.pref.kanagawa.jp/docs/ga4/cnt/f420454/ (accessed on 10 April 2022).

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Original Article

Factors Predicting Rubella Vaccination among Pregnant Women in Japan: an Interim Report from the Pregnant Women Health Initiative

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SUMMARY: Following the 2018 rubella outbreak in Japan, this study aimed to assess rubella prevention measures based on the vaccination and immunization status of pregnant women in Japan. Our cohort study involved 3 local core hospitals in Yokohama City, and a total of 666 pregnant women were recruited between June 2018 and September 2019 and answered an online questionnaire. In total, 67.5% of the pregnant women had received rubella vaccination. The rate of rubella vaccination among pregnant women in the present survey was lower than that among age-matched female participants in a nationwide survey conducted in 2018. Overall, the study results showed that pregnant women in their 20s had a higher vaccination rate than those in their 40s, women who were nonsmokers before pregnancy had a higher vaccination rate than those who were smokers, and pregnant women who were aware that rubella may affect their fetuses had a higher vaccination rate than those who were unaware of this. This survey elucidated multiple predictive factors for rubella vaccination among pregnant women in Japan. Our results confirm the recommendation that women considering pregnancy should be vaccinated against rubella.

INTRODUCTION

With the Japanese birth rate declining and women becoming pregnant at later ages, the costs and responsibilities associated with maternity care (known as "pregnancy checkups") have received significant attention. Since 2013, financial assistance measures have been adopted at a regional level to cover the costs associated with the number of recommended checkups. Furthermore, in 2015, the Desired Standards for Health Checkups for Pregnant Women established the recommended timing and frequency of pregnancy checkups (1,2). Although an increasing number of services support pregnancy and the maintenance and promotion of maternal and child health, little is known about the effect of this type of support.

The Pregnant Women Health Initiative (PWHI) is a Health and Labour Sciences research project in Japan. It was launched in 2018 by the Miyagi Team, with a particular focus on the following infectious diseases that are screened for early during pregnancy: rubella, hepatitis B virus, hepatitis C virus, syphilis, human T-cell leukemia virus, and cervical cancer. The aim of the PWHI was to clarify the effect of screening for these 6 diseases on the health of mothers and children.

In 2018, just before the launch of the PWHI study, a rubella outbreak occurred in Japan. By January 15, 2020, at least 5 children had been diagnosed with congenital rubella syndrome (3,4). The Japanese rubella immunization program has been modified multiple times. As of April 1, 2020, men and women aged approximately 13–30 years were vaccinated twice by the time they were students. Those aged approximately 30–32 years had the opportunity to be vaccinated once in early childhood, and those aged approximately 33–40 years had the same chance between 12 and 15 years of age. However, the actual vaccination rate was particularly low in men and women aged 30–40 years, because their vaccination opportunities occurred during the transitional stage of the program. Women aged 40–57 years received mandatory mass vaccination when they were in middle school. Additionally, men aged ≥ 40 years and women aged ≥ 58 years had no chance of being vaccinated against rubella.

To prevent new cases of rubella, a rapid reduction in the number of susceptible individuals, most of whom are currently men aged 30–50 years, is required. To achieve this reduction, the Ministry of Health, Labour and Welfare in Japan announced that it would conduct

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rubella antibody tests and administer routine rubella vaccinations to men who had low antibody titers or had never received routine rubella vaccinations from April 2019 to March 2022 (5).

This interim study aimed to assess the urgent issue of rubella prevention measures based on the uptake of prepartum rubella vaccination and the corresponding immunological status of pregnant women and their partners living in Yokohama City, an urban area of Japan. Specifically, we examined predictive factors for rubella vaccination among pregnant women and compared the rates of rubella vaccination between pregnant women in this survey and age-matched female participants in a nationwide survey conducted in 2018.

MATERIALS AND METHODS

After we launched the PWHI, with the cooperation of physicians from 3 local core hospitals with perinatal care units in Yokohama City in Japan, pregnant women were recruited from the obstetric departments at each hospital, from June 2018 to September 2019. Pregnant women with delivery appointments at the designated hospitals, excluding those aged under 20 years, were provided with a written explanation of the study purpose as well as a flyer with their potential study participant number and a QR code. Interested participants submitted a written consent form with their participant number to the coordinating doctors. Subsequently, the participants used their QR codes to access the study secretariat's e-mail address and complete their enrollment. After enrolling, the participants received an e-mail from the secretariat containing a link to a secure online questionnaire, where they could input their unique study participant numbers and answer relevant questions. An online survey tool, SurveyMonkey®, was used to administer the survey with an enhanced security option. The questionnaire inquired about each participant's background, general condition, medical history, screening results, and knowledge about the 6 infectious diseases targeted in this study.

For this interim study, the demographic and clinical characteristics and rubella-related data were extracted from the responses provided by women receiving care at the Yokohama City University Hospital, Yokohama City University Medical Center, and National Hospital Organization Yokohama Medical Center. Data from the questionnaires, as well as the women's medical data, including rubella antibody titer results submitted by collaborating physicians, were analyzed. Rubella antibody titers (hemagglutination inhibition) were categorized as "1:16 or less," or "1:32 or more." According to the Guidelines for Obestetrical Practice in Japan 2020, rubella antibody titers of 1:8 and 1:16 are considered low antibody titers, and rubella vaccination in the early postpartum period is recommended for pregnant women with no or low antibody titers (6). We used the same categories in our study. Finally, the rubella vaccination status of the pregnant women enrolled in this survey was compared with that of age-matched female participants enrolled in a nationwide survey conducted in 2018 by the National Epidemiological Surveillance of Vaccine-Preventable Diseases (7). In both the surveys, rubella vaccination status was determined by administering a questionnaire. Responses to the following question were tallied: "Have you ever received rubella vaccines (including measles-rubella vaccines)?" The responses were selected among 3 options in the present survey ("Yes," "No," or "Unknown") and 5 options in the national surveillance survey ("Yes [1 time]," "Yes [2 times]," "Yes [number of times unknown]," "No," or "Unknown.") To perform statistical analyses in the current study, the national surveillance survey options of "Yes (1 time)," "Yes (2 times)," and "Yes (number of times unknown)" were combined to form a composite option of "Yes" for comparison with answers from this survey.

Statistical analysis: First, a chi-squared test was used to compare the proportion of rubella-vaccinated participants in this study with that in the national surveillance study. Second, binary logistic regression analysis was performed to examine i) whether there were differences in the rubella vaccine status based on socioeconomic and clinical characteristics of the participants (for example, age, number of previous deliveries, or educational level) and ii) whether those differences remained after adjusting for each background variable. The same analysis was performed for the rubella antibody status. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. The level of significance was set to $p < 0.05$ (2-tailed). JMP Pro 12.2.0, for Windows, was used for the statistical analyses.

Ethical considerations: The protocol of this study was approved by the ethics review boards of each participating institution at the Yokohama City University, in line with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

RESULTS

In this study, 666 pregnant women responded to the questionnaire. After excluding participants who did not complete the consent sheet or did not answer the questions regarding vaccination status, the answers of 613 participants were analyzed.

Table 1 shows the characteristics of the study participants. Most of the surveyed women were aged 30–39 years, and 52.4% of the women were primiparous. The percentage of women with a rubella antibody titer of 1:16 or less was 26.2%. Altogether, 67.5% of the pregnant women had received rubella vaccination. Among the women's partners, 47.6% had received rubella vaccination.

Table 2 shows the predictive factors for rubella vaccination. Of the 613 women, 152 were excluded because they selected "Unknown" for the question on rubella vaccination status or did not answer the questions regarding educational background or household income; the remaining 461 women were included in the analysis. Overall, women in younger age groups had higher vaccination rates; specifically, women in their 20s had higher vaccination rates than those in their 40s (adjusted OR = 8.41, 95% CI: 3.08–23.00, $P < 0.0001$). Women who were nonsmokers before pregnancy had a higher vaccination rate than those who were smokers (adjusted OR = 2.59, 95%

Table 1. Characteristic ($N = 613$)

Characteristic	N	Rate, %
Age at enrollment (yr)		
20-29	146	23.8
30-39	414	67.5
40-49	53	8.6
Number of previous births		
0	321	52.4
1	219	35.7
2	66	10.8
≥3	7	1.1
Educational level		
≤ High school graduate	119	19.4
Junior college graduate	206	33.6
≥ University graduate	284	46.3
No answer	4	0.7
Household income (ten thousand yen)		
<500	191	31.2
≥500, <700	168	27.4
≥700	222	36.2
No answer	32	5.2
Smoking before pregnancy		
No	528	86.1
Yes	85	13.9
No answer	0	0.0
Rubella antibody titer (HI)		
≥32	451	73.6
≤16	162	26.4
Do you Know the outbreak of rubella in 2012-2013 in Japan?		
Yes	367	59.9
No	240	39.2
unknown	6	1.0
Do you think rubella affects your baby's health directly?		
Yes	413	67.4
No	200	32.6
Have you ever had the rubella vaccination?		
Yes	414	67.5
No	78	12.7
unknown	121	19.7
Has your partner ever had the rubella vaccination?		
Yes	292	47.6
No	55	9.0
unknown	266	43.4

CI: 1.24–5.41, $P = 0.0111$). Furthermore, women who knew that rubella may affect their fetuses had a higher vaccination rate than those who did not (adjusted OR = 2.28, 95% CI: 1.27–4.09, $P = 0.0060$). However, there was no difference in the vaccination rates of women who knew that a rubella outbreak had occurred in 2012–2013 in Japan and those who did not. Vaccination rates did not differ significantly according to the number of deliveries, educational background, household income, or rubella antibody titer.

Table 3 shows the relationship between rubella antibody titers and the factors predicting rubella vaccination in the 461 pregnant women. Age and pre-pregnancy smoking, listed as predictors of rubella vaccination in Table 2, were not associated with rubella antibody titers higher than 1:32. Women who knew that rubella may affect their fetuses were significantly more likely to have rubella antibody titers higher than 1:32 than those who did not.

Table 4 shows the comparison between the vaccination status of pregnant women in the present survey and that of age-matched female participants in the nationwide survey conducted in 2018 (7). This comparison excluded those who answered "Unknown"

Table 2. Factors predicting rubella vaccination among pregnant women ($N = 461$)

	rubella vaccine		OR (95%CI)	*P value*	Adjusted[1)] OR (95% CI)	*P value*
	vaccinated	not vaccinated				
Age group (yr)						
20-29	103	11	5.70 (2.31-14.47)	0.0002	8.41 (3.08-23.00)	<0.0001
30-39	266	44	3.68 (1.73-7.63)	0.0010	3.74 (1.70-8.19)	0.001
40-49	23	14	1.00		1.00	
Number of delivery						
0	196	39	1.00		1.00	
1	146	18	1.61 (0.90-2.99)	0.1098	1.69 (0.88-3.24)	0.1162
≥2	50	12	0.83 (0.41-1.76)	0.6125	0.96 (0.44-2.11)	0.9199
Educational level						
≤ High school graduate	61	20	1.00		1.00	
Junior college graduate	132	21	2.06 (1.04-4.10)	0.0393	1.83(0.85-3.96)	0.1234
≥ University graduate	199	28	2.33 (1.22-4.41)	0.0113	1.62 (0.76-3.45)	0.2120
Household income (ten thousand yen)						
<500	118	24	1.00		1.00	
≥500, <700	118	19	1.26 (0.66-2.45)	0.4825	1.10 (0.54-2.22)	0.7962
≥700	156	26	1.22 (0.66-2.24)	0.5188	1.15 (0.58-2.30)	0.6876
Did you smoke before pregnancy?						
No	357	53	3.08 (1.56-5.88)	0.0015	2.59 (1.24-5.41)	0.0111
Yes	35	16	1.00		1.00	
Rubella antibody titer (HI titer)						
≤16×	105	22	1.28 (0.72-2.20)	0.3879	1.08 (0.58-1.99)	0.7997
≥32×	287	47	1.00		1.00	
Do you Know the outbreak of rubella in 2012-2013 in Japan?						
Yes	260	37	1.70 (1.01-2.86)	0.0451	1.49 (0.84-2.65)	0.1770
No or Unknown	132	32	1.00		1.00	
Do you think rubella affects your baby's health directly?						
Yes	98	32	2.59 (1.53-4.39)	0.0005	2.28 (1.27-4.09)	0.0060
No	294	37	1.00		1.00	

[1)]: Model includes all variables for which values are shown in the column.

($N = 121$ in this survey and $N = 915$ in the nationwide survey conducted in 2018). The rate of rubella vaccination among pregnant women in this survey was lower than that among age-matched female participants in the nationwide survey (84.2% and 88.3%, respectively; $P = 0.0288$).

DISCUSSION

This study investigated the rubella vaccination status of pregnant Japanese women and the associated predictive factors for rubella vaccination. These factors were age, smoking status before pregnancy, and awareness of the effects of rubella on the fetus. The rate of rubella vaccination among pregnant women in this study was lower than that among age-matched female participants in the nationwide survey.

The effect of age on the vaccination rate is closely related to the rubella vaccination policy in Japan. Following the introduction of the rubella vaccination into the routine vaccination program in 1977, for a significant period of time the vaccine was only administered to female junior high school students. This policy was revised in April 1995 when vaccination was extended to male and female infants (4). Individuals who were infants around the time of this policy change are now approximately 32–40 years old. This change and the resulting confusion (that is, citizens being unaware of the policy change) may explain why Japanese women currently aged 30–39 years have a lower rate of vaccination. The actual vaccination rate in women aged over 40 years is likely to be higher than the rate reported in this study because mass vaccination is mandatory in secondary schools. This discrepancy is likely due to the fact that this study was based on self-reported data. It is possible that many respondents who answered "Unknown" for their vaccination history had been vaccinated. It is also possible that many respondents might have answered "No" despite being vaccinated.

The results of this study showed that the vaccination rate also varied based on smoking status before pregnancy and knowledge that rubella can affect a fetus, indicating that overall pregnancy and fetal health awareness leads to a higher vaccination rate. Women who pay closer attention to their health or are aware of the potential fetal effects of infection during pregnancy are more likely to consider their vaccination status

Table 3. Relationship between rubella antibody titers and factors predicting rubella vaccination of pregnant women ($N = 461$)

	rubella antibody titer (HI titer)		OR (95% CI)	*P value*	Adjusted[1] OR (95% CI)	*P value*
	≤16 ×	≥32 ×				
Age group (yr)						
20-29	43	71	1.00		1.00	
30-39	75	235	1.89 (1.19-3.00)	0.0068	1.64 (0.99-2.71)	0.0533
40-49	9	28	1.88 (0.84-4.58)	0.1284	1.73 (0.70-4.26)	0.2349
Number of delivery						
0	72	163	1.00		1.00	
1	37	127	1.52 (0.96-2.42)	0.0728	1.49 (0.92-2.43)	0.1063
≥2	18	44	1.08 (0.59-2.03)	0.8061	0.87 (0.45-1.68)	0.6833
Educational level						
≤ High school graduate	34	47	1.00		1.00	
Junior college graduate	39	114	2.11 (1.19-3.76)	0.0103	1.68 (0.91-3.11)	0.0975
≥ University graduate	54	173	2.32 (1.35-3.97)	0.0023	1.75 (0.96-3.21)	0.0680
Household income (ten thousand yen)						
<500	47	95	1.00		1.00	
≥500, <700	39	98	1.24 (0.75-2.08)	0.4020	1.05 (0.61-1.80)	0.8524
≥700	41	141	1.70 (1.04-2.79)	0.0342	1.30 (0.76-2.23)	0.3419
Did you smoke before pregnancy?						
No	112	298	1.11 (0.57-2.07)	0.7536	1.34 (0.67-2.70)	0.4115
Yes	15	36	1.00		1.00	
Rubella vaccine						
vaccinated	105	287	1.28 (0.72-2.20)	0.3879	1.08 (0.59-1.99)	0.7992
not vaccinated	22	47	1.00		1.00	
Do you Know the outbreak of rubella in 2012-2013 in Japan?						
Yes	73	224	1.51 (0.99-2.29)	0.0566	1.19 (0.76-1.88)	0.4483
No or Unknown	54	110	1.00		1.00	
Do you think rubella affects your baby's health directly?						
Yes	49	81	1.96 (1.27-3.03)	0.0027	1.75 (1.10-2.81)	0.0191
No	78	253	1.00		1.00	

[1]: Model includes all variables for which values are shown in the column.

Table 4. Comparison of vaccination rates among the pregnant women enrolled in the present survey and women enrolled in the national surveillance survey

Survey	Rubella vaccination (exclude "unknown")				*P* value[2]
	Yes		No		
	N	(%)	*N*	(%)	
This survey	414	84.2	78	15.9	0.0288
National survey[1]	771	88.3	102	11.7	

[1]: National epidermiologocal surveillance of vaccine-preventable diseases 2018 in Japan.

[2]: *P* value was caliculated by Chi-square test.

when they consider pregnancy; therefore, they are more likely to request and receive a vaccination if they have no record of one.

We hypothesized that women who knew about the recent rubella outbreak would have a higher vaccination rate; however, the results showed no significant difference between women who were and were not aware of this fact (Table 2). This suggests that information about a rubella outbreak is not sufficient to influence vaccination decisions. Based on our results, it is essential to raise awareness of how rubella affects the fetus to promote rubella vaccination. Women of childbearing age should be educated about the effect rubella can have on a fetus, and they should receive relevant information about a rubella outbreak to prevent these effects from occurring.

In this study, vaccination rates did not differ according to the number of previous deliveries, educational background, or household income. Although there have been no large-scale studies of the association

between rubella vaccination and social background, several studies have investigated the association between seroprevalence of rubella antibodies and social background (8,9). Previous studies have reported an association between rubella seroprevalence and geographical region or country where the pregnant women were born or raised, reflecting the influence of rubella vaccination policy in each region (10–15). In Japan, Hanaoka et al. measured rubella antibodies in pregnant women and reported that 16.1% of pregnant women had a low level of rubella antibodies (1:16 or less) (16). However, it is noteworthy that no previous research has investigated the association between the vaccination rate and social background in pregnant women.

We predicted that women who delivered more number of babies would report higher vaccination rates than those who deliver less. We also hypothesized that those who had delivered previously and had low rubella antibody titers would have received the rubella vaccine after delivery. However, we found no correlation between the number of deliveries and vaccination history in this study. Postpartum vaccination recommendations may be inadequate, and pregnant women with low antibody titers may not have been vaccinated after delivery.

We also examined the associations between rubella antibody titers and factors that predicted rubella vaccination in pregnant women. Among the 3 factors predictive of rubella vaccination, the only factor associated with rubella antibody titers was the knowledge that rubella affects fetuses; no association was found with regard to age or smoking history. Notably, we did not divide the low-antibody group into "less than 1:8" and "1:8 to 1:16" groups in this study. To facilitate data entry by clinicians at each hospital, we placed individuals with antibody titers of 1:16 or less in one group. Therefore, some individuals in the low-antibody group may have been vaccinated previously. Nonetheless, the knowledge that rubella affects fetuses was strongly correlated with vaccination history.

The rate of rubella vaccination among pregnant women in this survey was lower than that among age-matched female participants in the nationwide survey conducted in 2018. We hypothesized that women considering pregnancy would have a heightened awareness of their health, check their vaccination status, and seek vaccination if they were not already vaccinated; however, the results of this study were contrary to this. This may be related to the fact that many respondents to this survey and the nationwide survey answered "Unknown" for their vaccination history; altogether, 19.7% (N = 121) respondents in this survey and 51% (N = 915) respondents in the nationwide survey indicated that they did not know their vaccination status. The actual vaccination rate may differ depending on how many of these respondents were vaccinated. Hence, a simple comparison between this survey and the nationwide survey was difficult.

Furthermore, the vaccination rate of the participants' partners was lower than that of the pregnant women. The vaccination rate was at least 10% lower for males than for females; this statement applies to both this and national surveillance surveys (7). In Japan, there was a period when rubella vaccination was provided only to females; thus, many males have not had the opportunity to be vaccinated against rubella making it difficult to control a rubella outbreak. To address this situation, men aged 40–57 years should be included in Japan's rubella immunization program from 2019 to 2021 (4,17).

Some limitations must be considered when interpreting the results of the present study. First, this was a questionnaire-based survey, and the history of rubella vaccination was self-reported. The accuracy of this information was not assessed against the maternal and child health handbook, through which healthcare professionals can validate the information. Second, this survey was restricted to Yokohama City. It is possible that vaccination rates vary among geographical areas; however, assessing this aspect of vaccination uptake was beyond the scope of this study. Considering the critical situation in Japan, we prioritized the analysis of data that could be easily and immediately obtained to issue an early alert regarding an outbreak of rubella. In the near future, we plan to examine nationwide survey data in Japan by referring to this study.

This interim study showed that the rate of rubella vaccination among pregnant women in Yokohama City was lower than that among age-matched women who responded to a nationwide survey conducted in 2018. The predictive factors for rubella vaccination were age, smoking status before pregnancy, and the awareness of rubella's potential effects on the fetus. To prevent congenital rubella syndrome, most women should be vaccinated against rubella before pregnancy. Women aware of maternal and fetal health might likely seek vaccination; however, the results of this study suggest that this may not be sufficient to ensure herd immunity.

In conclusion, this survey showed that the rubella vaccination rate and positive rubella antibody rate were low among pregnant Japanese women, and predictive factors for rubella vaccination were determined. The rubella outbreak in Japan is ongoing. Thus, women who are considering pregnancy should have antibodies against rubella. Public awareness campaigns are needed to address this issue. Furthermore, the entire population, including men, should be aware of the risks of the rubella outbreak and the fact that all individuals should be vaccinated against this disease.

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Conflict of interest None to declare.

REFERENCES

1. Japanese Ministry of Health, Labour and Welfare. Desirable criteria for health checkups for pregnant women. Available at <https://www.mhlw.go.jp/web/t_doc?dataId=82ab4662&dataType=0&pageNo=1>. Accessed February 7, 2020. Japanese.
2. Japanese Ministry of Health, Labour and Welfare. About the survey results regarding the status of public expenditure of

pregnant women's health checkups. Available at <https://www.mhlw.go.jp/file/04-Houdouhappyou-11908000-Koyoukintoujidoukateikyoku-Boshihokenka/H28kouhihutan_1.pdf>. Accessed February 7, 2020. Japanese.
3. National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare. Rubella virus isolation /detection status 2012–2019 (as of January 15, 2020). Available at <https://www.niid.go.jp/niid/ja/rubella-m-111/2265-idsc/iasr-rubella/5736-iasr-rv20150611.html>. Accessed February 7, 2020. Japanese.
4. National Institute of Infectious Diseases. Epidemiological information on rubella: as of January 29, 2020. Available at <https://www.niid.go.jp/niid/images/epi/rubella/2020/rubella200129.pdf>. Accessed February 7, 2020. Japanese.
5. Japan Ministry of Health, Labour and Welfare. About additional measures against rubella. Available at <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/rubella/index_00001.html>. Accessed February 7, 2020. Japanese.
6. Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists. Guidelines for Obstetrical Practice in Japan 2020. Available at <http://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf>. Accessed June 28, 2021. Japanese.
7. National Institute of Infectious Diseases. Age distribution of rubella vaccination history in Japan, 2018. Available at <https://www.niid.go.jp/niid//images/epi/yosoku/2018/Vaccination/r2018vaccine-e.pdf>. Accessed February 7, 2020.
8. Gilbert NL, Rotondo J, Shapiro J, et al. Seroprevalence of rubella antibodies and determinants of susceptibility to rubella in a cohort of pregnant women in Canada, 2008–2011. Vaccine. 2017;35:3050-5.
9. Muliyil DE, Singh P, Jois SK, et al. Sero-prevalence of rubella among pregnant women in India, 2017. Vaccine. 2018;36:7909-12.
10. Azami M, Jaafari Z, Soleymani A, et al. Rubella immunity in pregnant Iranian women: a systematic review and meta-analysis. Int J Fertil Steril. 2019;13:169-77.
11. Sert UY, Ozgu-Erdinc AS, Saygan S, et al. The prevalence of anti-rubella antibodies in pregnant women of Turkey, results of 94508 patients in a tertiary referral center. Z Geburtshilfe Neonatol. 2019;223:281-4.
12. Pandolfi E, Gesualdo F, Rizzo C, et al. Global seroprevalence of rubella among pregnant and childbearing age women: a meta-analysis. Eur J Public Health. 2017;27:530-7.
13. Shih C-T, Chang Y-C, Wang H-L, et al. Comparing the rubella seronegativity in pregnant women who received one dose of rubella vaccine at different ages in Taiwan. Vaccine. 2016;34:4787-91.
14. Alsibiani SA. Rubella immunity among pregnant women in Jeddah, Western region of Saudi Arabia. Obstet Gynecol Int. 2014;2014:659838.
15. Tahita MC, Hübschen JM, Tarnagda Z, et al. Rubella seroprevalence among pregnant women in Burkina Faso. BMC Infect Dis. 2013;13:164.
16. Hanaoka M, Hisano M, Watanabe N, et al. Changes in the prevalence of the measles, rubella, varicella-zoster, and mumps virus antibody titers in Japanese pregnant women. Vaccine. 2013;31:2343-7.
17. National Institute of Infectious Diseases. Rubella and congenital rubella syndrome in Japan as of May 2019. Available at <https://www.niid.go.jp/niid/en/865-iasr/9094-474te.html>. Accessed February 7, 2020.

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Ⅱ　副論文

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Ⅲ　参考論文

1. Trends in Pregnancy-Associated Cervical Cancer in Japan between 2012 and 2017: A Multicenter Survey
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