Persistence and Titer Changes of Rubella Virus Antibodies in Primiparous Women Who Had Been Vaccinated with Strain RA 27/3 in Junior High School

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Taiwan’s rubella vaccination program was launched in 1986; each schoolgirl in the third grade of junior high school received one dose of rubella (RA 27/3) vaccine. We reviewed the results of 14,090 prenatal rubella tests for primiparas from three areas of Taiwan during 2002 to 2008 to investigate seronegativity rates and titer changes. In all primiparous women, the average rubella virus seronegativity rate was 6.5% (95% confidence interval [95% CI], 6.1 to 6.9%), and the average rubella virus antibody titer was 65.9 IU/ml (95% CI, 64.7 to 67.1 IU/ml). There were 1,220 women (8.7%) with weakly positive antibody titers (10 to 20 IU/ml). The rubella virus seronegativity rates, which varied from 5.4 to 9.7%, did not exhibit a linear trend from 9 to 22 years after vaccination (P = 0.201); in contrast, a significant trend appeared in the average rubella virus IgG titer (P = 0.003), dropping from 69.9 IU/ml in the 9th year after vaccination to 54.8 IU/ml in the 22nd year. The mean annual antibody decay rate was −0.77 IU/ml. This study reveals that the level of rubella virus antibodies declined slowly in women of childbearing age who were vaccinated with RA 27/3 at junior high school age. The number of women who were seronegative or had weakly positive antibody titers was still high (15.2%). Therefore, in countries that implement a single-dose regimen in children or teenagers, it should remain an important policy to encourage voluntary immunization in seronegative women and to immunize all postpartum women who are susceptible to rubella virus infection before they leave the hospital.

Rubella virus is a single-stranded RNA virus that is transmitted by aerosol via the respiratory tract. It generally causes a mild self-limiting disease characterized by rash, fever, and lymphadenopathy. In 1941, an Australian ophthalmologist, Norman Gregg, recognized the association between rubella virus infection in pregnancy and congenital rubella syndrome (CRS). The common manifestations of CRS include neurological deficits, hearing impairment, eye defects, and heart defects (1, 25). In 1962, a rubella pandemic began in Europe, spreading to the United States in 1963 and 1964 and to Asian countries in 1965 to 1969. During the period 1963–1964, the rubella outbreak infected 12.5 million people, caused 11,000 fetal deaths, and led to 20,000 CRS cases in the United States. This pandemic accelerated the development of rubella vaccines. Attenuated rubella vaccines were licensed in the United States and Europe in 1969; five rubella vaccines were also licensed and used in Japan during 1975 to 1980. Many developed countries implemented single-dose vaccination of target populations shortly after the vaccine first became available; at present, a two-dose measles-mumps-rubella (MMR) vaccine is provided to all children at 12 to 18 months and at preschool or school age (18, 20). These vaccination programs have successfully prevented rubella virus infection and CRS worldwide. Finland and the United States are currently documented as being free of indigenous rubella (9, 15, 17).

By the end of 2009, 130 countries had included the rubella vaccine in their national vaccination programs. Although global rubella vaccine coverage is estimated at 42% (26), many African and Asian countries have no rubella immunization programs. In Africa and Southeast Asia, the rubella vaccine coverages are estimated to be only 0.1 and 4%, respectively (26). It is believed that over 100,000 cases of CRS occur worldwide annually (19). Therefore, it remains an important public health challenge to prevent CRS in developing countries, especially in African and Southeast Asian regions.

Prior to the introduction of the vaccination program in Taiwan, four reported epidemics occurred, roughly about once every decade: in 1944, 1957–1958, 1968–1969, and 1977 (7). Since 1977, the disease appears to have become endemic, with no large-scale outbreaks of rubella. Taiwan’s rubella vaccination program was launched in 1986. Schoolgirls in the third grade of junior high school each received one dose of rubella (RA 27/3) vaccine. This program was extended, with one dose of MMR (RA 27/3) vaccine being given to all junior high and elementary school students and preschool children in 1992 to 1994. The rubella vaccination programs among junior high school girls had a high coverage rate.
TABLE 1 Rubella virus seronegativity rates and GMTs for primiparous women 9 to 22 years after vaccination in the third grade of junior high school

<table>
<thead>
<tr>
<th>Time (yr) after vaccination</th>
<th>Age (yr)</th>
<th>Sample size</th>
<th>No. of seronegative women</th>
<th>% Seronegativity (95% CI)</th>
<th>GMT (IU/ml) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>24</td>
<td>142</td>
<td>11</td>
<td>7.7 (3.3–12.1)</td>
<td>69.9 (57.8–81.9)</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>323</td>
<td>24</td>
<td>7.4 (4.6–10.3)</td>
<td>70.3 (62.2–78.4)</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>576</td>
<td>30</td>
<td>5.2 (3.4–7.0)</td>
<td>63.6 (58.3–69.0)</td>
</tr>
<tr>
<td>12</td>
<td>27</td>
<td>956</td>
<td>65</td>
<td>6.8 (5.2–8.4)</td>
<td>65.6 (60.8–70.4)</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>1,445</td>
<td>94</td>
<td>6.5 (5.2–7.8)</td>
<td>66.6 (62.8–70.4)</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>1,832</td>
<td>109</td>
<td>5.9 (4.9–7.0)</td>
<td>66.8 (63.5–70.1)</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>1,899</td>
<td>119</td>
<td>6.3 (5.2–7.4)</td>
<td>68.1 (64.7–71.6)</td>
</tr>
<tr>
<td>16</td>
<td>31</td>
<td>1,983</td>
<td>137</td>
<td>6.9 (5.8–8.0)</td>
<td>68.2 (64.8–71.7)</td>
</tr>
<tr>
<td>17</td>
<td>32</td>
<td>1,682</td>
<td>91</td>
<td>5.4 (4.3–6.5)</td>
<td>67.5 (63.9–71.1)</td>
</tr>
<tr>
<td>18</td>
<td>33</td>
<td>1,455</td>
<td>95</td>
<td>6.3 (5.3–7.8)</td>
<td>64.0 (60.3–67.8)</td>
</tr>
<tr>
<td>19</td>
<td>34</td>
<td>886</td>
<td>74</td>
<td>8.4 (6.5–10.2)</td>
<td>59.3 (54.8–63.7)</td>
</tr>
<tr>
<td>20</td>
<td>45</td>
<td>560</td>
<td>42</td>
<td>7.5 (5.3–9.7)</td>
<td>59.7 (54.8–64.6)</td>
</tr>
<tr>
<td>21</td>
<td>36</td>
<td>258</td>
<td>17</td>
<td>6.6 (3.6–9.6)</td>
<td>64.4 (56.4–72.4)</td>
</tr>
<tr>
<td>22</td>
<td>37</td>
<td>93</td>
<td>9</td>
<td>9.7 (3.7–15.7)</td>
<td>54.8 (46.8–62.9)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>14,090</td>
<td>917</td>
<td>6.5 (6.1–6.9)</td>
<td>65.9 (64.7–67.1)</td>
</tr>
</tbody>
</table>

RESULTS

A total of 14,090 primiparas were included in this study. The women were aged 24 to 37 years; between 9 and 22 years have elapsed since they received the vaccine, when they were third-grade students in junior high school. For all primiparous women (Table 1), the average seronegativity of rubella virus was 6.5% (917/14,090 women; 95% CI, 6.1 to 6.9%), and the average rubella virus antibody titer was 65.9 IU/ml (95% CI, 64.7 to 67.1 IU/ml). The rubella virus seronegativity rates, which ranged from 5.2 to 9.7% (Fig. 1), did not exhibit a linear trend from 9 to 22 years after vaccination (P = 0.201); in contrast, the average rubella virus IgG levels of <10 IU/ml were considered to be seronegative, susceptible, or nonimmune.

MATERIALS AND METHODS

Study design. This study involved an analysis of the results of 14,090 rubella virus antibody tests for native Taiwanese primiparas who received routine prenatal examinations at two hospitals in northern Taiwan (Taipei), one hospital in central Taiwan (Chiayi), and two hospitals in southern Taiwan (Koshsiung and Pingtung). These two medical centers and three regional hospitals specialize in obstetric health care. All of these pregnant women received routine prenatal examinations at one of the five hospitals, which supplied obstetric health care, between 2002 and 2008, when the rubella virus antibody test was a compulsory checkup item during routine prenatal examinations in Taiwan. The subjects had received the rubella (RA 27/3) or MMR (RA 27/3) vaccine when they were third-grade students in junior high school (15 years old), during 1986 to 1994. The Fooyin University Hospital Ethics Review Board approved this study protocol (FYH-IRB-97003).

SeroLOGY tests. Rubella virus IgG antibodies were determined through a microparticle enzyme immunoassay (MEIA), using an AsXYM analyzer (Abbott Laboratories, Chicago, IL). The lower and upper detection limits for rubella virus IgG were 0.1 and 500 IU/ml, respectively. Serum IgG levels of ≥10 IU/ml were considered to be seropositive or immune; those
Rubella Virus Antibodies in Primiparous Women

The vaccine strain is the key factor influencing the persistence of rubella virus antibodies. The RA 27/3 strain is the most widely used vaccine in the world—except in Japan, where five attenuated rubella vaccines have been licensed and are now in use (23). The RA 27/3 vaccine strain generally induces higher antibody titers and produces antibody responses that most resemble natural infection. The resulting rubella immunity probably persists for a long time (>20 years). Therefore, it is the most widely used vaccine in the world. Previous studies demonstrated a 100% seroconversion rate in children who had each been vaccinated with a single dose of RA 27/3 vaccine (6, 16). From a study of the expression of interleukin-2 receptor alpha and CD45RO antigen on T lymphocytes, Toyoda and colleagues noted that T-cell-mediated immunity and humoral immunity persisted for at least 20 years after vaccination (22). Kremer and colleagues demonstrated that the minimal annual antibody decay rate for vaccinees is −2.9% (10). The concentration of antibodies significantly decayed among high-titer individuals and did not significantly decrease in the low-titer group. O’Shea et al. found that 97.9% of RA 27/3 vaccinees were seropositive 10 to 21 years after immunization (14). Horstmann and colleagues reported that the RA 27/3 vaccine provided high immunogenicity and resulted in high antibody titers; after 11 years, 95% of subjects who seroconverted were tested for hemagglutination inhibition (HI), and 100% had neutralizing antibodies (8). In this study, we found that the seronegativity rate was 9.7% for primiparous women who had been vaccinated with the RA 27/3 strain 22 years ago.

Vaccine dose is also an important point for the persistence of rubella virus antibodies. At present, to interrupt endemic virus circulation, two doses of MMR vaccine are provided to all children at 12 to 18 months and at preschool or school age. In the present study, we observed a relatively low seronegativity rate (6.5%) among women of childbearing age who had each been vaccinated with a single dose of rubella vaccine at 15 years of age; nevertheless, women with weakly positive antibody titers (10 to 20 IU/ml) accounted for 8.7% of the cohort. Based on the annual decay rate (−0.77 IU/ml), we estimate that approximately 6.4% (900/14,090 women) of women will likely become seronegative in the next decade. Therefore, we suggest that it should remain an important policy to encourage voluntary immunization of susceptible women of childbearing age.

In the present analysis, the study subjects were primiparous women, thereby reducing the interference of postpartum immunization. Some of the women might, however, have obtained immunity by checking their rubella virus antibody levels and being vaccinated prior to getting married or through natural infection.

FIG 2 Rubella virus antibody titers with 95% confidence intervals for primiparous women 9 to 22 years after vaccination in the third grade of junior high school (at 15 years of age).

FIG 3 Distribution of rubella virus antibody titers in primiparous women 9 to 22 years after vaccination in the third grade of junior high school (at 15 years of age).
In Taiwan’s national health insurance system, however, the code for rubella testing for nonpregnant women is different from that for pregnant women. We found that the number of rubella tests for nonpregnant women accounted for only 0.08% of the total number of tests during the study period in these hospitals. Thus, subjects who checked their levels of rubella virus antibodies and underwent immunization prior to marriage were rare. According to the statistics from the CDC in Taiwan, the lower annual incidence rate of rubella ranged from 0.009 to 0.235 per 100,000 individuals during the period 1999–2008 (3); nevertheless, many patients with rubella have only mild symptoms or even no symptoms, so their numbers may have been underreported. Wang et al. reported the probability of natural infection in unvaccinated women who had high titers, averaging 214 IU/ml (24). In the present study, we found that 3.4% of the primiparous women had antibody titers of ≥200 IU/ml; these women may have had a large immune response to a previous vaccination, had contact with the wild-type virus, or been revaccinated recently.

Our findings suggest that mandatory vaccination programs with a high coverage rate in junior high school students have been successful. Although the levels of rubella virus antibodies have declined slowly in women of childbearing age who were vaccinated with the RA 27/3 vaccine, their seronegativity rate at present is relatively low (6.5%). The number of women who were seronegative or provided weakly positive antibody titers accounted for 15.2% of the cohort. Therefore, in countries that implement a single-dose regimen in children or teenagers, it should remain an important policy to encourage voluntary immunization in seronegative women and to immunize all postpartum women who are susceptible to rubella virus infection before they leave the hospital.

REFERENCES