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Original Article

Is birth cohort 1985/9–1990/8 a susceptibility window for congenital rubella syndrome in Taiwan?

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ABSTRACT

Objective: The worldwide prevalence of congenital rubella syndrome has drastically decreased after the uptake of vaccine to prevent the infection. However, outbreaks have occurred in some countries due to their own vaccination policies, and this phenomenon has not yet been investigated in Taiwan. Our study aims to fill this gap.

Materials and Methods: We constructed an analytical database containing 10,824 pregnant women at the Taipei City Hospital, Taipei, Taiwan from January 2004 to July 2012. They were categorized into five birth cohorts according to the different vaccination programs in Taiwan: those born before 1971; those born between September 1971 and August 1976; between September 1976 and August 1979; between September 1979 and August 1985; and between September 1985 and August 1990. Differences of the seronegative rate and titers were compared using the Chi-square and Kruskal–Wallis tests among the five cohorts.

Results: The seronegative rates for the five cohorts were 15.00%, 4.07%, 2.88%, 4.21%, and 10.98%, respectively, and were statistically significant different ($p < 0.001$). The first and fifth cohorts were higher than the average of seronegativity (5%). The mean of log transformed titers were 3.69 IU/mL, 4.22 IU/mL, 4.22 IU/mL, 4.05 IU/mL, and 3.44 IU/mL, which were statistically significant different ($p < 0.001$). Our study also found that the equivocal rates (7.58%) were the highest in the cohort born between September 1985 and August 1990, among those who had been vaccinated. Our study showed that women younger than 27 years had a lower geometric mean titer of antibody titer than the average (60.60 IU/mL).

Conclusion: The previous vaccination policy in Taiwan has created a susceptibility window for rubella and congenital rubella syndrome over the past decades. We recommend having the antibody test before pregnancy for women born between September 1985 and August 1990, and implement a catch-up vaccine for those who were either seronegative or equivocal to prevent reinfection during their childbearing period.

Introduction

Rubella, also known as German measles, is an acute, contagious, mild viral infection, which unfortunately has serious consequences for pregnant women [1]. It is usually transmitted via the respiratory tract by aerosol and caused by a single-stranded RNA virus, which belongs to the Togaviridae family and was first isolated from cell culture in 1962. The typical symptoms included low-grade fever, malaise, lymphadenopathy, arthritis, arthralgia, and a characteristic rash lasting for about 3 days, with up to 50% of those infected being asymptomatic [2,3]. In 1941, an Australian ophthalmologist, Norman Gregg, first recognized the association between congenital cataract cases and maternal rubella in 78 cases [4]. When a pregnant woman catches rubella, the virus can cross the placenta, infect the fetus, and lead to devastating consequences such as miscarriage, stillbirth, preterm delivery, and single or multiple birth defects such as deafness, glaucoma, cataract, microcephaly, mental retardation, and heart disease, which is generally referred to as congenital rubella syndrome (CRS) [5]. The risk of the fetus with

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CRS is greatest in early pregnancy: 90% before the 10th week, 25% within the first trimester, and negligible by 20 weeks. Some cases could be diagnosed a few months or years after birth due to the late presentation of the clinical signs of CRS, while most are noted at the time of delivery [6].

There are three ways to decrease the susceptibility of the rubella infection: passively acquired antibody from the mother, wild-type virus infection, and vaccination. Maternal derived immunoglobulin G (IgG) decays exponentially after birth with protection lasting for 6–15 months [6,7], and even shorter by half in vaccinated mothers [8]. Naturally acquired rubella antibodies, predominantly IgG, which appear a few days after primary infection, have more persistent and two times higher titers than vaccine-induced. Rubella vaccines are available either in monovalent formulation, or more commonly in combinations with other vaccines, namely rubella-containing vaccines (RCVs), such as with vaccines against measles; measles and mumps (MMR); or measles, mumps, and varicella. After the rubella vaccination, the high avidity antibody takes 2 years to reach its peak and then declines significantly in the 15–20 years after a single dose of RCV unless in circumstances where the wild rubella virus was still endemic and natural boosters were frequent [9,10]. Therefore, the timing of the second rubella dose is critical to ensure that immunity against rubella is maintained in women of childbearing age [11]. In Taiwan, four reported epidemics occurred, in 1944, 1957–1958, 1968–1969, and 1977, and rubella then became endemic [12]. Taiwan's rubella vaccination program was launched in 1986 with third grade schoolgirls in junior high school receiving one dose of rubella (RA 27/3) vaccine. This program was modified to one dose of MMR (RA 27/3) vaccine being given to all junior high and elementary school students and preschool children in 1992–1994 with high coverage rate (~98%) [13]. CRS in Taiwan is currently a category 3 reportable disease, and rubella category 2. Suspected cases must be reported to the Centers for Disease Control, and samples must be sent to the Centers for Disease Control laboratory for confirmation. The number of confirmed rubella cases has fluctuated yearly from 2 to 60, with 362 in total during the periods of 1992 and 2013, with only five cases of CRS being confirmed since 1994, 3 in 2001 and one each in 2007 and 2008. Two of them were indigenous cases [14].

According to previous studies in Taiwan, the proportion of seronegativity among pregnant women is high, ranging from 10% to 30% [15–18]. Among them, those who were born before 1971 had the highest seronegativity (20.1%), and those who were born after 1971 had a lower rate of around 6–8%. In addition, those who were born after 1991 had the lowest seronegativity rate (1%) [15,18,19]. Moreover, about 6.5% of pregnant women who had received the vaccination still did not have any immunity [15]. Although many studies have suggested that women with the seronegative antibody should have a catch-up vaccination before they were discharged from the hospital, the revaccination rate was still low, such as 60–70% in Japan, < 20% in the USA, and an even lower rate of 10–20% in Taiwan [15,16,20,21].

Large-scale rubella vaccination over the last decades has drastically reduced, or practically eliminated rubella and CRS in many developed as well as in some developing countries. Nevertheless, rubella outbreaks have still occurred recently in several countries, including China [22], Poland [23], Romania [24], and Japan [25], and deserve more attention. The most probable reason for this might be that these countries failed to ensure that adequate protection was provided at the time of the changes in the rubella vaccination programs, thereby continuously causing important public health issues. Furthermore, the low level of protective immunity amongst women of childbearing age underlines the importance of the appropriate screening programs for rubella susceptibility. Therefore, serological surveillance could provide valuable information with which to evaluate a nationwide vaccination program [26]. In Taiwan, no study has, as yet, paid any attention to this issue. It is likely that the outbreaks of rubella and CRS might have occurred due to some susceptible women being infected by other sources such as travelling to endemic regions or overseas visitors. Therefore, this study aims to use hospital data sets to investigate whether the different cohorts have a different seronegativity, and whether some of them are susceptible to the infection. The findings from our study might provide further evidence for Taiwan's public health authority to take some preventative measures in order to avert any outbreaks and/or to eliminate CRS in the future.

Materials and methods

Data source

This is a retrospective study. We used four datasets from the Taipei City hospital, Fuyou Branch, Taipei, Taiwan, including the rubella antibody test results from the Laboratory Information System, the Pregnancy Risk Assessment Monitory System, the Birth Registry Databank, as well as the Hospital Information System, and linked them by their patient identifiers to construct an analytical database containing pregnant women from January 2004 to July 2012. The earliest rubella test record was retained for those women who had more than two records in the databank after linking all the datasets mentioned above. After excluding the missing values in nationality (401, 3.09%), foreigners (1036, 7.97%), and those who were born after August 1990 [vaccinated with 2 doses of MMR (39, 0.30%)], with the total study sample being 10,824. The Ethics Review Board of Taipei City Hospital approved this study protocol (No. TCHIRB-1030326-E).

Serological tests

Rubella IgG antibodies were determined through an enzyme immunoassay. The test results for our study sample were all obtained using IMMULITE 2000 (Siemens, Munich, Germany). The antibody titers were obtained in the IU/mL based on the International Standard for Anti-Rubella (2nd international standard preparation) sera of the World Health Organization, included as the reference sera by the manufacturer. The lower and upper detection limits for the rubella virus IgG were 0 IU/mL and 500 IU/mL, respectively. Currently, an antibody level of > 10 IU/mL is recognized to be protective but < 15 IU/mL has been reported to allow reinfection [27]. Based on the previous literature and the International Standards, serum IgG levels of $\geq$ 15 IU/mL were considered to be seropositive or immune; those of 10–15 IU/mL were considered to be equivocal, susceptible or weakly positive [28–30]; those < 10 IU/mL were considered to be seronegative or nonimmune [31].

Statistical analysis

The women were categorized into five birth cohorts according to the history of the rubella vaccination programs in Taiwan. Cohort 1 was born before September 1971 and no rubella vaccination program was provided during their childhood. Cohort 2 was born between Septembers 1971 and August 1976, and received one dose of rubella vaccine when they were 15 years old. Cohort 3a was born between September 1976 and August 1979, and received one dose of MMR when they were age 15 years old. Cohort 3b was born between September 1979 and August 1985, and received one dose of MMR when they were 7–12 years old. Cohort 3c was born between September 1985 and August 1990, and received one dose of MMR when they were 6 years old (Table 1).

Table 1
Vaccine doses and uptake rates under national programs by birth cohorts.

Birth cohort	Birth year	Vaccination program against rubella in Taiwan							RCV total doses	Estimated uptake rate of RCV[a]
		Universal administration at the age of:				Booster campaigns	Childbearing-age-women catch-up vaccination[b]			
		15 mo	5 y	7–12 y	15 y	2001/12–2004/3	1987–2001/6	After 2001/9		
1	Prior to 1971	—	—	—	—	—	Rubella	MMR	0+[c]	NA
2	1971/9–1976/8	—	—	—	Rubella[d]	—	Rubella	MMR	1+[c]	98%
3a	1976/9–1979/8	—	—	—	MMR	—	Rubella	MMR	1+[c]	NA
3b	1979/9–1985/8	—	—	MMR	—	—	Rubella	MMR	1+[c]	NA
3c	1985/9–1990/8	—	MMR	—	—	—	Rubella	MMR	1+[c]	NA
3d	1990/9–1994/8	MMR	—	—	—	MMR	—	MMR	2+[c]	90.57%[e]
4	1994/9–1998/8	MMR	—	—	—	MMR	—	MMR	2+[c]	96.31%[f]

Adapted from the document of the Centers for Disease Control, Taiwan [6].
MMR = measles–mumps–rubella vaccine; NA = not available; RCV = rubella-containing vaccine.
[a] Excludes catch-up vaccination.
[b] Catch-up vaccination is voluntary.
[c] Doses of voluntary catch-up vaccine.
[d] Female only.
[e] 1994–1995.
[f] 1996–1997.

Those whose antibody levels were below the lower limits of quantification, which is 0 IU/mL, were assumed to be equivalent to half of the lower limit of quantification (0.02 IU/mL for rubella) [8]. Due to the positive skewness of the raw titers, we used the log-transformed titer to conduct a statistical test across the five cohorts [18]. We first confirmed whether the homogeneity assumption holds for the log-transformed Rubella titers using Levene's test, and found that heterogeneity existed across the cohorts; therefore, we chose the nonparametric method, the Kruskal–Wallis test, to compare the differences in the titers among the five cohorts. The geometric mean titer (GMT) was calculated using the log-transformed values from the individual titers; the GMT was taken as the antilog of the mean of the transformed values [32]. We presented seronegative rates, mean of the log-transformed titers, the GMT, and a 95% confidence interval of the GMT. The participants were categorized by birth cohorts, age, and the time after vaccination (TAV). The TAV was calculated as the difference between the test year and the earliest year of receiving the vaccination. Since there is no specific test date, therefore, the age at the test date was calculated in months. Differences of the seronegative rate among the birth cohorts were compared using the Chi-square test. *Post hoc* comparisons were also used to identify the difference of seronegative rates between two cohorts. All statistical analyses were conducted using the SAS version 9.4 software by SAS Institute Inc., Cary, NC, USA.

Results

The mean of the rubella IgG antibody is 105.46 IU/mL with a standard deviation of 113.61 IU/mL. The minimum and maximum values were 0.01 IU/mL and 500 IU/mL, respectively. Table 2 shows that the seronegative rate was relatively higher in Cohort 1 and Cohort 3c, which were all above the average of all cohorts. However, since the equivocal rate for Cohort 3c is higher than Cohort 1, the seropositive rate (not shown in Table 2) is actually slightly lower than that of Cohort 1. According to the Chi-square test, the seronegative rate was shown to be statistically significant different across the five cohorts ($p < 0.001$). After conducting *post hoc* comparisons, Cohort 3c was statistically different from other cohorts ($p < 0.001$) except Cohort 1 ($p = 0.0943$; not shown in the table). Titers among the five cohorts were also shown to have statistically significant difference based on the Kruskal–Wallis test ($p < 0.001$).

Figure 1 shows that those who were younger than 27 years had a lower GMT than the average and had a lower seropositive rate than the average. For women who were 21 years old, the GMT was the lowest (24.3 IU/mL) and had the lowest seropositive rate (69.05%). Within this age group, ~78.57% ($n = 33$) were from Cohort 3c, accounting for 12.5% of all women in Cohort 3c ($n = 264$). The equivocal rates were higher than the average for those who were age 20–26 years (range, 2.86–7.14%). The peak of the GMT occurred in women who were age 32 years, which was 70.92 IU/mL. In addition, those who were aged 36 and over had a lower seropositive rate as well as GMT than that of the average.

Figure 2 shows the different GMT patterns for Cohort 2 and Cohort 3 (including Cohorts 3a, 3b, and 3c) based on the TAV. For both cohorts, the GMT increased and then declined after a number of years. For Cohort 2, the GMT reached its peak of 90.93 IU/mL at 21 years, and it was 125.47 IU/mL at 14 years for Cohort 3. The level of GMT remained stable after it declined to approximately 49 IU/mL. However, it has been noted that the highest level of the GMT for Cohort 2 had never exceeded the highest level of the GMT for Cohort 3. The increasing rate of the GMT for Cohort 3 was higher than that of Cohort 2, but declined more rapidly than that of Cohort 2.

Table 2
Cohort-specific seronegative rate and geometric mean titers of rubella in 10,824 women.

Cohort	*n*	Seronegative rate (%) (95% CI)	Equivocal rate (%) (95% CI)	Mean of ln (titers of rubella) (95% CI)	GMT (IU/mL) (95% CI)
1	1,053	15.00 (12.90–17.31)	2.09 (1.31–3.15)	3.69 (3.56–3.82)	68.30 (65.50–71.23)
2	3,444	4.07 (3.43–4.78)	2.21 (1.74–2.75)	4.22 (4.18–4.27)	68.24 (65.79–70.78)
3a	3,094	2.88 (2.32–3.53)	2.36 (1.85–2.96)	4.22 (4.19–4.26)	57.26 (55.11–59.50)
3b	2,969	4.21 (3.52–5.00)	2.93 (2.35–3.60)	4.05 (4.01–4.09)	31.33 (27.19–36.10)
3c	264	10.98 (7.48–15.39)	7.58 (4.69–11.46)	3.44 (3.30–3.59)	40.04 (35.23–45.51)
Total	10,824	5.00 (4.60–5.43)	2.57 (2.28–2.88)	4.10 (4.08–4.13)	60.60 (59.16–62.08)

CI = confidence interval. GMT = geometric mean titer.

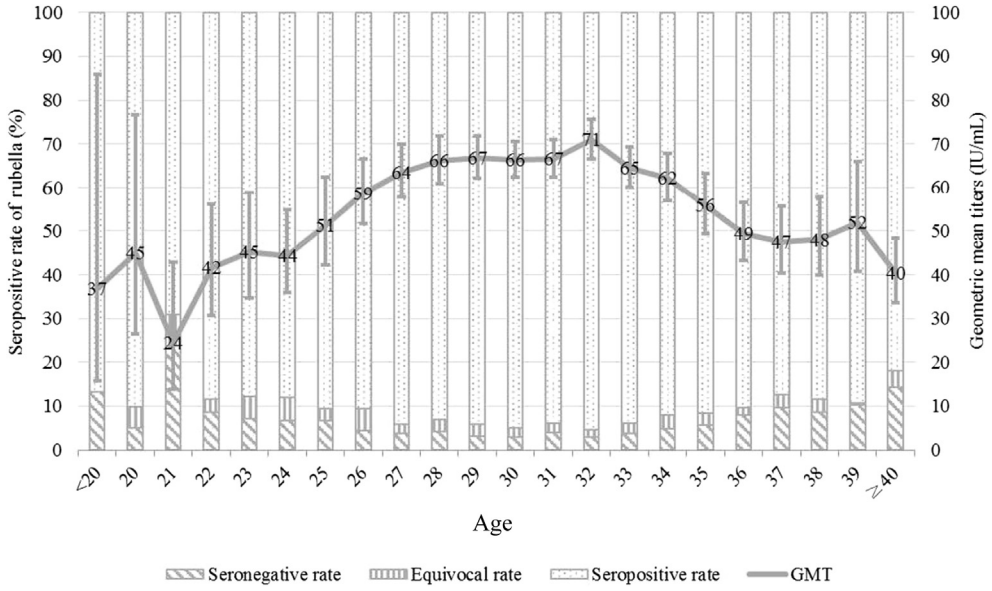

Figure 1. Age-specific seronegative rate, geometric mean titers, and the confidence limit of rubella in 10,824 women.

Discussion

This study used a large sample from the Taipei City hospital, Fuyou Branch, containing 10,824 pregnant women from 2004 to 2012. Our results showed that both the seronegative rate and the GMT were statistically different across the five birth cohorts. In addition, women born between September 1985 and August 1990 (Cohort 3c) had a higher seronegative rate as well as equivocal rate. This group was exposed to a higher risk of being affected. It is possible that such a susceptibility window for this cohort is due to the vaccination policy implemented during recent decades.

In our data, women in Cohort 1 did not receive any RCV and they acquired immunity through natural infection [18]. For Cohort 2 and Cohort 3a, the women received one dose of rubella and MMR vaccination, respectively, when they were 15 years old. Our findings showed that the low seronegative rate for these two cohorts were consistent with Wang et al's [18] study, which might be partly due to the vaccination, and partly due to naturally-acquired immunity. Although Cohorts 3b and 3c both received only one dose of the MMR vaccine when they were 7–12 years old and 5 years old in an environment where there was little chance for natural infection, the seronegative rate for Cohort 3b was still low, while it was surprisingly high for Cohort 3c. This finding is different from that of Wang et al [18] where the seronegative rate for the cohort born between 1982 and 1985 was 7.6% and 3.2% for those born between 1987 and 1989. However, our findings support those of Lin et al [15,31] and Davidkin et al [10] that antibody titers declined with time. The possible explanation was that the TAV was shorter for Cohort 3b, and even though the titers were decreasing, they were not below the threshold of seronegativity. For Cohort 3c, due to the longer TAV, the rubella antibody titers had declined to lower than the seronegativity level at a larger proportion.

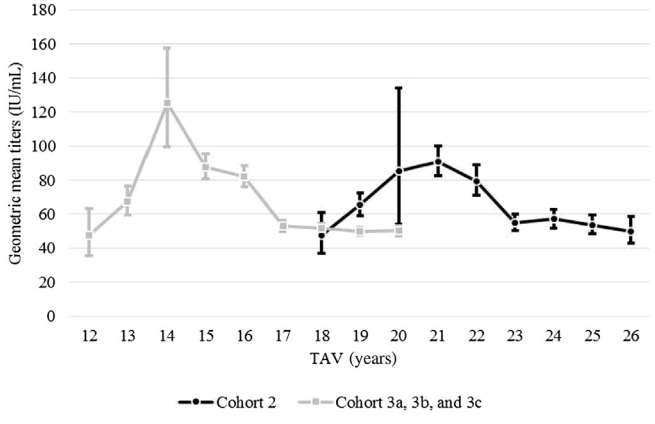

Figure 2. Time after vaccination-specific geometric mean titers of rubella in 10,824 women. TAV = time after vaccination.

Galazka [33] showed that, as long as the seronegative rate among women was 2–3%, then it was very likely that an outbreak would occur. Therefore, many previous studies suggested that women with a seronegative antibody level could have a catch-up vaccine before being discharged from hospital after delivering their babies [15,16,31,34–36]. Davidkin et al [28] showed that the titers were much higher for those who had the lowest antibody levels after revaccination than that of women who were naturally immunized or those who received vaccines. In Taiwan, the rubella IgG test is routine for prenatal care with high implementation, but the rate of the catch-up MMR vaccine, as per the government's recommendation, is very limited [15]. Moreover, the screening program does not reduce mother-to-baby transmission and has no advantage for the current pregnancy [37]. Yamada et al [36,38] further suggested that in order to prevent CRS, for those who did not have protective level of antibody, the government should adjust its vaccination policy, especially for the younger population regardless of their sex. A good model is the *Blessing your Pregnancy* program launched by the Taipei City government, which has provided free rubella IgG tests for those married couples before their pregnancy and free catch-up MMR vaccine if seronegative. Unfortunately, it has not been a nationwide campaign.

Our study found that the GMT for these two cohorts did reveal different patterns in terms of the TAV. For Cohort 2, it took ~21 years for the GMT to achieve the maximum value, and the waning rate was slower; by contrast, the increasing rate of the GMT for Cohort 3 was much higher than that of Cohort 2 and it took approximately 14 years to achieve the maximum value with a

much higher waning rate. This pattern has shown that the effect of rubella and the MMR vaccine was different.

Skendzel [30] and the US Centers for Disease Control have proposed that the cutoff points for seronegativity should be reduced from 15 IU/mL to 10 IU/mL since those whose antibodies were above this level could be prevented from becoming infected. However, there were some cases with titers above 10 IU/mL that were still previously infected. In our study, we defined 10–15 IU/mL as equivocal to suggest that those who fall within this level might receive more attention as they could have a higher chance of becoming infected years later. It is suggested that future research should focus on how to establish a standard for the immunity level of rubella. In addition, since our study only focused on women with one dose of MMR, it is suggested that future research should analyze those with two doses and investigate the changes of titers across the TAV.

Our study had some limitations. One is that the sample taken is only from the Taipei City Hospital and may not represent the whole picture nationwide. Second, we were not able to confirm as to whether the women had received a catch-up vaccine after delivery; however, since the catch-up rate was very low, we expected that this limitation would not affect our results in any significant way. Third, we were not able to assure that immunity is totally from the vaccination, especially for Cohort 2 and Cohort 3a, who experienced an outbreak of rubella in Taiwan.

Our study suggested that for those whose antibody is seronegative or equivocal, they should all have a catch-up vaccine after the birth of their baby. In addition, it is highly recommended that the government should stimulate rubella IgG tests for Cohort 3c, and catch-up vaccine for them when the test results were either seronegative or equivocal as the titers for those who fell within the equivocal range would keep decreasing. Moreover, it is possible that the antibody will fall below 10 IU/mL when they were pregnant under the condition that most of the women delayed childbearing. Finally, comparing the patterns of the GMT for Cohort 2 and Cohort 3 across the TAV, we found that only one dose of vaccine could not protect all women of childbearing age. It is suggested that the best time for the second dose of MMR is probably 14 years after the first dose.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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