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1Page 1: Title page

**2Rubella susceptibility in pregnant women and results of a postpartum
3immunization strategy in Catalonia, Spain.**

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34

35 **Abbreviations:**

36 AVC- Adult Vaccination Centre; CI - Confidence interval; CRS - Congenital

37 Rubella Syndrome (CRS); HCB - Hospital Clinic of Barcelona; IgG -

38 Immunoglobulin G; IU - International Units; MMR - Measles, Mumps and

39 Rubella vaccine; OR – Odds Ratio; SD – Standard deviation; WHO – World

40 Health Organization

41Abstract**42Background:**

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

49Methods:

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

57Results:

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

661.4-1.8) were more likely to be susceptible. The second dose of MMR vaccine
67was received by 57.2% (718/1256) of rubella-susceptible women, with the
68highest proportion being immigrant women compared with women born in
69Spain. After vaccination, all women showed rubella immunity.

70

71Conclusions:

72The higher rubella susceptibility found in the three youngest age groups and in
73immigrant women highlights the relevance of antenatal screening, in order to
74ensure identification and postpartum immunization. The postpartum
75immunization strategy is an opportunity to protect women of childbearing age
76and consequently prevent occurrence of CRS, and to increase vaccination
77coverage against rubella and other vaccine-preventable diseases.

78

79**Keywords:** rubella; pregnancy; susceptibility; postpartum immunization;
80adherence; MMR vaccine.

81Main text**82Introduction**

83Rubella infection occurring just before conception and during early pregnancy
84may result in miscarriage, fetal death, or congenital defects known as
85congenital rubella syndrome (CRS) [1–4]. The extent of the involvement
86depends on the time of pregnancy at which infection occurs. The highest risk of
87CRS is found in countries with high rates of rubella susceptibility among women
88of childbearing age[2].

89

90In 1998, the World Health Organization (WHO) European Region approved the
91aims of eliminating indigenous measles and rubella, and controlling congenital
92rubella [2,5,6]. The most important strategy for preventing rubella is
93immunization of susceptible individuals. However, individuals may be
94immunized by past vaccination or natural infection [2]. The effectiveness of the
95rubella vaccine has been demonstrated by the elimination of rubella and CRS
96from the Region of the Americas [2,7]. The aim of interrupting the endemic
97transmission of measles and rubella in Europe in 2015 will only be achieved
98with a high coverage of vaccination (> 95% with two doses of measles, mumps
99and rubella (MMR) vaccine) in all geographical areas and all population groups,
100together with a high-quality surveillance system [8].

101

102Post-delivery vaccination strategies should include MMR vaccination in women
103susceptible to these diseases. In susceptible pregnant women, immunization
104with this live attenuated vaccine should be administered during the postpartum
105period [2,9,10].

106In Spain, rubella is a notifiable disease and is monitored through the Spanish
107Surveillance System [11]. Reported cases of rubella in 2012 were the highest
108since 2008 (64 confirmed cases: 0.14 cases per 100,000 inhabitants) and most
109cases occurred in unvaccinated adolescents and young adults. In the 2008-
1102012 period, 4 rubella outbreaks and 3 cases of CRS have been recorded in
111immigrants from countries where the rubella vaccine is not routinely
112administered in childhood [8]. Although the viral circulation of rubella in Spain is
113supposedly low, it is important to monitor rubella susceptibility, especially in
114immigrant women, given the observed increase in the immigrant population in
115recent years, with Spain being one of the main receptor countries in the
116European Union [12]. In Catalonia, the region where this study was conducted,
117all pregnant women are screened for rubella antibodies in the first antenatal
118blood test [11,13].

119

120The objectives of this study were to assess rubella susceptibility in the antenatal
121rubella serology screening; to identify factors associated with susceptible
122women and to evaluate the adherence and the immunological response to
123postpartum immunization strategy with MMR vaccine in rubella susceptible
124women.

125

126**Materials and Methods**

127

128*Study characteristics*

129We made a cross-sectional study of women who gave birth at the Hospital
130Clinic of Barcelona (HCB) between January 2008 and December 2013.

131

132Rubella immunization practices

133In Catalonia, an autonomous region in the northeast of Spain with nearly 7.5
134million inhabitants, rubella-containing vaccine was introduced into the routine
135immunization schedule in 1978 for all girls aged 11 years (women born after
1361967) [14]. In 1980, in order to improve measles control, the MMR vaccine was
137introduced in children aged 15 months. In 1987, the MMR replaced the rubella
138vaccine at 11 years of age. In 1998, the age of administration of the second
139MMR dose was advanced from 11 to 4 years. Finally, in 2008, it was
140recommended that the age of administration of the first dose of MMR should be
141changed from 15 to 12 months [15]. Similar schedules for rubella-containing
142vaccine have been introduced in other Spanish regions [8].

143

144Laboratory methods

145Following the recommendations of the Department of Health of Catalonia,
146serological screening for rubella was made in all pregnant women during their
147first blood test, which is usually made during the first trimester of pregnancy
148[13]. Levels of rubella IgG antibodies were determined using the ADVIA®
149Centaur G™ Rubella Assay (Siemens Healthcare Diagnostics Inc.). The
150immune status was determined using the following cut-off values: <15.0 IU/ml
151(Susceptible), ≥15 IU/ml (Immune). According to the manufacturer, the
152sensitivity and specificity of the method are 97.2% and 99.5%, respectively. The
153intra-assay and inter-assay coefficients are less than 5% and 6.1%,
154respectively. All samples were analyzed at the HCB microbiology laboratory.

155In women susceptible to rubella, two doses of MMR vaccine were
156recommended in the postpartum period. The vaccine used was Priorix
157(GlaxoSmithKline, S.A.) which contains live attenuated measles, mumps and
158rubella viruses [16]. The first dose was administered in the immediate
159postpartum period, before discharge. After a minimum of one month, a visit was
160scheduled at the Adult Vaccination Centre (AVC) of the HCB for the
161administration of the second dose of MMR vaccine. A postvaccination sample
162was obtained approximately one month later in the AVC to assess rubella
163antibody titers. Only mothers who returned to the AVC to determine the
164postvaccination immunological response were included in the immunogenicity
165assessment.

166

167*Collection of variables*

168Variables were limited to information recorded in the medical records, including
169maternal date of birth, country of birth, parity, delivery date, date of
170administration of first and second dose of MMR vaccine, and date of post-
171vaccination blood sample. All women not born in Spain were considered
172immigrants. Rubella antibody levels during pregnancy were established as the
173main endpoint and adherence to the second MMR dose and post-vaccination
174rubella response as the secondary endpoints. We merged data extracts from
175medical information systems from Maternal-Fetal Medicine department and the
176AVC.

177

178*Statistical Analysis*

179In the univariate analysis, absolute frequencies and percentages were used to
180describe categorical variables and means and standard deviation (SD) or 95%
181confidence intervals (CI) to describe quantitative variables with a normal
182distribution, and medians and interquartile range otherwise. We calculated the
183proportion of women susceptible to rubella with the odds ratios (OR) and 95%
184CI. To determine variables independently associated with rubella susceptibility
185and adherence to MMR immunization, the crude odds ratios were calculated for
186different variables. For each variable studied, we took the group with the lowest
187rubella susceptibility as the reference group. Odds ratios were adjusted using
188multiple logistic regression analysis. The statistical analysis was performed
189using the STATA® statistical package v12.1. Statistical significance was
190established as <0.05.

191

192*Ethical considerations*

193The study investigators followed the principles of the Declaration of Helsinki.
194Since this study is based on routinely collected medical records, individual
195informed consent was not obtained. Patient records/information were
196anonymized and de-identified prior to analysis. The study was approved by the
197HCB Clinical Research Ethics Committee (HCB/2014/0619).

198

199**Results**

200*Characteristics of the study population*

201A total of 22,681 pregnant women were included in the study. The number of
202deliveries decreased during the study period, from 4,394 in 2008 to 3,298 in
2032013. The mean age of all participants was 32.3 years (DE 5.6) and 73.6%

204were primiparas. The proportion of immigrants ranged from 43.4% in 2010 to
20538.5% in 2012. Sixty-seven percent of patients were born in Europe, followed
206by the Americas (17.5%). By country, 58.5% were born in Spain, 10.7%
207(1,010/9,413) in China, 10.2% (962/9,413) in Morocco and 6.9% (651/9,413) in
208Ecuador. The demographic characteristics are shown in **Table 1**.

209

210*Factors associated with susceptibility to rubella*

211During the study period, 87.9 % (19,925), 11.5% (2,601) and 0.7% (148) of
212pregnant women had one, two or three rubella serology tests, respectively
213(corresponding to different pregnancies). Of the 1,328 susceptible women, 46%
214(611) were born in Spain, 9.6% (128) in China, 5.7% (76) in Morocco, and 4.4%
215(58) in the Philippines. Total susceptibility to rubella was 5.9% (1,328). There
216was a variation in susceptibility by year, ranging from 3.6% in 2008 to 7.6% in
2172011 ($p < 0.001$) (**Figure 1**). The highest susceptibility rate was in the <20 years
218age group, with an overall susceptibility of 8%. Susceptibility to rubella declined
219with increasing maternal age, with women aged ≥ 40 years having the lowest
220susceptibility (4.4%). Immigrant women had higher susceptibility (7.6%) than
221pregnant women born in Spain (4.6%), OR 1.7 (95% CI 1.5-1.9). **Table 2 and 3:**
222univariate and multivariate analyses showed that the age group, parity, and the
223region of birth were independently associated with the prevalence of rubella
224antibodies. Women were more likely to be susceptible if they were younger (\leq
22519 years, aOR 1.7 (95% CI 1.1- 2.5)), primiparas aOR 1.3 (95% CI 1.1-1.5) or
226not born in Spain aOR 1.6 (95% CI 1.4-1.8). A total of 94.6% (1256/1328) of
227women susceptible to rubella received the first dose of MMR vaccine.

228*Factors associated with adherence to the second dose of MMR vaccine*

229A total of 57.2% (718/1256) of women susceptible to rubella received the
230second dose of MMR vaccine. The median time between the first and second
231doses was 43 days. Adherence was 29.7% and 40.1% in women aged ≤ 19
232years and 20-24 years, respectively. Adherence was $>50\%$ in women aged $>$
23330 years. During the entire study period, women born in Spain were less
234adherent to the second dose than immigrant women (52.7% vs. 55.2%) but this
235proportion changed in the last year of the study (58.0% vs. 55.3%) (**Figure 2**).
236After stratification by region of origin, women born in the rest of Europe, Africa
237and the Americas had lower adherence than Spanish women. Asian women
238were more likely to receive the second dose, compared to women born in Spain
239(OR 1.6 (95% CI 1.2-2.2)) (**Table 3**). Women who gave birth in 2013 were more
240likely to receive the second dose compared with those who gave birth in 2008,
241OR 1.9 (95% CI 1.2-2.8).

242

243*Immunological response to two doses of MMR vaccine.*

244Around 60% (429/718) of women who received the second MMR dose returned
245for the assessment of the antibody response. After the two doses of MMR, all
246women showed protective antibody titers (≥ 15 IU/ml) against rubella.

247

248**Discussion**

249To our knowledge this is the largest study assessing rubella susceptibility
250among pregnant women in Spain, and the only one evaluating vaccine
251adherence and immunological response to the second MMR dose in the
252postpartum period. Our results showed that overall rubella susceptibility among
25322,681 pregnant women between 2008 and 2013 was 5.9%, and was 7.6% in

254immigrant women. These numbers are higher than the susceptibility of 5%
255recommended by the WHO European Region within the aim of interrupting the
256endemic transmission of measles and rubella in Europe by 2015 [17,18].

257

258Previous Spanish studies have reported rubella antibody prevalence ranging
259from 88.3% to 94.8%[15,19–22], and our results are within this range (94.1%).
260Recent studies in other European countries reported similar data: the
261prevalence observed in Norway was 94.4% [23] and in England between
26294.9%[24] and 97.4%[25]. In the United States, the prevalence was 91.5% [26],
263while in Canada the prevalence was 93.2% in Canadian-born mothers but was
264lower in immigrants from Northern Africa, the Middle East, China and the South
265Pacific [27].

266

267In recent years, the incidence of rubella has been very low in Spain, with limited
268outbreaks among immigrants from Eastern European countries [8,14,28–30]. As
269a consequence, the lack of natural boosting due to an absence of circulating
270virus may result in higher susceptibility, particularly among younger women [31].
271Higher susceptibility may also reflect a decline in the antibody levels from
272childhood vaccinations, as this cohort would have been eligible for two doses of
273rubella-containing vaccine, although data from surveillance of rubella and CRS
274suggest that waning immunity with increased susceptibility to rubella does not
275occur [10,25,32,33]. In 2012, Spanish national coverage of the first dose of
276MMR vaccine in infants was > 95%, but only 90% for the second dose[34].

277

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

286

287 Increased travel to and from countries with circulating rubella, combined with
288 social interaction with populations presenting lower levels of rubella-specific
289 antibodies, may give rise to local outbreaks when protection falls below 90%
290 [25,35]. In the present study, immigrant pregnant women presented greater
291 susceptibility to rubella (7.6%) compared to those born in Spain (4.6%). These
292 findings were also observed in other Western European countries [19,20,36]. It
293 is reported that the African and South-East Asian regions have the highest
294 estimated number of CRS cases and also have the lowest uptake of the
295 vaccine [2]. In our study, women born in Asia had the greatest susceptibility
296 (10.8%) to rubella. Similar results were observed in other Spanish studies
297 where susceptibility in Asian women was 7.7% [22] and 10.4% [36], respectively.
298 Many hospitals have adopted standing orders for women not immune to rubella:
299 post-partum standing orders have been shown to be effective in increasing
300 rubella immunization among non-immune women, prior to hospital
301 discharge [31]. We found good acceptance from susceptible women although
302 adherence to the second dose was less than 55%. One reason for this may be

303that it is difficult to motivate adults to be vaccinated, particularly when there are
304no outbreaks [37]. Language barriers may also affect adherence, but this was
305not the case in our study, as immigrant women from Asia had greater
306adherence. We observed an increase in adherence over the study period from
30741.1% (2008) to 67.6% (2012). This may be related to improvements in the
308postpartum immunization strategy, including better coordination between
309Maternal-Fetal Medicine department and the AVC.

310

311It is reported that all licensed rubella vaccines induce seroconversion rates of
312approximately 95% or higher after a single dose [2]. In our case, all pregnant
313women were immune after the second postpartum MMR vaccination, confirming
314the high immunogenicity of the vaccine in this population.

315

316Our study has some limitations. First, the serological results do not distinguish
317between vaccine- and disease-induced immunity. However, as rubella is not
318endemic in Spain and the number of cases has decreased dramatically in the
319last 30 years [8], our results are probably a true reflection of vaccine-induced
320immunity. Secondly, the length of residence in Spain of immigrant pregnant
321women was not available, and consequently they may have received
322vaccination according to the Spanish routine immunization schedule. Thirdly,
323there was no available information on previously-administered doses of vaccine
324with the rubella component, or on rubella immunization policies in other
325countries. Likewise, the second dose might have been administered in other
326health facilities, which would mean adherence would be greater than shown by
327our results. Finally, since not all women returned for the postvaccination

328serology, we were not able to assess the vaccine response in all vaccinated
329women.

330

331**Conclusions**

332The higher rubella susceptibility found in the three youngest age groups and in
333immigrant women highlights the relevance of antenatal screening, in order to
334ensure identification and postpartum immunization of rubella susceptible
335women. In the context of Spain, with observed increase in immigrant population
336in recent years, the postpartum immunization strategy is an opportunity to
337protect women of childbearing age and to increase vaccination coverage
338against rubella and other vaccine-preventable diseases. Consequently, MMR
339vaccination would reinforce the achievement of eliminating endemic rubella and
340measles in the European region.

341

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348

349

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- 483

484 **Figure legends**

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

487

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

490

491**Table 1:** Demographic characteristics of pregnant women included in the study,
492Barcelona, 2008-2013. (n=22,681)

493

494**Table 2:** Factors associated with susceptibility to rubella-specific IgG,
495Barcelona, 2008-2013. (n=1328)

496

497**Table 3.** Adherence to two doses of MMR vaccine in women immunized
498postpartum, Barcelona, 2008-2013 (n=718).

499