Rubella Immunity in Pregnant Native Taiwanese and Immigrants from Asian Countries

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Abstract. Vaccination is considered the most effective method to prevent rubella spread and congenital rubella syndrome (CRS). The aim of the present study was to investigate the rubella immunity among native and immigrant pregnant women in Taiwan. From 2000 to 2014, a total of 16,879 pregnant women who received routine prenatal examinations were recruited in this study. The rubella IgG antibodies were assayed using a microparticle enzyme immunoassay or chemiluminescent microparticle immunoassay. Subjects were categorized by nationality and subcategorized by specific periods of time for comparison. The rubella susceptibility was 12.7% in total, 11.1% in Taiwanese and 20.3% in immigrant population from 2000 to 2014. Among the immigrant women, those from Vietnam had the highest susceptibility (22.3%) and those from Thailand had the lowest susceptibility (3.8%). The immigrant women from Vietnam and China showed a significantly higher susceptibility compared with the native Taiwanese women in which the odds ratio was 2.30 (95% confidence interval [CI]: 2.04–2.60), 1.96 (95% CI: 1.59–2.41), respectively ($P < 0.001$). It meant that immigrants from Vietnam and China had a higher likelihood of rubella susceptibility and related CRS sequela than native women. From 2000–2004 to 2010–2014 cohort, there was no obvious change in rubella susceptibility in native women, which varied between 10.0% and 11.9%. However, there was a decreasing trend of rubella susceptibility in the immigrant women overall, from 24.5% to 11.5% ($P < 0.001$). To eliminate congenital rubella in Taiwan, additional catch-up immunization strategies are needed.

INTRODUCTION

Rubella infection mostly causes mild self-limiting illness in nonpregnant women. However, when the infection occurs in pregnant women, especially in the first trimester of pregnancy, it can cause serious consequences, including miscarriages, fetal deaths, and infants born with congenital rubella syndrome (CRS).¹ At present, two doses of rubella vaccination are considered the most effective methods to prevent rubella spread and CRS. According to the global immunization report published by World Health Organization (WHO) in 2014, 140 countries have already introduced rubella vaccine into their routine immunization schedules.² In Taiwan, the mass rubella immunization program started in 1986. One dose of rubella vaccine was given to 15-year-old female students in the third year of junior high school. From 1992 to 1994, school and preschool children aged 15 months to 15 years were given a single dose of rubella vaccine in specific birth cohorts, yearly. Since 2001, a second, booster dose of rubella vaccine has been administered to all students in the first year of elementary school. Therefore, all children born after September 1994 have received two doses of rubella-containing vaccine.³ The elimination of congenital rubella depends not only on effective childhood immunization but also on the identification and immunization of susceptible women of childbearing age. Over the past 15 years (2001–2015), a total of 358,029 Taiwanese men have married foreign wives from China and other southeast Asian countries, accounting for 16.0% of total number of marriages.⁴ Some of these countries have not introduced rubella vaccination into their national immunization programs, which has caused a higher risk of contracting rubella among immigrant

women in Taiwan. There has been increasing concern about the high rubella susceptibility among the immigrant women from these countries after a large-scale rubella epidemic that occurred from 2012 to 2014.^{5,6} The investigation of the rubella susceptibility rates of both native Taiwanese and immigrant women is essential to preventing rubella and congenital rubella. Nevertheless, there are relatively few articles on comparison of rubella immunity among native mothers and that among foreign-born mothers in Asian countries. Accordingly, the aim of the present study was to investigate the rubella immunity among native and immigrant pregnant women in Taiwan.

MATERIALS AND METHODS

Subjects. From 2000 to 2014, a total of 16,879 pregnant women who received prenatal rubella IgG tests were recruited into this retrospective cohort study. We collected their birthdates, birthplaces, test dates, and test results from the Hospital information system. These pregnant women received routine prenatal examinations at Fooyin University Hospital, a regional teaching hospital that specializes in obstetric health care in southern Taiwan. The rubella IgG antibody was a compulsory test during their prenatal care visits. The study protocol was reviewed and approved by the Fooyin University Hospital Ethics Review Board (Institutional Review Board [IRB] no. FYH-IRB-970003 and FYH-IRB-104-03-01-A).

Serological tests of anti-rubella IgG. Anti-rubella IgG antibodies were measured from the blood samples collected from the subjects during their early second trimester prenatal examinations. These antibodies were assayed using a microparticle enzyme immunoassay on an AsXYM Analyzer (Abbott Laboratories, Chicago, IL) before May 2010. Thereafter, the chemiluminescent microparticle immunoassay was used on an ARCHITECT i2000 SR Analyzer (Abbott Laboratories). According to Portella's report, these two test

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modalities have an excellent qualitative concordance (97.3%) and only 0.3% truly discordant occurred between AsXYM and ARCHITECT in 3,264 clinical samples.⁷ Therefore, this change in laboratory equipment should have little effect on the evaluation of rubella immunity. Serum IgG levels of 10 IU/mL or above were considered to be seropositive or immune; those below 10 IU/mL were considered to be seronegative, susceptible, or nonimmune.

Statistical analysis. Subjects were categorized by nationality and subcategorized by specific periods of time. The differences between native and immigrant women were compared using a χ^2 test, and the odds ratio (OR) was calculated for rubella susceptibility in native and immigrant women. χ^2 test for trend was used to assess the changes in rubella susceptibility over time. To compare seronegativity of rubella antibodies, we stratified our data into three cohort groups: 2000–2004, 2005–2009, and 2010–2014 cohort, to obtain a quick, but yet comprehensive view of the changes in rubella seronegativity over this long period of time. A *P* value of less than 0.05 was regarded as statistically significant. Data were analyzed using the software SPSS 18.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

A total of 16,879 pregnant women, with 14,401 (82.9%) native Taiwanese and 2,878 (17.1%) immigrants, were included in this study from 2000 to 2014. The rubella susceptibility was 12.7% (95% confidence interval [CI]: 12.2–13.2%) in total—11.1% (95% CI: 10.6–11.6%) in native Taiwanese, whereas 20.3% (95% CI: 18.8–21.72%) in immigrant population. Among the immigrant women, women from Vietnam had the highest susceptibility (22.3%) and those from Thailand had the lowest susceptibility (3.8%). The immigrant women from Vietnam and China showed a 2.30-fold (95% CI: 2.04–2.60) and 1.96-fold (95% CI: 1.59–2.41) significantly higher rubella susceptibility compared with the native Taiwanese women, respectively (both *P* < 0.001) (Table 1).

Table 2 shows the rubella susceptibility among pregnant women in Taiwan and from other Asian countries during 2000–2014. For native Taiwanese, there was no obvious change in rubella susceptibility. However, the immigrant women showed a decreasing trend in rubella susceptibility. The rubella susceptibility decreased from 24.5% in 2000–2004 cohort to 11.5% in 2010–2014 cohort (*P* < 0.001).

Table 3 shows that in the 2000–2004 cohort, immigrant women from Vietnam, China, and Indonesia had significantly higher rubella susceptibility than the native Taiwanese (*P* < 0.05). Immigrant women showed a 2.40-fold (95% CI: 2.06–2.79, *P* < 0.001) higher likelihood of contracting rubella than that of the Taiwanese women. In the 2005–2009 cohort, immigrant women continued to have higher susceptibility than the Taiwanese (OR = 2.07, 95% CI: 1.74–2.46, *P* < 0.001), which implied that the immigrant pregnant women had a higher likelihood of rubella infection and CRS sequela than native women. However, this phenomenon changed in the 2010–2014 cohort, where there was no significant difference in rubella susceptibility between native pregnant women and immigrants (OR = 1.01, 95% CI: 0.73–1.38, *P* = 0.968).

DISCUSSION

The rubella susceptibility has dropped in the immigrant pregnant women during the past 15 years while the native Taiwanese has remained unchanged. The rubella susceptibility was 12.7% in all women, 11.1% in Taiwanese and 20.3% in immigrant. Although up to 140 countries in the world have introduced rubella vaccine into their national immunization programs, the population in Africa and southeast Asia has the lowest rates of rubella immunization.² Many studies, conducted in Italy, Spain, Canada, England, and Australia, have found that the immigrants from China and other Asian countries had higher susceptibility to rubella than the native population.^{8–12} In Taiwan, Cheng and others¹³ investigated the genotypes of rubella virus in the confirmed cases from 2005 to 2011. He found that 75% (93/124) of genotypes of rubella virus were imported from Vietnam, Malaysia, and China.¹³ According to WHO 2014 surveillance data on the rubella cases, the home countries of immigrant women in this study reported a total of 15,714 rubella cases.¹⁴ These reports show that the rubella virus remains rampant in China and southeast Asian countries; therefore, the immigrant women from these Asian countries pose the highest risk for imported rubella and CRS.

Since the year 2002, immigrant women have had to present proof of rubella immunization or positive rubella antibodies results when applying for temporary and permanent residency in Taiwan.³ After the implementation of this policy, we found the percentage of rubella seronegativity in immigrants dropped gradually, from 24.5% in 2000–2004 cohort to 11.4% in 2010–2014 cohort. It is unclear whether

TABLE 1
The rubella susceptibility among Taiwanese and immigrant pregnant women from 2000 to 2014

	Sample size	%	No. of seronegative	Susceptibility (%) (95% CI)	OR (95% CI)	<i>P</i>
Taiwanese	14,001	82.9	1,554	11.1 (10.6 to 11.6)	1 (Reference)	
Immigrant	2,878	17.1	583	20.3 (18.8 to 21.7)	2.04 (1.83 to 2.26)	< 0.001
Vietnam	1,828	10.8	408	22.3 (20.4 to 24.2)	2.30 (2.04 to 2.60)	< 0.001
China	600	3.6	118	19.7 (16.5 to 22.8)	1.96 (1.59 to 2.41)	< 0.001
Indonesia	293	1.7	39	13.3 (9.4 to 17.2)	1.23 (0.87 to 1.73)	0.235
Cambodia	57	0.3	6	10.5 (2.6 to 18.5)	0.94 (0.40 to 2.20)	0.891
Philippines	63	0.4	11	17.5 (8.1 to 26.8)	1.69 (0.88 to 3.25)	0.113
Thailand	26	0.2	1	3.8 (–3.5 to 11.2)	0.32 (0.04 to 2.37)	0.263
Others*	11	0.1	0	0.0 (0.0 to 0.0)	NE	–
Total	16,879	100	2,137	12.7 (12.2 to 13.2)		

CI = confidence interval; NE = not estimated due to small sample size; OR = odds ratio.
*Others include Malaysia, Myanmar, South Korea, and Turkey.

TABLE 2
Rubella susceptibility among pregnant women from different Asian countries from 2000 to 2014

Cohort	No. susceptible/total (%) (95% confidence interval)		
	2000–2004	2005–2009	2010–2014
Taiwanese	613/5,156 (11.9) (11.0 to 12.8)	498/4,956 (10.0) (9.2 to 10.9)	443/3,889 (11.4) (10.4 to 12.4)
Immigrant	316/1,292 (24.5) (22.1 to 26.8)	219/1,167 (18.8) (16.5 to 21.0)	48/419 (11.5) (8.4 to 14.5)
Vietnam	224/857 (26.1) (23.2 to 29.1)	155/758 (20.4) (17.6 to 23.3)	29/213 (13.6) (9.0 to 18.2)
China	53/193 (27.5) (21.2 to 33.8)	51/278 (18.3) (13.8 to 22.9)	14/129 (10.9) (5.5 to 16.2)
Indonesia	25/144 (17.4) (11.2 to 23.5)	9/86 (10.5) (4.0 to 16.9)	5/63 (7.9) (1.3 to 14.6)
Cambodia	5/37 (13.5) (2.5 to 24.5)	1/19 (5.3) (–4.9 to 15.3)	0/1 (0) (0.0 to 0.0)
Philippines	8/44 (18.2) (6.8 to 29.6)	3/11 (27.3) (1.0 to 53.6)	0/8 (0) (0.0 to 0.0)
Thailand	1/12 (8.3) (–7.3 to 24.0)	0/12 (0) (0.0 to 0.0)	0/2 (0) (0.0 to 0.0)
Others*	0/5 (0) (0.0 to 0.0)	0/3 (0) (0.0 to 0.0)	0/3 (0) (0.0 to 0.0)

*Others include Malaysia, Myanmar, South Korea, and Turkey.

the immigrant women became seropositive due to the wild rubella infection or the rubella immunization at their home countries. They could have received a catch-up immunization in Taiwan after a rubella seronegative blood test. Regardless of these reasons, immigrant women showed a decreasing trend in their rubella susceptibility from 2000 to 2014.

As for the native Taiwanese women, the rubella seronegativity remained unchanged during this period of time, ranging from 10.0% to 11.9% (Table 2). In our study, the native Taiwanese women received only one dose of rubella vaccine, and waning immunity after one dose of rubella vaccine may account for the relatively high seronegative rates observed. According to the WHO goal for achieving elimination of rubella, the incidence of CRS should be below 1/100,000 live births per year. To attain this goal, it would require at least 95% vaccination coverage with two-dose rubella vaccination in children and catch-up vaccinations of susceptible adolescents and women of childbearing age.¹⁵ How to identify susceptible women and perform catch-up immunization remains a challenging process. Important strategies include premarital and perinatal rubella antibody screenings. This is followed by vaccination of all seronegative women detected by the above mentioned screening efforts. Taiwan's National Health Insurance (NHI) program, launched in 1995, has been in practice for over 20 years. However, the premarital rubella antibody test and the subsequent immunization are not covered by the NHI. If these payments were to be covered by NHI, it would effectively increase the rubella antibody positive rates among fertile women. The perinatal rubella screening leads to postpartum rubella vaccination. The postpartum rubella vaccination is also recommended

to reduce the risk of congenital rubella in subsequent pregnancies.¹⁶ These strategies have been introduced into regular obstetrics care and have shown good performance in the United Kingdom, Canada, Japan, and other countries.^{17–19}

Therefore, to eliminate rubella infection, the postpartum immunization should be launched and vaccination should be provided to the susceptible women, either native or immigrant, before they are discharged from hospitals.²⁰ In Taiwan, almost all women have prenatal checkups. The bills are paid by NHI, regardless of whether childbirths take place in hospitals or at obstetrics clinics. The rubella tests are mandatory, and the results should be recorded in the maternal health booklet. However, free measles, mumps, and rubella vaccination is not available in hospitals or obstetrics clinics but is offered instead at local public health centers, which would miss the best opportunity to vaccinate susceptible women. If the postpartum immunization can be allowed in hospitals or obstetrics clinics, the susceptible women will receive rubella vaccination before they are discharged after delivery.

Our study has some limitations. First, the results were collected from a regional hospital, which might not truly reflect the susceptibility of the rest of Taiwan. Second, we were unable to check the immunization record of the studied women and assumed that native women were vaccinated in the mass immunization program due to the high vaccination coverage rate (over 95%) in Taiwan. Third, because of the lack of immunization record, we could not know how immigrant women became seropositive. The strength of the present study is that we continuously observed the changes of susceptibility of all pregnant women for 15 years. The results

TABLE 3
OR estimation of rubella susceptibility in pregnant women from different Asian countries, 2000–2014

Cohort	2000–2004		2005–2009		2010–2014	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Taiwanese	1 (Reference)		1 (Reference)		1 (Reference)	
Immigrant	2.40 (2.06–2.79)	< 0.001	2.07 (1.74–2.46)	< 0.001	1.01 (0.73–1.38)	0.968
Vietnam	2.62 (2.20–3.12)	< 0.001	2.30 (1.89–2.81)	< 0.001	1.23 (0.82–1.84)	0.323
China	2.81 (2.02–3.89)	< 0.001	2.01 (1.46–2.76)	< 0.001	0.95 (0.54–1.67)	0.850
Indonesia	1.56 (1.00–2.42)	0.048	1.05 (0.52–2.10)	0.899	0.67 (0.27–1.68)	0.394
Cambodia	1.16 (0.45–2.98)	0.761	0.50 (0.07–3.73)	0.497	NE	–
Philippines	1.65 (0.76–3.56)	0.205	3.36 (0.89–12.69)	0.074	NE	–
Thailand	0.67 (0.09–5.23)	0.706	NE	–	NE	–
Others*	NE	–	NE	–	NE	–

CI = confidence interval; NE = not estimated due to small sample size; OR = odds ratio.
*Others include Malaysia, Myanmar, South Korea, and Turkey.

are an important finding for future policies for achieving the goal of eliminating rubella and CRS in Taiwan.

In conclusion, the rubella susceptibility decreased significantly in immigrant women, but the overall susceptibility remained about 11% in both immigrant and native Taiwanese women. To eliminate congenital rubella in Taiwan, additional catch-up immunization strategies are undoubtedly needed.

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