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Rubella seroprevalence among the general population in Dongguan, China

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Summary: In order to assess immunity to rubella infection in Dongguan, China, we conducted a seroprevalence survey on rubella and measured rubella-specific IgG in serum samples by ELISA. A total of 1017 individuals aged 0–59 years were selected with a multistage cluster sampling. Among them, 904 (88.9%) were seropositive to rubella. Two groups (20–29 and ≥40 years) had seropositivity rates <90%. Compared to participants age ≥20 years, rubella protection rates were higher in participants aged <20 years (93.7% vs. 83.2%; $\chi^2=28.063$, $p<0.001$). Among women aged 20–29 years, only 63.8% had antibodies above the protective level. Multivariate analysis revealed that only sex and age were significantly associated with rubella protective antibody levels. Our results suggest that the women of childbearing age have greater serological susceptibility to rubella in our area. Additional vaccination of susceptible young adults with rubella-containing vaccine should be considered, especially in women before pregnancy.

**Key words:** rubella, seroprevalence, vaccination, antibody

1. Introduction

Rubella is a mild self-limiting infectious disease that mainly occurs in children. However, infection with rubella virus in the first trimester of pregnancy may lead to miscarriage, stillbirth or a child born with congenital rubella syndrome (CRS). CRS is one of the greatest risks to newborn infants and may entail a variety of birth defects, like sensorineural deafness, cataract, and cardiac defects (1, 2).
Therefore, in 2000, the World Health Organization (WHO) recommended the use of rubella-containing vaccine (RCV) in all national childhood immunization schedules to prevent congenital rubella infection, including CRS (3). Moreover, goals to eliminate rubella and CRS were established by WHO in America in 2010 and will be proposed in the European and Western Pacific regions in 2015 (4, 5).

Rubella has been included in the surveillance system in China since 2004. The reported incidence of rubella in China was 9.11 per 100,000 population in 2008 and 5.26 per 100,000 population in 2009. The proportion of rubella cases aged <20 years was 82.54%. In Eastern China (RCV was introduced earlier than in central and western areas), cases aged 15–35 years accounted for 52.35% and 55.60% of the total in the two study years, respectively, and the proportion of cases in this age group was higher than that in central and western areas (6).

In China, a single dose of rubella vaccine was introduced in 1995, and in 2007 RCV was implemented in the national immunization program with a catch-up campaign targeting children aged 1–14 years (7, 8) In Guangdong province, rubella vaccine was included into the Guangdong Expanded Program of Immunization (EPI) in 2001, but recipients should charge for the vaccine until 2008 (9). According to the national vaccination program, RCV is planned in children at age 8 months and 18–24 months. Before 2008, the rubella vaccine coverage in 1-year-old children was 50–60% in China (7, 10).

Sero logical survey can provide useful information to identify the subpopulation at risk and address possible immunization strategies for rubella. In
this study, we collected serum and used ELISA kits to determine rubella antibody (IgG) to evaluate immunity to rubella following implementation of the rubella vaccination program in Dongguan city, Southern Guangdong province, and to assess factors influencing immunity against rubella.

2. Materials and methods

2.1. Study design

A multistage sampling design was used. The 33 towns in Dongguan were stratified into five regions (east, south, central, west and north) to account for geographic variations. One town in each region was sampled and two villages in each town were then selected. A starting household was identified from a list of households in each selected village. Simple random sampling selection was used for the towns, villages and starting households. The house was then examined to determine if anyone of eligible age (0–59 years) was living there. Subsequently, the nearest household to the right was visited and the steps repeated until the desired number of persons (at least 100 participants for each village) was obtained.

Sera were stratified into seven age groups: <2 years, 2–4 years, 5–9 years, 10–19 years, 20–29 years, 30–39 years, and ≥40 years. The formula

\[ n_i = \frac{z^2 N_i P_i (1 - P_i)}{z^2 P_i (1 - P_i) + (N_i - 1) e^2 P_i^2} \]

was used to calculate the sample size for each age group [11], which estimated the age-specific seroprevalence as 80–90% [12], with a precision of 0.1; the calculated sample size was between 42 and 96 in
different age group. The serological survey was conducted from March to April 2012. A total of 1367 individuals in 414 households from which eligible subjects were invited to participate, 1017 (74.4%) eventually participated by filling out a questionnaire and by donating a single blood sample.

Approval for the study was obtained each year from the Medical Ethics Committee of the Guangdong Medical College (PJ2012035). Written informed consent forms were signed by individuals or by parents of children.

2.2. Data collection

Each participant was asked to fill out a questionnaire anonymously about personal information such as sex, date of birth, occupation, education status, marital status, residential status (local residents or immigrants, the immigrant were those lived in Dongguan at least 3 months before sampling), and date of sampling. Information regarding the RCV vaccination (routine and campaign) was collected from the China Information Management System for Immunization Programming.

2.3. Laboratory assay

Rubella antibody (IgG) was estimated using commercially available ELISA kits (VirionSerion, Würzburg, Germany). The laboratory results were interpreted according to the manufacturer's instructions. The positive cut-off value was 20 IU/mL, and weakly positive samples (10–20 IU/mL) were considered equivocal. A
value of <10 IU/mL was considered negative.

2.3. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0. The total seropositivity rate was calculated by the adjusted sampling weight, and the formula \( w = \frac{\sum n_i}{C_i} \) was used to calculate the adjusted sampling weight, where \( C_i \) is the age group proportion, and \( n_i \) is the sample size in the age group. The age group proportion was based on the data from the 6th Chinese Population Census.

The associations between rubella antibody positivity and age, sex, occupation, education status, marital status, and residential status were analyzed using the Pearson \( \chi^2 \) test or \( \chi^2 \) test with continuity correction. The Kruskal–Wallis H and Mann–Whitney U tests were used for comparisons of rubella antibody titers between groups. Multivariate logistic regression was applied to determine the factors that influenced rubella antibody positivity. Variance inflation factor (VIF) was used to check for multi-collinearity. A \( p \) value <0.05 was taken as the level of significance.

3. Results

3.1. Demographics

A total of 1017 individuals in Dongguan city aged 0–60 years [502 (49.4%) male and 515 (50.6%) female] were enrolled in the seroprevalence study. There were 341 (33.5%) students, 227 (22.4%) workers and 207 (20.4%) children.
Education status was low (primary school or below) in 493 (48.5%) individuals (included 420 children and 73 adults), middle level (high school) in 413 (40.6%), and high (college or graduate school) in 111 (10.9%). For marital status, 601 (59.1%) individuals were unmarried, 390 (38.3%) were married, and 26 (2.6%) were of other status. There were 485 (47.7%) local residents and 532 (52.3%) immigrants.

3.2. Coverage rate of RCV

In the catch-up campaign in 2008, a total of 395,590 eligible children (aged 1-14 years old) were identified in Dongguan and the coverage rate was 100%.

In the birth cohort during November 2007 to October 2011, there were 656,627 eligible children for the first dose of RCV and the coverage rate was 100%. There were 789,312 eligible children for the second dose of RCV; 456,985 children received the second dose and the coverage rate was only 58.9%.

3.3. Prevalence of seropositivity and antibody against rubella

The median rubella antibody titer was 44.36 IU/mL (interquartile range: 31.21–60.71 IU/mL). The titer differed among the age groups ($\chi^2=78.264$, $p<0.001$). Rubella antibody titer was significantly higher in males than females (48.30 IU/mL, interquartile range: 36.27–75.32 IU/mL vs. 40.57 IU/mL, interquartile range: 25.06–54.54 IU/mL; Z=8.645, $p<0.001$) (Table 1).
3.4. Factors associated with rubella seroprevalence

Of the 1017 individuals, 904 (88.9%) were positive for rubella antibodies, 93 (9.1%) were equivocal, and 20 (2.0%) were negative. This corresponds to an adjusted prevalence of 86.2% in the Dongguan population. Five age groups (<2, 2–4, 5–9, 10–19 and 30–39 years) had seropositivity rates >90%, and two groups (20–29 and ≥40 years) had seropositivity rates <90%. The lowest seropositivity rate was 77.0% in the 20–29 years age group (Table 2). When considering age and sex, all five female age groups (≥5 years) had seropositivity rates <90%, and the lowest seropositivity rate was 63.8% in the 20–29 years age group (Table 2). Compared to people aged ≥20 years, rubella protection rates were higher in those aged <20 years (93.7% vs. 83.2%; χ^2=28.063, p<0.001).

In bivariate analyses, the seropositive rate among females was 81.7% (421/515), which was lower than that among males [96.2% (483/502)] [odds ratio (OR) =0.85, 95% confidence interval (CI): 0.81, 0.89; χ^2=53.87, p<0.001]. Seropositivity differed among the age groups (χ^2 =58.078, p<0.001). Education level, occupation and marital status were associated with seropositivity (p<0.001). There was no significant association between residential status and rubella antibody positivity (p>0.05) (Table 2).

Multiple logistic regression models were used to control potential confounders, which showed that compared with people aged 20–29 years, those aged 10–19 years and 30–39 years were 2.82 (95% CI: 1.23, 6.48) and 4.37 (95% CI: 1.97, 9.69) times more likely to be seropositive for rubella, respectively. Compared with
males, females had lower seropositivity to rubella virus (OR=0.14, 95% CI: 0.08–0.24). VIF was used to check for multi-collinearity. None of the VIF values was up to 5, which meant there was no colinearity in the model (Table 2).

4. Discussion

Our study showed a total seropositivity of 86.2% in the general population in Dongguan. Rubella appears in periodic epidemics in countries without routine immunization programs. Before routine administration of RCV in children, the seropositivity in the general population in Shenzhen was 68.09% in 2001 (13), and it was 73.07% in Guangzhou population during 1986 to 1987 (14). After the inclusion of rubella vaccine in the EPI, two seroepidemiology surveys were conducted in Shandong province (2009–2010) and Hefei city (2011), with seropositivity rates of 83.13% and 80.8%, respectively (12,15). The results were similar our data, and compared to the pre-vaccine era, the seropositivity in the general population was increased.

In our study, the seropositivity rate was high in people aged <20 years, which may have been due to routine rubella vaccination and the catch-up campaign in 2008 (which targeted children aged 1–14 years). Our study was conducted in 2012, which means that most of the participants aged 5–19 years had received RCV in this catch-up campaign. Children aged 1–4 years were more likely to have received routine rubella vaccination. Similarly, the seropositivity rate in children aged <15 years in Shandong province (80.9%) and Hefei city (73.2%) was higher.
than 39.9% in this age group in Guangzhou (12-15).

Our results were consistent with previous studies in which age was an independent predictor of anti-rubella antibody positivity (16, 17). As mentioned before, the use of rubella vaccine may result in high positivity in participants aged <20 years. Most participants aged ≥20 years (people born before 2008) acquired immunity from natural infection. Differences in circulation of the virus and epidemics of rubella in the community may explain the positivity variation. In addition, there is evidence that inadequate rubella vaccination coverage (≤80%) may disturb transmission dynamics. As a result, the susceptibility age increases, and susceptibility among women of childbearing age may increase the risk of CRS (18). It has been reported that the susceptibility age increased after rubella immunization of children in Shandong province (10). In Dongguan, during 2007–2011, the incidence of rubella was 1.24 per 100,000 population, and the highest proportion of 36.18% of the total cases was in those aged 20–29 years (19). Routine RCV administration in our area only started in 2008, thus, the effect of the vaccination program should be investigated further, especially the impact on the age-susceptibility pattern. Our current data show that two age groups (20–29 and ≥40 years) had comparatively low rates of rubella antibody positivity, and, notably, only 63.8% of women aged 20–29 years had antibodies above the protective level. The legal age for marriage is 20 years for women in China (Law of Marriage of People’s Republic of China, amended on April 28, 2001). In 2010, the mean childbearing age was 28.18 years (20). This means that the peak
childbearing age of women in China is 20–29 years. Together with the epidemiological characteristics of rubella in Dongguan (18), our results provide seroepidemiological evidence confirming the high disease burden in women of childbearing age during rubella outbreaks and the high risk of CRS in our area.

Similar to previous studies (21), our results showed that women had lower seropositivity rates than men. However, inconsistent results have been reported in previous studies. Some studies have shown that women were more likely to have high seropositivity against rubella (4), and other studies have reported no significant sex difference in seropositivity against rubella (22). This inconsistency may be partly explained by differences in rubella infection and vaccination histories between study populations.

There were some limitations to the present study. First, few of the participants reported a history of rubella vaccination, and we excluded data of vaccination history in the final analysis. So, we could not identify the effect of vaccination on the seroprevalence of rubella in the population. Second, the number of younger children (<2 years) was relatively small, because the parents (especially those with children <1 year) were unwilling to donate a blood sample from their children. The number of samples from children aged <1 year was so small that we could not stratify this age group and analyze it independently. Third, the serology results may be biased, because the first and the second sampling stages were not conducted by probability proportionate to size sampling, number of cluster is relatively small, and sampling design was not considered when calculate
prevalence.

In conclusion, our study showed that people aged 20–29 and ≥40 years had low rates of rubella seropositivity, especially women. Two doses of RCV have been given routinely to children in our area since 2008. The vaccination may disturb transmission dynamics of the disease, and inadequate vaccination coverage may result in an increase in susceptibility age (18). Therefore, maintaining high vaccination coverage in children and implementation of sensitive disease surveillance are necessary for controlling the disease and RCV. Women of childbearing age have high serological susceptibility to rubella in our area, which suggests that additional RCV vaccination of susceptible young adults should be considered, especially in women before pregnancy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgements
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References


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<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total median (IU/ml) (QIR)</th>
<th>Male Seropositive (n/N*,%)</th>
<th>Female Seropositive (n/N*,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>36.73(31.61,44.86)</td>
<td>22/23(95.7)</td>
<td>22/24(91.7)</td>
</tr>
<tr>
<td>2–4</td>
<td>43.07(33.16,50.57)</td>
<td>57/60(95.0)</td>
<td>57/58(98.3)</td>
</tr>
<tr>
<td>5–9</td>
<td>48.14(34.19,60.12)</td>
<td>89/91(97.8)</td>
<td>88/100(88.0)</td>
</tr>
<tr>
<td>10–19</td>
<td>49.94(36.33,68.06)</td>
<td>97/99(98.0)</td>
<td>86/98(87.8)</td>
</tr>
<tr>
<td>20–29</td>
<td>36.04(20.83,50.59)</td>
<td>84/93(90.3)</td>
<td>66/94(63.8)</td>
</tr>
<tr>
<td>30–39</td>
<td>49.88(37.25,82.35)</td>
<td>72/72(100)</td>
<td>61/69(88.4)</td>
</tr>
<tr>
<td>≥40</td>
<td>40.50(21.26,97.81)</td>
<td>62/64(96.9)</td>
<td>47/72(65.3)</td>
</tr>
</tbody>
</table>

*n/N* = seropositive samples/total
Table 2 Demographic characteristic of individuals with seropositivity to rubella

<table>
<thead>
<tr>
<th>Classification</th>
<th>Seropositive (n/N*, %)</th>
<th>95% CI (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>483/502 (96.2)</td>
<td>93.5, 97.9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>421/515 (81.7)</td>
<td>78.4, 85.0</td>
<td>0.85 (0.81, 0.89)</td>
<td>0.14 (0.08, 0.24)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>201/211 (95.3)</td>
<td>92.4, 98.2</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>310/341 (90.9)</td>
<td>87.9, 94.0</td>
<td>0.46 (0.21, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Worker</td>
<td>192/227 (84.6)</td>
<td>79.9, 89.3</td>
<td>0.25 (0.12, 0.53)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>201/238 (84.5)</td>
<td>79.9, 89.1</td>
<td>0.24 (0.12, 0.52)</td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school (Children)</td>
<td>398/420 (94.8)</td>
<td>92.7, 96.9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Primary school (Adults)</td>
<td>58/73 (79.5)</td>
<td>70.2, 88.8</td>
<td>0.21 (0.11, 0.42)</td>
<td>0.132 (0.02, 1.19)</td>
</tr>
<tr>
<td>High school</td>
<td>354/413 (85.7)</td>
<td>82.3, 89.1</td>
<td>0.33 (0.20, 0.55)</td>
<td>0.13 (0.02, 1.06)</td>
</tr>
<tr>
<td>College or graduate school</td>
<td>94/111 (84.7)</td>
<td>78.0, 91.4</td>
<td>0.31 (0.16, 0.60)</td>
<td>0.14 (0.02, 1.20)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>548/601 (91.5)</td>
<td>89.3, 93.7</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>330/390 (84.6)</td>
<td>81.0, 88.2</td>
<td>0.51 (0.34, 0.76)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>24/26 (92.3)</td>
<td>75.0, 99.0</td>
<td>1.21 (0.28, 5.24)</td>
<td></td>
</tr>
<tr>
<td><strong>Residential status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>476/485 (89.5)</td>
<td>86.8, 92.2</td>
<td>1.13 (0.77, 1.67)</td>
<td></td>
</tr>
<tr>
<td>Immigrants</td>
<td>428/532 (88.2)</td>
<td>85.5, 90.9</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Age groups (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>44/47 (93.6)</td>
<td>83.0, 98.0</td>
<td>4.38 (1.30, 14.81)</td>
<td>0.63 (0.05, 7.41)</td>
</tr>
<tr>
<td>2–4</td>
<td>114/118 (96.6)</td>
<td>93.3, 99.9</td>
<td>8.51 (2.97, 24.41)</td>
<td>1.22 (0.11, 13.09)</td>
</tr>
<tr>
<td>5–9</td>
<td>177/191 (92.7)</td>
<td>89.0, 96.4</td>
<td>3.78 (1.99, 7.17)</td>
<td>0.56 (0.06, 5.11)</td>
</tr>
<tr>
<td>10–19</td>
<td>183/197 (92.9)</td>
<td>89.3, 96.5</td>
<td>3.90 (2.06, 7.41)</td>
<td>2.82 (1.23, 6.48)</td>
</tr>
<tr>
<td>20–29</td>
<td>144/187 (77.0)</td>
<td>71.0, 83.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>30–39</td>
<td>133/141 (94.3)</td>
<td>90.5, 98.1</td>
<td>4.08 (2.07, 8.04)</td>
<td>4.37 (1.97, 9.69)</td>
</tr>
<tr>
<td>≥40</td>
<td>109/136 (80.1)</td>
<td>73.4, 86.8</td>
<td>0.99 (0.56, 1.76)</td>
<td>0.95 (0.48, 1.89)</td>
</tr>
</tbody>
</table>

* Reference category
* n/N= seropositive samples/total
* VIF=1.00