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Rubella susceptibility in pregnant women and results of a postpartum immunization strategy in Catalonia, Spain.

Alba VILAJELIU[a,b]; Alberto L. GARCÍA-BASTEIRO[b,c]; Salomé VALENCIA[a,b]; Saul BARREALES[a,b]; Laura OLIVERAS [a,b];Valentín CALVENTE[a]; Anna GONCÉ[d]; José M. BAYAS[a,b].

[a]Department of Preventive Medicine and Epidemiology. Hospital Clínic - Universitat de Barcelona, Barcelona, Spain

[b]ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain.

[c]Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique.

[d]Department of Maternal-Fetal Medicine. BCNatal - Barcelona Center of Maternal-Fetal and Neonatal Medicine. Hospital Clínic and Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain.

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Corresponding author:

Alberto L. García-Basteiro

Barcelona Institute for Global Health (ISGlobal).

Rosselló, 132, 5/1,

08036 Barcelona, Spain.

Telephone: +34 93 227 1806

Fax: +34 932 279 853

alberto.garcia-basteiro@isglobal.org

Abbreviations:

AVC- Adult Vaccination Centre; CI - Confidence interval; CRS - Congenital Rubella Syndrome (CRS); HCB - Hospital Clinic of Barcelona; IgG - Immunoglobulin G; IU - International Units; MMR - Measles, Mumps and Rubella vaccine; OR – Odds Ratio; SD – Standard deviation; WHO – World Health Organization

41**Abstract**

42**Background:**

43Elimination of congenital rubella syndrome depends not only on effective
44childhood immunization but also on the identification and immunization of
45rubella susceptible women. We assessed rubella susceptibility among pregnant
46women and evaluated the adherence and response to postpartum
47immunization with measles, mumps and rubella (MMR) vaccine.

48

49**Methods:**

50Cross-sectional study of women who gave birth at the Hospital Clinic de
51Barcelona (Spain) between January 2008 and December 2013. Antenatal
52serological screening for rubella was performed in all women during pregnancy.
53In rubella-susceptible women, two doses of MMR vaccine were recommended
54following birth. We evaluated rubella serological response to MMR vaccination
55in mothers who complied with the recommendations.

56

57**Results:**

58A total of 22,681 pregnant women were included in the study. The mean age
59was 32.3 years (SD 5.6), and 73.6% were primipara. The proportion of
60immigrants ranged from 43.4% in 2010 to 38.5% in 2012. The proportion of
61women susceptible to rubella was 5.9% (1328). Susceptibility to rubella
62declined with increasing maternal age. Immigrant pregnant women were more
63susceptible to rubella (7.6%) than women born in Spain (4.6%). Multivariate
64analyses showed that younger age (≤ 19 years) aOR 1.7 (95% CI 1.1- 2.5),
65primiparas aOR 1.3 (95% CI 1.1-1.5) and immigrant women aOR 1.6 (95% CI

1.4-1.8) were more likely to be susceptible. The second dose of MMR vaccine was received by 57.2% (718/1256) of rubella-susceptible women, with the highest proportion being immigrant women compared with women born in Spain. After vaccination, all women showed rubella immunity.

Conclusions:

The higher rubella susceptibility found in the three youngest age groups and in immigrant women highlights the relevance of antenatal screening, in order to ensure identification and postpartum immunization. The postpartum immunization strategy is an opportunity to protect women of childbearing age and consequently prevent occurrence of CRS, and to increase vaccination coverage against rubella and other vaccine-preventable diseases.

Keywords**:** rubella; pregnancy; susceptibility; postpartum immunization; adherence; MMR vaccine.

Main text

Introduction

Rubella infection occurring just before conception and during early pregnancy may result in miscarriage, fetal death, or congenital defects known as congenital rubella syndrome (CRS) [1–4]. The extent of the involvement depends on the time of pregnancy at which infection occurs. The highest risk of CRS is found in countries with high rates of rubella susceptibility among women of childbearing age[2].

In 1998, the World Health Organization (WHO) European Region approved the aims of eliminating indigenous measles and rubella, and controlling congenital rubella [2,5,6]. The most important strategy for preventing rubella is immunization of susceptible individuals. However, individuals may be immunized by past vaccination or natural infection [2]. The effectiveness of the rubella vaccine has been demonstrated by the elimination of rubella and CRS from the Region of the Americas [2,7]. The aim of interrupting the endemic transmission of measles and rubella in Europe in 2015 will only be achieved with a high coverage of vaccination (> 95% with two doses of measles, mumps and rubella (MMR) vaccine) in all geographical areas and all population groups, together with a high-quality surveillance system [8].

Post-delivery vaccination strategies should include MMR vaccination in women susceptible to these diseases. In susceptible pregnant women, immunization with this live attenuated vaccine should be administrated during the postpartum period [2,9,10].

In Spain, rubella is a notifiable disease and is monitored through the Spanish Surveillance System [11]. Reported cases of rubella in 2012 were the highest since 2008 (64 confirmed cases: 0.14 cases per 100,000 inhabitants) and most cases occurred in unvaccinated adolescents and young adults. In the 2008-2012 period, 4 rubella outbreaks and 3 cases of CRS have been recorded in immigrants from countries where the rubella vaccine is not routinely administered in childhood [8]. Although the viral circulation of rubella in Spain is supposedly low, it is important to monitor rubella susceptibility, especially in immigrant women, given the observed increase in the immigrant population in recent years, with Spain being one of the main receptor countries in the European Union [12]. In Catalonia, the region where this study was conducted, all pregnant women are screened for rubella antibodies in the first antenatal blood test [11,13].

The objectives of this study were to assess rubella susceptibility in the antenatal rubella serology screening; to identify factors associated with susceptible women and to evaluate the adherence and the immunological response to postpartum immunization strategy with MMR vaccine in rubella susceptible women.

Materials and Methods

Study characteristics

We made a cross-sectional study of women who gave birth at the Hospital Clinic of Barcelona (HCB) between January 2008 and December 2013.

Rubella immunization practices

In Catalonia, an autonomous region in the northeast of Spain with nearly 7.5 million inhabitants, rubella-containing vaccine was introduced into the routine immunization schedule in 1978 for all girls aged 11 years (women born after 1967) [14]. In 1980, in order to improve measles control, the MMR vaccine was introduced in children aged 15 months. In 1987, the MMR replaced the rubella vaccine at 11 years of age. In 1998, the age of administration of the second MMR dose was advanced from 11 to 4 years. Finally, in 2008, it was recommended that the age of administration of the first dose of MMR should be changed from 15 to 12 months [15]. Similar schedules for rubella-containing vaccine have been introduced in other Spanish regions [8].

Laboratory methods

Following the recommendations of the Department of Health of Catalonia, serological screening for rubella was made in all pregnant women during their first blood test, which is usually made during the first trimester of pregnancy [13]. Levels of rubella IgG antibodies were determined using the ADVIA® Centaur G™ Rubella Assay (Siemens Healthcare Diagnostics Inc.). The immune status was determined using the following cut-off values: <15.0 IU/ml (Susceptible), ≥15 IU/ml (Immune). According to the manufacturer, the sensitivity and specificity of the method are 97.2% and 99.5%, respectively. The intra-assay and inter-assay coefficients are less than 5% and 6.1%, respectively. All samples were analyzed at the HCB microbiology laboratory.

In women susceptible to rubella, two doses of MMR vaccine were recommended in the postpartum period. The vaccine used was Priorix (GlaxoSmithKline, S.A.) which contains live attenuated measles, mumps and rubella viruses [16]. The first dose was administered in the immediate postpartum period, before discharge. After a minimum of one month, a visit was scheduled at the Adult Vaccination Centre (AVC) of the HCB for the administration of the second dose of MMR vaccine. A postvaccination sample was obtained approximately one month later in the AVC to assess rubella antibody titers. Only mothers who returned to the AVC to determine the postvaccination immunological response were included in the immunogenicity assessment.

Collection of variables

Variables were limited to information recorded in the medical records, including maternal date of birth, country of birth, parity, delivery date, date of administration of first and second dose of MMR vaccine, and date of post-vaccination blood sample. All women not born in Spain were considered immigrants. Rubella antibody levels during pregnancy were established as the main endpoint and adherence to the second MMR dose and post-vaccination rubella response as the secondary endpoints. We merged data extracts from medical information systems from Maternal-Fetal Medicine department and the AVC.

Statistical Analysis

In the univariate analysis, absolute frequencies and percentages were used to describe categorical variables and means and standard deviation (SD) or 95% confidence intervals (CI) to describe quantitative variables with a normal distribution, and medians and interquartile range otherwise. We calculated the proportion of women susceptible to rubella with the odds ratios (OR) and 95% CI. To determine variables independently associated with rubella susceptibility and adherence to MMR immunization, the crude odds ratios were calculated for different variables. For each variable studied, we took the group with the lowest rubella susceptibility as the reference group. Odds ratios were adjusted using multiple logistic regression analysis. The statistical analysis was performed using the STATA® statistical package v12.1. Statistical significance was established as <0.05.

Ethical considerations

The study investigators followed the principles of the Declaration of Helsinki. Since this study is based on routinely collected medical records, individual informed consent was not obtained. Patient records/information were anonymized and de-identified prior to analysis. The study was approved by the HCB Clinical Research Ethics Committee (HCB/2014/0619).

Results

Characteristics of the study population

A total of 22,681 pregnant women were included in the study. The number of deliveries decreased during the study period, from 4,394 in 2008 to 3,298 in 2013. The mean age of all participants was 32.3 years (DE 5.6) and 73.6%

were primiparas. The proportion of immigrants ranged from 43.4% in 2010 to 38.5% in 2012. Sixty-seven percent of patients were born in Europe, followed by the Americas (17.5%). By country, 58.5% were born in Spain, 10.7% (1,010/9,413) in China, 10.2% (962/9,413) in Morocco and 6.9% (651/9,413) in Ecuador. The demographic characteristics are shown in **Table 1**.

Factors associated with susceptibility to rubella

During the study period, 87.9 % (19,925), 11.5% (2,601) and 0.7% (148) of pregnant women had one, two or three rubella serology tests, respectively (corresponding to different pregnancies). Of the 1,328 susceptible women, 46% (611) were born in Spain, 9.6% (128) in China, 5.7% (76) in Morocco, and 4.4% (58) in the Philippines. Total susceptibility to rubella was 5.9% (1,328). There was a variation in susceptibility by year, ranging from 3.6% in 2008 to 7.6% in 2011 ($p < 0.001$) (**Figure 1**). The highest susceptibility rate was in the <20 years age group, with an overall susceptibility of 8%. Susceptibility to rubella declined with increasing maternal age, with women aged ≥40 years having the lowest susceptibility (4.4%). Immigrant women had higher susceptibility (7.6%) than pregnant women born in Spain (4.6%), OR 1.7 (95% CI 1.5-1.9). **Table 2 and 3**: univariate and multivariate analyses showed that the age group, parity, and the region of birth were independently associated with the prevalence of rubella antibodies. Women were more likely to be susceptible if they were younger (≤ 19 years, aOR 1.7 (95% CI 1.1- 2.5)), primiparas aOR 1.3 (95% CI 1.1-1.5) or not born in Spain aOR 1.6 (95% CI 1.4-1.8). A total of 94.6% (1256/1328) of women susceptible to rubella received the first dose of MMR vaccine.

Factors associated with adherence to the second dose of MMR vaccine

A total of 57.2% (718/1256) of women susceptible to rubella received the second dose of MMR vaccine. The median time between the first and second doses was 43 days. Adherence was 29.7% and 40.1% in women aged ≤19 years and 20-24 years, respectively. Adherence was >50% in women aged > 30 years. During the entire study period, women born in Spain were less adherent to the second dose than immigrant women (52.7% *vs.* 55.2%) but this proportion changed in the last year of the study (58.0% *vs.* 55.3%) (**Figure 2**). After stratification by region of origin, women born in the rest of Europe, Africa and the Americas had lower adherence than Spanish women. Asian women were more likely to receive the second dose, compared to women born in Spain (OR 1.6 (95% CI 1.2-2.2)) (**Table 3**). Women who gave birth in 2013 were more likely to receive the second dose compared with those who gave birth in 2008, OR 1.9 (95% CI 1.2-2.8).

Immunological response to two doses of MMR vaccine.

Around 60% (429/718) of women who received the second MMR dose returned for the assessment of the antibody response. After the two doses of MMR, all women showed protective antibody titers (≥15 IU/ml) against rubella.

Discussion

To our knowledge this is the largest study assessing rubella susceptibility among pregnant women in Spain, and the only one evaluating vaccine adherence and immunological response to the second MMR dose in the postpartum period. Our results showed that overall rubella susceptibility among 22,681 pregnant women between 2008 and 2013 was 5.9%, and was 7.6% in

immigrant women. These numbers are higher than the susceptibility of 5% recommended by the WHO European Region within the aim of interrupting the endemic transmission of measles and rubella in Europe by 2015 [17,18].

Previous Spanish studies have reported rubella antibody prevalence ranging from 88.3% to 94.8%[15,19–22], and our results are within this range (94.1%). Recent studies in other European countries reported similar data: the prevalence observed in Norway was 94.4% [23] and in England between 94.9%[24] and 97.4%[25]. In the United States, the prevalence was 91.5% [26], while in Canada the prevalence was 93.2% in Canadian-born mothers but was lower in immigrants from Northern Africa, the Middle East, China and the South Pacific [27].

In recent years, the incidence of rubella has been very low in Spain, with limited outbreaks among immigrants from Eastern European countries [8,14,28–30]. As a consequence, the lack of natural boosting due to an absence of circulating virus may result in higher susceptibility, particularly among younger women [31]. Higher susceptibility may also reflect a decline in the antibody levels from childhood vaccinations, as this cohort would have been eligible for two doses of rubella-containing vaccine, although data from surveillance of rubella and CRS suggest that waning immunity with increased susceptibility to rubella does not occur [10,25,32,33]. In 2012, Spanish national coverage of the first dose of MMR vaccine in infants was > 95%, but only 90% for the second dose[34].

Women aged ≥40 years, who were born before the introduction of the rubella vaccination program in 1967, had a significantly-lower susceptibility to rubella than those born later. The significant increase in immunity with increasing maternal age ($p<0.001$) may be attributable to an increase in past exposure to natural infection, and to greater opportunities for immunization in the childbearing years, either as a result of pre-conception screening or in the post-partum period. Women in older age groups are also more likely to be multipara and therefore to have been offered postpartum vaccination.

Increased travel to and from countries with circulating rubella, combined with social interaction with populations presenting lower levels of rubella-specific antibodies, may give rise to local outbreaks when protection falls below 90% [25,35]. In the present study, immigrant pregnant women presented greater susceptibility to rubella (7.6%) compared to those born in Spain (4.6%). These findings were also observed in other Western European countries[19,20,36]. It is reported that the African and South-East Asian regions have the highest estimated number of CRS cases and also have the lowest uptake of the vaccine[2]. In our study, women born in Asia had the greatest susceptibility (10.8%) to rubella. Similar results were observed in other Spanish studies where susceptibility in Asian women was 7.7% [22] and 10.4%[36], respectively. Many hospitals have adopted standing orders for women not immune to rubella: post-partum standing orders have been shown to be effective in increasing rubella immunization among non-immune women, prior to hospital discharge[31]. We found good acceptance from susceptible women although adherence to the second dose was less than 55%. One reason for this may be

that it is difficult to motivate adults to be vaccinated, particularly when there are no outbreaks [37]. Language barriers may also affect adherence, but this was not the case in our study, as immigrant women from Asia had greater adherence. We observed an increase in adherence over the study period from 41.1% (2008) to 67.6% (2012). This may be related to improvements in the postpartum immunization strategy, including better coordination between Maternal-Fetal Medicine department and the AVC.

It is reported that all licensed rubella vaccines induce seroconversion rates of approximately 95% or higher after a single dose [2]. In our case, all pregnant women were immune after the second postpartum MMR vaccination, confirming the high immunogenicity of the vaccine in this population.

Our study has some limitations. First, the serological results do not distinguish between vaccine- and disease-induced immunity. However, as rubella is not endemic in Spain and the number of cases has decreased dramatically in the last 30 years [8], our results are probably a true reflection of vaccine-induced immunity. Secondly, the length of residence in Spain of immigrant pregnant women was not available, and consequently they may have received vaccination according to the Spanish routine immunization schedule. Thirdly, there was no available information on previously-administered doses of vaccine with the rubella component, or on rubella immunization policies in other countries. Likewise, the second dose might have been administered in other health facilities, which would mean adherence would be greater than shown by our results. Finally, since not all women returned for the postvaccination

serology, we were not able to assess the vaccine response in all vaccinated women.

Conclusions

The higher rubella susceptibility found in the three youngest age groups and in immigrant women highlights the relevance of antenatal screening, in order to ensure identification and postpartum immunization of rubella susceptible women. In the context of Spain, with observed increase in immigrant population in recent years, the postpartum immunization strategy is an opportunity to protect women of childbearing age and to increase vaccination coverage against rubella and other vaccine-preventable diseases. Consequently, MMR vaccination would reinforce the achievement of eliminating endemic rubella and measles in the European region.

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Figure legends

Figure 1. Prevalence of susceptibility to rubella-specific IgG among pregnant women, Barcelona, 2008-2013.

Figure 2. Adherence to the second dose of MMR vaccine among postpartum women by country of birth, Barcelona, 2008-2013.

Table 1: Demographic characteristics of pregnant women included in the study, Barcelona, 2008-2013. (n=22,681)

Table 2: Factors associated with susceptibility to rubella-specific IgG, Barcelona, 2008-2013. (n=1328)

Table 3. Adherence to two doses of MMR vaccine in women immunized postpartum, Barcelona, 2008-2013 (n=718).