Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam

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ARTICLE INFO

ABSTRACT

To investigate susceptibility to and factors associated with rubella infection among pregnant mothers and to estimate the burden of congenital rubella infection (CRI) in Vietnam where rubella-containing vaccine (RCV) is not included in the routine immunization program, we conducted a prospective cohort study in Nha Trang, Vietnam between 2009 and 2010. Rubella-specific immunoglobulin-M and immunoglobulin-G were investigated in cord blood samples by enzyme immunoassay. Corresponding clinical–epidemiological data were analyzed and the national congenital rubella syndrome (CRS) incidence was estimated using modeling. We enrolled 1988 pairs of mothers aged 17–45 years and their newborn babies. No mothers had received RCV. Multivariate analysis revealed that mothers aged 17–24 (aOR 2.5, 95% CI: 1.7–3.8) or 25–34 (1.4, 1.0–2.1) years were more likely to be susceptible than those aged 35–45 years. Overall 28.9% (574/1988, 95% CI: 26.9–30.9%) of mothers were seronegative. The CRI rate was 151 (95% CI: 0–322) per 100,000 live births. Modeling estimated that 3788 babies (95% CI: 3283–4143) were born with CRS annually in Vietnam with an overall CRS incidence of 234 (95% CI: 207–262) cases per 100,000 live births. A substantial proportion of women of childbearing age (WCBA) are at risk of rubella infection during pregnancy and this can result in a high frequency of miscarriage or burden of CRS across Vietnam. Prompt introduction of RCV into national immunization program with catch-up vaccination to children and WCBA will reduce CRI in Vietnam.

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1. Introduction

Rubella is a mild self-limiting infection associated with fever and rash and mainly occurring in children. However, if infected in their first 8–10 weeks of gestation, up to 90% of pregnant women may face miscarriage, stillbirth or a child born with congenital rubella syndrome (CRS). This is associated with significant disability, including sensorineural deafness, cataract, and cardiac defects [1–3]. Therefore the primary goal in controlling rubella is to prevent miscarriage and CRS by an adequate rubella immunization program [2].

The epidemiology and burden of CRS in Vietnam is poorly understood. The number of WHO member countries which had introduced rubella-containing vaccine (RCV) into their routine immunization program increased from 83 (43%) in 1996 to 131 (68%) in 2010, resulting in an 82% decline in the number of reported rubella cases by 2009 [4,5]. However, out of 36 countries in the Western Pacific Region, Vietnam remains one of 6 countries which have not used RCV as of 2009, and has been experiencing periodic rubella outbreaks and, potentially, a large burden of CRS. Adolescents and adults comprised most of the reported cases of rubella in outbreaks, and, notably, 60% of female cases were WCBA in 2009 [6,7].

Due to under-reporting of rubella cases and difficulties with diagnosing CRS, estimates of the incidence of rubella and burden of CRS obtained from surveillance data are often unreliable. However, adequate population-based serological data collected through a prospective cohort study may provide insight into these statistics. Such data have not been available in Vietnam before 2012.

In this paper, we describe a prospective cohort study of rubella serological survey in Nha Trang, Central Vietnam which aimed to (1) investigate susceptibility to and factors associated with rubella infection among pregnant mothers, (2) investigate the rate and outcomes of congenital rubella infection (CRI), and (3) estimate the burden of CRS in Vietnam.

2. Materials and methods

2.1. Study design, period and location

A prospective cohort study was conducted from May 2009 to May 2010 in Nha Trang. This study site has a population of approximately 390,000 and is located in Khanh Hoa Province, Central Vietnam. Khanh Hoa General Hospital (KHGH) is a provincial hospital with 900 beds which covers the whole Khanh Hoa Province, and provides comprehensive medical services, with approximately 6000 babies delivered annually. The study was conducted in 16 out of 24 communes in Nha Trang because detailed population and demographic data were available for these communes from our census surveys in 2006 and 2010. Since Nha Trang is a tourist city, communes which have big blocks of government administrative buildings, hotels and restaurant areas were not included in the survey. RCV has not been introduced into the national immunization program at the time of the study. A negligible proportion of the population is believed to get access to RCV at the private sector/clinics in Nha Trang, although private sector vaccination services have been expanding in Hanoi and Ho Chi Minh City [7].

2.2. Subjects and recruitment process

The samples were collected as part of a birth cohort study. Mothers aged $\geq$17 years residing in 16 target communes in Nha Trang who delivered a single child at KHGH without severe complications on weekdays during this study period were recruited, together with their newborn babies. The study recruited pregnant women with no serious complications on admission during the study period because it is unethical or difficult to ask a pregnant mother who is in a serious condition on admission for informed consent. We did not recruit women who give birth to two or more babies in the study because the CRI rate of the babies may differ and it will be difficult to analyze the risk factors. We did not collect samples during weekends due to a shortage of staff, but recorded all the deliveries, including those on weekends, to calculate the CRI incidence. Written informed consent was obtained from participants, and clinical–epidemiological information was collected through interview using a structured questionnaire before the delivery and from medical charts or maternal health cards. The whole process was done by two trained research nurses and supervised by a research clinician.

2.3. Sample collection and testing

Cord blood samples were collected at the time of delivery. The blood was centrifuged for 5 min at 1500 rpm, and separated plasma was kept in $-80\,^{\circ}$C freezers. The plasma samples were transported to Nagasaki, Japan [8], and tested for rubella-specific immunoglobulin-M (IgM) and immunoglobulin-G (IgG) by enzyme immunoassay (EIA) (Mini VIDAS). The cut-off values of the assay were 1.2 and 4.0, respectively, in accordance with the company recommendation.

2.4. Characteristic categorization definition

Maternal educational level was categorized into three groups, based on the educational system in Vietnam, namely none–primary, lower–upper secondary and higher education, which were defined as 0–5, 6–12, and $\geq$13 years of schooling, respectively [9]. Paternal occupations were classified into four groups: 1, unemployed (including students); 2, unskilled workers/farmers/soldiers; 3, officers/skilled workers; and 4, professionals/owners of enterprise. Residential areas where the mothers lived were defined as urban and rural according to Vietnam government administrative categorization. The number of mothers who visited antenatal care (ANC) $\geq$4 times was calculated, following WHO recommendations [10]. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters (kg/m^2) and underweight was classified as BMI < 18.5 by WHO criteria [11]. Anemia was defined for pregnant women according to WHO criteria as hemoglobin of <11.0 g/dl [12]. Births were considered preterm if they occurred after less than 37 gestational weeks (GWs), and low birth weight (LBW) if the birth weight (BW) was less than 2500 g, following the guidelines in the International Classification of Diseases-10: version 2010 [13]. A diagram of BW percentiles by GWs was created based on data collected from subjects, using previous methods [14,15], with a mean BW at 40 weeks of 3379.6 g and a standard deviation of 11.4% of the mean BW. Babies who were "light-for-dates" (defined as those with BW below the 10th percentile [13]) were identified from this figure (Appendix A). CRI was defined using the WHO case definition [15] as infection with no clinical signs of CRS but positive for rubella-specific IgM.

2.5. Data management, statistical analysis

All the collected information was managed confidentially throughout the process. The data were double-entered and cleaned, and statistical analysis was conducted with IBM SPSS Statistics 18. Odds ratio (OR) or adjusted OR (aOR) with its 95% confidence interval (95% CI) and *p*-values for factors associated with seronegativity were calculated by either chi-square or logistic regression for univariate analysis and by logistic regression for multivariate analyses. A *p*-value of less than 0.05 was considered statistically significant. The overall proportion of individuals who were seronegative based on rubella-specific IgG and the proportion who were rubella-specific IgM-positive were calculated together with their 95% CI. The age distribution of the enrolled mothers and the age-specific proportion that were seronegative were plotted. Infants with CRI were invited for medical follow-up including physical, neurodevelopment and auditory examinations at 10 months and 24 months of age. Auditory function tests were conducted with distortion product otoacoustic emission for the former session and automated auditory brainstem response for the latter (echo-screen II). Furthermore, cardiovascular examination was conducted with echocardiogram (Viamo SSA-640A) for the latter session. Japanese pediatricians performed the above examinations in cooperation with Vietnamese staff.

2.6. Estimating the CRS incidence using modeling

Following previous methods [16], an age-structured catalytic model was fitted to the observed age-stratified serological data using maximum likelihood to estimate the force of infection for rubella (defined as the rate at which susceptible are infected per unit time). The force of infection was assumed to differ