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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).