Fetal Risk Associated With Rubella Vaccination During Pregnancy

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Background: Costa Rica implemented a nationwide measles-rubella vaccination campaign among men and women (15–39 years old) in May 2001. A protocol was developed to follow-up the vaccinated women who were unknowingly pregnant, to determine the risk of congenital rubella syndrome (CRS) or congenital rubella infection only associated with the administration of the rubella vaccine RA27/3 during pregnancy.

Methods: To classify the prevaccination maternal immune status, a serum sample was taken at the initial evaluation to detect IgM and IgG rubella antibodies (enzyme-linked immunosorbent assay). All pregnancies were followed up and all newborns were evaluated. A cord serum sample of their children was taken at birth. We calculated odds ratio, OR (95% confidence interval, 95% CI) associated with miscarriage, stillbirth, prematurity, low birth weight, and the presence of defects compatible with CRS.

Results: The prevaccination immune status was established in 797 women and 1191 mother and child pairs were analyzed. Adjusted OR for miscarriage (OR = 0.60, 95% CI = 0.26–1.39), stillbirth (OR = 1.32, 95% CI = 0.10–16.81), prematurity (OR = 0.25, 95% CI = 0.03–2.39), low birth weight (OR = 0.25, 95% CI = 0.03–2.23) and defects compatible with CRS (OR = 1.09, 95% CI = 0.34–3.54) showed no association between immune and susceptible maternal status. There were no cases of CRS and no children were IgM positive.

Conclusions: No adverse pregnancy outcome such as miscarriages or CRS was documented in women who were vaccinated and unknowingly pregnant. These results support RA27/3 rubella vaccine safety.

Key Words: rubella vaccine, pregnancy, congenital rubella syndrome, rubella, vaccine safety

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After reviewing the available worldwide databases, the Advisory Committee on Immunization Practices reported in 2001 that no case of congenital rubella syndrome (CRS) was identified among 680 live births from susceptible vaccinated mothers during the first trimester of gestation with any of the rubella vaccines (HPV-77, Cendehill, or RA 27/3).[1]

Scientific reports have not found an increased risk of congenital abnormalities consistent with CRS after rubella vaccination.[2–4] Based on mathematical calculations, the maximum theoretical risk of birth defects attributed to rubella vaccine administered 1–2 weeks before to 4–6 weeks after conception is 1.3%. This rate is substantially less than the reported risk of rubella infection during the first 20 weeks of pregnancy and does not differ from the background risk of congenital defects in the absence of infection.[5–7] Because the evidence of risk from the rubella vaccination to the fetus is theoretical, the main reason for not recommending the vaccine to pregnant women is to avoid its implication in adverse events during the pregnancy that are not related to the vaccine itself.

The region of the Americas established the goal of eliminating indigenous rubella and CRS. To achieve this goal by year 2010, the countries are implementing adolescent and adult vaccination campaigns.[8,9] Because of the possibility of vaccinating women who are unknowingly pregnant during mass vaccination campaigns, there is an urgent need to support the evidence on the real risk of infection and potential defects of the fetus caused by the administration of rubella containing vaccine during pregnancy.

Experience in rubella vaccination campaigns of millions of women of childbearing age in the Americas has allowed follow-up of several thousand reported women who were vaccinated and unknowingly pregnant. None of their children had CRS. Follow-up of 2.292 pregnant women in Brazil (292 of whom were susceptible) revealed no cases of CRS because of rubella vaccination.[10]

During the national vaccination campaign against rubella implemented in May 2001 in Costa Rica, in which the measles-rubella vaccine was administered to all men and women between 15 and 39 years of age,[11] a follow-up protocol for women who were vaccinated and unknowingly pregnant was included as a component of the Vaccine Adverse Events Reporting System. The main purpose of this protocol was to assure an appropriate response to the safety concerns and to provide optimum prenatal care, delivery, and attention to the newborn. It was approved by the National Immunization Committee and by the Institutional Review

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This article reports the results of the follow-up of those women. The objective of this study was to determine the risk of CRS or congenital rubella infection (CRI) only associated with the administration of the rubella vaccine (RA27/3) during pregnancy.

METHODOLOGY

Detection, Evaluation, and Monitoring. Figure 1 shows the activities established for the initial evaluation, monitoring, and final evaluation of women who were vaccinated and unknowingly pregnant. According to the vaccination card and the last day of menstruation, all women that were pregnant at the time of receiving the measles-rubella vaccine or who became pregnant shortly after this time were followed up. When recruited, all the information regarding rubella vaccination and potential risks during pregnancy was shared with them and they were monitored throughout their pregnancy and delivery.

The initial evaluation included the detection of serum IgM and IgG antibodies against rubella. The women's prenatal and delivery care were provided within the national health service system, regardless of their immune status or point in gestation before vaccination. These services included periodic check-ups and routine prenatal examinations. Women included in the monitoring process were supervised until the conclusion of their pregnancy. If any complication was detected that required extra attention, the case was referred to the appropriate specialist.

At birth, all the children were evaluated by pediatricians to detect clinical manifestations consistent with CRS, and a blood sample was taken from the umbilical cord for the determination of rubella IgM and IgG concentrations. If IgM antibody was detected, a second serum sample was taken, as well as nasopharyngeal and urine specimens for viral isolation.

A specialized service for the evaluation of children was established at the Department of Infectious Diseases in the National Children's Hospital. All pediatricians in the country must refer any case with possible CRS manifestations and all offspring born to susceptible mothers to this center. All IgM positive cases also had to be referred to this hospital to be evaluated. Ophthalmologic, cardiac, and audiologic evaluations were performed. In the case of compatible clinical manifestations of congenital infection, serology assays to test for toxoplasmosis, cytomegalovirus (CMV), parvovirus, herpes simplex, syphilis, and human immunodeficiency virus were done, as well as head and long bones radiology, abdomen and brain sonograms.

Specimen Collection and Laboratory Testing. All specimens were sent and processed at the National Reference Virology Laboratory of the Costa Rican Institute for Research and Training in Nutrition and Health (INCIENSA). Serum samples were processed by Enzyme Immunoassays Dade Behring to detect rubella IgM and IgG antibodies and the other serologic tests for congenital infections were processed by usual laboratory methods at the National Children's Hospital. The urine and throat swab specimens, in addition to being performed at INCIENSA, were sent to the Centers for Disease Control to be cultured. In the case of virus detection, molecular typing reverse transcription nested polymerase chain reaction assay for the detection of rubella virus RNA would be performed to distinguish between vaccine and wild rubella virus.

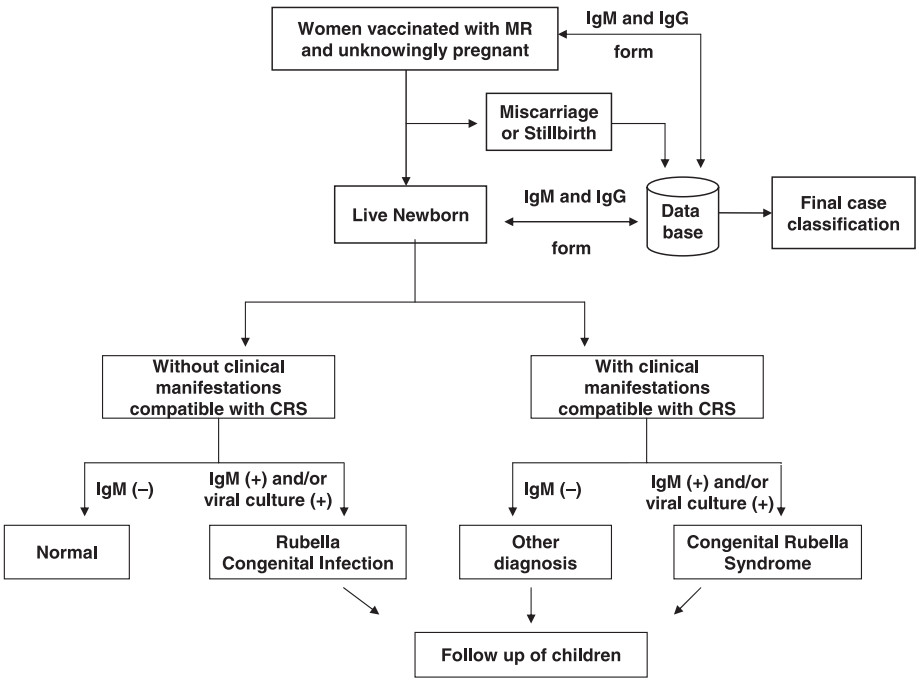

FIGURE 1. Follow-up protocol for women vaccinated against rubella who were unknowingly pregnant.

Data Collection and Sources of Information. Physicians responsible for prenatal care completed the investigation form for the evaluation and monitoring of women who were vaccinated and unknowingly pregnant. After evaluating the child, the neonatologist or pediatrician completed the newborn form. Data included the results of the serologic evaluation of both mother and the newborn, the pediatric evaluation of the child, and the pregnancy outcome in terms of miscarriage, stillbirth, or live birth.

A national database was designed to enter data collected from the maternal and newborn forms. It included demographic variables, obstetric evaluation, perinatal and clinical manifestations, laboratory, otoacoustic emissions or auditory brain response, and other specialized results. To complete and validate the demographic variables, the national ID register data base was used to verify the mother's identification number, name, and residence.

To ensure for quality and completion of data, the cases were cross-referenced with the national perinatal database of the Social Security System, which covers 98% of total births in the country. This database was also used to compare the rates of miscarriage, stillbirth, prematurity, and low birth weight (LBW) between followed-up cases and the total births registered in the country during the 9 months after the campaign.

Classification of the Prevaccination Maternal Immune Status. The classification of the maternal rubella immune status before the administration of the vaccine was established based on the level of IgM and IgG, taking into consideration the interval of days between the date of vaccination and the serum sample collection. All the women with IgM (+) were considered "susceptible", independent of the number of days that passed between the vaccination and the collection of the serum sample. Women who were IgM (−) and IgG (−) were also classified as susceptible. In these cases, it was recommended to take a second sample to determine whether there was seroconversion.

The women whose samples were taken before 30 days after the day of vaccination, and whose serologic results were IgM (−) and IgG (+), were classified as "immune". In the cases of women whose samples were taken after 30 days, and whose rubella serology results showed IgM (−) and IgG (+), it was not possible to determine whether these mothers were immune to the rubella virus before vaccination or if they became immune as result of it. In these cases the prevaccination immune status of the mother was classified as "unknown".

The gestation age of the fetus at the time of vaccination was established according to the last day of menstruation and the date of vaccination. In addition, that date was corroborated with the evaluation of the gestational age of the newborn using Capurro or Usher at birth.[12]

Evaluation and Classification of the Child. The cases were classified as suspected, confirmed, or discarded according to case classification of CRS.[13] A case of CRS was defined as a child having 2 primary manifestations from group "A": cataracts, congenital glaucoma, congenital heart defect, hearing impairment, pigmentary retinopathy, or a manifestation from "A" and a secondary manifestation of "B": purpura, hepatosplenomegaly, jaundice, developmental delay, meningoencephalitis, radiolucent bone disease, without evidence of another cause. Laboratory confirmation and deafness as single defect was considered a case of CRS.

The IgM (+) cases without clinical manifestations would be classified as CRI and those cases having both laboratory confirmation and clinical manifestations should be classified as CRS. In these cases, a specimen must be obtained for viral isolation to determine whether it was a wild or vaccine related strain. The final classification of each case was made by a team of specialists in pediatrics, infectology, virology, audiology, and epidemiology.

Association of Defects and Maternal Immune State. The odds ratio, OR (95% confidence interval, 95% CI) was calculated comparing the condition of prevaccination maternal immunity (susceptible, immune, or unknown) and the occurrence of miscarriage, stillbirth, LBW, prematurity, and clinical manifestations compatible with the case definition of CRS. The statistical analysis of the data was performed using SPSS 10.0. Univariate analysis were performed using χ^2 test. The OR and 95% CIs adjusted to the maternal age in years and the province of residence were performed using EGRET version 2.0.3 software.

RESULTS

Characterization of the Population. A total of 3810 women who became pregnant during 3 months after the vaccination or who were pregnant at the time of vaccination were followed up (Fig. 2). These women represent 6.7% (range = 3.7%–11.1%) of the total estimated women who were pregnant during the month of the campaign.

Of the 3.810 women, 22.1% had blood taken within the 30 day period after vaccination. The prevaccination immune state for the remaining women (n = 3.013) was catalogued as "unknown". Of the 797 women whose immune state was possible to classify, 163 (20%) were "susceptible" and 634 (80%) were "immune".

At the completion of the study, information was available for 1191 pairs of mother-offspring. Of these, 219 were born to immune mothers, 104 to susceptible mothers, and in 868 cases the maternal immune status was unknown.

Table 1 shows the demographic characteristics of the mothers according to the immune status and variables regarding the outcome of the gestation: 11.4% were <20 years of age, 45.9% of the mothers were between the ages of 20 and 29 years, and 32.7% were ≥30 years. The susceptible women had a significantly higher average age (average = 29.1 years, $P < 0.05$) when compared with the immune women (average = 26.9 years) and those with unknown immune status (average = 26.7 years).

The percentage of mothers vaccinated the month before conception or during the first trimester of pregnancy was 89.1%. Nearly 50% of the women were vaccinated during the first month of pregnancy, 67.8% were vaccinated 2 weeks before to 6 weeks after conception, and only 0.9% of women were vaccinated after the third month of gestation.

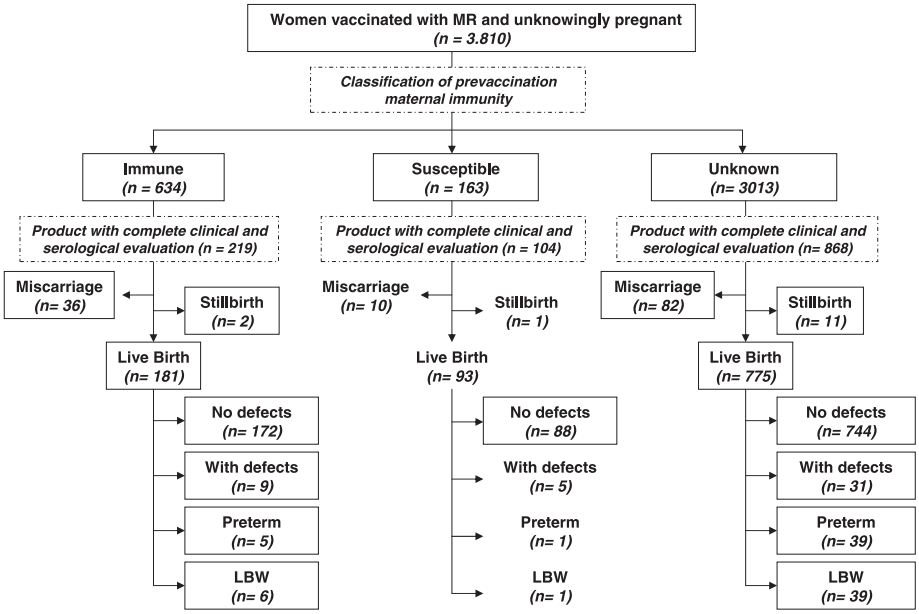

FIGURE 2. Results of the follow-up of women vaccinated against rubella who were unknowingly pregnant.

TABLE 1. Variables and Outcomes of Women Vaccinated Against Rubella Who Were Unknowingly Pregnant According to Prevaccination Maternal Immune Status

Variable	Total No. (%)	Maternal Prevaccination Immune Status		
		Immune No. (%)	Susceptible No. (%)	Unknown No. (%)
Total	1191 (100.0)	219 (100.0)	104 (100.0)	868 (100.0)
Age (yr)				
<20	116 (11.4)	22 (12.6)	5 (6.0)	89 (12.0)
20–24	274 (27.0)	46 (26.3)	18 (18.0)	210 (28.4)
25–29	293 (28.9)	55 (31.4)	33 (33.0)	205 (27.7)
30–34	183 (18.0)	31 (17.7)	21 (21.0)	131 (17.7)
35 and more	149 (14.7)	21 (12.0)	23 (23.0)	105 (14.2)
Blood sample taken <30 d postvaccination				
Yes	261 (22.1)	219 (100.0)	42 (40.4)	0 (0.0)
No	930 (77.9)	0 (0.0)	62 (59.6)	868 (100.0)
Gestational age at vaccine administration				
1–3 mo preconception	119 (10.0)	5 (2.3)	6 (5.8)	108 (12.4)
<1 mo preconception	272 (22.8)	17 (7.8)	18 (17.3)	237 (27.3)
First month	586 (49.2)	130 (59.4)	53 (51.0)	403 (46.4)
Second month	161 (13.5)	48 (21.9)	18 (17.3)	95 (10.9)
Third month	42 (3.5)	16 (7.3)	8 (7.7)	18 (2.1)
>3 months	11 (0.9)	3 (1.4)	1 (1.0)	7 (0.8)
Gestational age at birth (wk)				
<37	45 (4.3)	5 (2.8)	1 (1.1)	39 (5.0)
⩾37	1004 (95.7)	176 (95.0)	92 (98.9)	736 (95.0)
Birth condition				
Live born	1049 (88.1)	181 (82.6)	93 (89.4)	775 (89.3)
Miscarriage	128 (10.7)	36 (16.4)	10 (9.6)	82 (9.4)
Stillbirth	14 (1.2)	2 (0.9)	1 (1.0)	11 (1.3)
Weight at birth (g)				
<2500	46 (4.4)	6 (3.3)	1 (1.1)	39 (5.0)
⩾2500	1003 (95.6)	175 (96.7)	92 (98.9)	736 (95.0)
Defects compatible with CRS*				
Yes	45 (4.3)	9 (5.0)	5 (5.4)	31 (4.0)
No	1004 (95.7)	172 (95.0)	88 (94.6)	744 (96.0)

*Includes hearing impairment, retinopathy, congenital heart disease, hepatosplenomegaly, microcefaly, jaundice, developmental delay, and low birth weight.

Association Between Maternal Immune State and the Gestation Outcome. The gestational outcome for the women followed included miscarriage (n = 128, 10.7%), stillbirth (n = 14, 1.2%), prematurity (n = 45, 4.3%), and LBW (n = 46, 4.4%). Compatible defects with CRS were identified in 4.3% of the cases: intrauterine growth and developmental delay (n = 28),

hearing impairment (n = 6), congenital heart disease (n = 4), microcephaly (n = 3), hepatosplenomegaly (n = 2), and jaundice (n = 2).

In general, the frequencies of the effects on the fetus were similar between the different categories of maternal immunity, with the exception of the occurrence of miscarriage that was higher in offspring born to immune mothers (χ^2, $P < 0.05$). When comparing the rates of fetal effects to the greatest risk period for fetal damage (2 weeks before conception to 6 weeks of pregnancy) no statistical significance was found between maternal immune status and frequency of fetal effects (χ^2, $P < 0.05$).

Ultimately all suspected CRS cases were discarded and infection by the rubella virus was not documented for any of the children. All the reports of IgM were negative in the umbilical cord blood with the exception of 1 case that initially was reported as having a positive result. This child was premature (gestational age = 35 weeks), weighing 1000 g at birth, with neonatal jaundice and microcephaly. An echocardiogram performed at 28 days of age reported a mild stenosis of pulmonary valve but the control echocardiogram at 5 months of age was normal. Audiology, bone radiology, and brain sonogram were normal. The case was discarded by subsequent laboratory analysis (2 rubella IgM negatives), and viral cultures performed at both INCIENSA and Centers for Disease Control were reported as negative. Clinical manifestations were attributed to prematurity.

The detected congenital anomalies were classified as 2 CMV infections; 1 congenital syphilis, 1 Epstein disease, 1 Pierre Robin Syndrome, several developmentally retarded infants resulting from neonatal hypoxia, and other neonatal clinical manifestations that were associated with prematurity.

No significant statistical association was found between the state of maternal immunity (immune, susceptible, or unknown) and the occurrence of miscarriage, stillbirth, prematurity, LBW, or the presence of compatible defects with CRS (Table 2). The OR (95% CI) adjusted for maternal age and province of residence, did not show a significant association between those defects and any of the categories of prevaccination maternal immunity.

The rates of miscarriage (10.7%), stillbirth (1.2%), LBW (4.4%), and prematurity (4.3%) determined by this study were smaller than the national reported rates. The national rates during the 9 months after the campaign, showed that of the total number of infants registered in the country-wide perinatal database, 7407 (10.2%) were miscarriages and 514 (0.7%) stillbirths. Of all live births (n = 64,651), 4111 (6.4%) were LBW and 3658 (5.7%) were preterm infants.

DISCUSSION

The results of this study provide additional evidence to support existing data showing an absence of risk associated with the administering of the rubella vaccine before conception or during gestation. Follow-up procedures conducted among 1.191 mother-infant pairs who were vaccinated and unknowingly pregnant during the campaign, independent of the immune state, did not result in one single case of CRS or CRI. In addition, no statistical significance was determined when comparing the frequency of defects among offspring when the woman was vaccinated 2 weeks before to 4–6 weeks after conception to other periods of pregnancy.

The rates of miscarriages and stillbirths were similar to the reported national rates and no significant statistical asso-

TABLE 2. Adjusted and Crude OR (CI 95%) of Gestational Outcomes of Women Vaccinated Against Rubella Who Were Unknowingly Pregnant According to Prevaccination Maternal Immune Status

Variables	No. (Cases/Controls)	OR*	CI 95%*	OR Adjusted†	CI 95%†
Miscarriage					
Immune	36/181	1.00	—	1.00	—
Susceptible	10/93	0.54	0.24–1.19	0.60	0.26–1.39
Unknown immunity	82/775	0.53	0.34–0.83	0.68	0.39–1.16
Stillbirth					
Immune	2/181	1.00	—	1.00	—
Susceptible	1/93	0.97	0.03–13.89	1.32	0.10–16.81
Unknown immunity	11/775	1.28	0.27–8.46	1.20	0.26–5.51
Prematurity					
Immune	5/176	1.00	—	1.00	—
Susceptible	1/92	0.38	0.01–3.43	0.26	0.03–2.39
Unknown immunity	39/736	1.87	0.69–5.46	1.58	0.60–4.11
Low birth weight					
Immune	6/175	1.00	—	1.00	—
Susceptible	1/92	0.31	0.01–2.71	0.25	0.03–2.23
Unknown immunity	39/736	1.54	0.61–4.12	1.28	0.53–3.12
Defects compatible with CRS‡					
Immune	9/172	1.00	—	1.00	—
Susceptible	5/88	1.08	0.30–3.68	1.09	0.34–3.54
Unknown immunity	31/744	0.80	0.36–1.84	0.72	0.33–1.56

*Crude OR and confidence intervals (CI) 95%.

†OR and confidence intervals (CI) 95% adjusted by maternal age (yr) and province of residence.

‡Includes hearing impairment, retinopathy, congenital heart disease, hepatosplenomegaly, microcefaly, jaundice, developmental delay, and low birth weight.

ciation was found between maternal immunity and fetal effects when using the incidence of miscarriages, stillbirths, prematurity, LBW, or congenital defects as evaluation criteria. The frequency of the compatible CRS defects documented in this study ranged from 4.0% to 5.4% and no significant differences were found among those with differing prevaccination maternal immune status. All suspected CRS cases were attributed to other etiologies such as congenital infection by CMV or syphilis or to congenital defects associated with craniofacial syndromes.

Although the national rate of congenital defects compatible with CRS in the general population of Costa Rica remains unknown, a recent study in Canada reported rates of 3.7% and 3.4% among CRS compatible clinical cases and controls, respectively.[14] These findings reinforce the importance of investigating and evaluating suspected CRS cases, including the differential diagnosis of congenital infections as well as other causes of defects.

One of the major difficulties faced by the present study was the classification of the prevaccination maternal immune status, because the period of interpretation of the serologic results is short and the immunologic response to the vaccination is fast. In addition, there are individual variations among the human immune response. The IgM antibodies appear a few days after the vaccination, reaching maximum levels between 7 and 10 days after vaccination. Although they are rarely detected after 6 weeks, there are some reports that document its persistence up to several months.[15] This situation explains the high percentage of women with unknown prevaccination immune status in this study.

The multiplicity of ethical considerations impedes the implementation of controlled and randomized studies to determine the risk of vaccine administration before conception or during gestation. For this reason, information about vaccine safety during pregnancy is scarce and current recommendations on rubella vaccination during pregnancy are based mainly on case reports and some observational studies.[16] The possibility of using vaccine safety surveillance as a source of information, such as the one used in this study, generates useful knowledge to strengthen the immunization programs.

In countries that have adopted strategies of elimination of rubella and CRS, vaccination in adults is the recommended intervention.[17,18] In this sense, the implementation of adult vaccination campaigns brings out important considerations for vaccine safety event surveillance, because of the increased possibility of vaccinating unknowingly pregnant women. For this reason, during mass campaigns it is important that the entire population is informed about the characteristics and safety procedures of the vaccine and to assure that all health personnel are trained about the importance of not vaccinating pregnant women.

In the case of inadvertent vaccination, given the available evidence on its safety, it is important to offer appropriate information for the continuation of the pregnancy, to provide effective support to answer all the concerns of the vaccinated pregnant woman and her relatives, as well as to emphasize that the rubella vaccination is not an indication to terminate the pregnancy.

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