Follow-up Study of Unknowingly Pregnant Women Vaccinated Against Rubella in Brazil, 2001–2002

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Background. Brazil conducted mass immunization of women of childbearing age in 2001 and 2002. Surveillance was initiated for vaccination of women during pregnancy to monitor the effects of rubella vaccination on fetal outcomes.

Methods. Women vaccinated while pregnant or prior to conception were reported to the surveillance system. Susceptibility to rubella infection was determined by anti-rubella immunoglobulin (Ig) M and IgG immunoassays. Susceptible women were observed through delivery. Live-born infants were tested for anti-rubella IgM antibody; IgM-seropositive newborns were tested for viral shedding and observed for 12 months for signs of congenital rubella syndrome. Incidence of congenital rubella infection was calculated using data from 7 states.

Results. A total of 22 708 cases of rubella vaccination during pregnancy or prior to conception were reported nationwide, 20 536 (90%) of which were from 7 of 27 states in Brazil. Of these, 2332 women were susceptible to rubella infection at vaccination. Sixty-seven (4.1%) of 1647 newborns had rubella IgM antibody (incidence rate, 4.1 congenital infections per 100 susceptible women vaccinated during pregnancy [95% confidence interval, 3.2–5.1]). None of the infants infected with rubella vaccine virus was born with congenital rubella syndrome.

Conclusions. As rubella elimination goals are adopted worldwide, evidence of rubella vaccine safety aids in planning and implementation of mass adult immunization.

Rubella is typically a mild viral infection characterized by febrile rash illness. However, rubella infection during pregnancy can cause fetal damage that results in a range of malformations (including hearing impairment, congenital cataracts, and heart disease) referred to collectively as congenital rubella syndrome (CRS) [1, 2]. Considering the severity and long-term disability associated with CRS, its prevention is the main objective of rubella control strategies. Recognition of the burden of rubella and CRS, the highly favorable cost-benefit ratio of vaccination, and the availability of an efficacious, safe, and affordable vaccine prompted the Pan American Health Organization (PAHO) and its member countries to set a goal of eliminating rubella and CRS in the Americas by 2010 [3].

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Rubella seroprevalence studies in the late 1980s and early 1990s laid the groundwork for rubella vaccination strategies in Brazil [4, 5]. However, the magnitude of rubella as a public health problem became evident only after implementation of measles elimination strategies. Universal vaccination of children with measles-mumps-rubella (MMR) vaccine was introduced into Brazilian state immunization programs in a phased manner over a nine-year period from 1992 to 2000. Mass ''catch-up'' vaccination campaigns, based on measles elimination strategies targeting children aged 1–11 years, preceded introduction of MMR vaccine into the immunization schedule.

From 1999 through 2000, several Brazilian states, including São Paulo, Rio Grande do Norte, Amazonas, and Acre, reported increased incidence of rubella among young adults, with higher incidence rates among persons aged 15–29 years than among young children (Brazilian Ministry of Health, unpublished data). Transmission of rubella to women of childbearing age resulted in 876 notifications of suspected CRS cases from 1997 through 2001, with 113 laboratory-confirmed and 42 clinically compatible CRS cases (Brazilian Ministry of Health, unpublished data). To prevent additional CRS cases, the Brazilian Ministry of Health conducted mass rubella vaccination campaigns among women of childbearing age, with a target population of 30 million women aged 12–39 years in 2001 and 2002.

Rubella vaccines are live, attenuated viral strains. Vaccine viruses can cross the placenta and cause congenital infection [6–9]. There is concern regarding the hypothetical risk that rubella vaccination during pregnancy could adversely affect fetal development and lead to congenital malformation, although follow-up of pregnant women who received the rubella vaccine has not identified cases of CRS associated with vaccination [10–12]. Rubella vaccination is contraindicated during pregnancy on the basis of the hypothetical risk, and current recommendations advise women to avoid conception for 28 days after receipt of vaccine [10]. Recognizing that some women would be unknowingly pregnant at the time of mass immunization campaigns targeting women of childbearing age, the Brazilian Ministry of Health implemented surveillance for women vaccinated during pregnancy or prior to conception to detect adverse outcomes potentially associated with vaccination. We report here on the follow-up of >20 000 pregnant women identified through this surveillance system.

METHODS

Surveillance System

Prior to rubella vaccination campaigns in 2001, the Brazilian Ministry of Health convened a committee of rubella experts to develop 2 national protocols (1) for follow-up of women vaccinated with live attenuated rubella vaccine (RA 27/3) during or preceding pregnancy and (2) for follow-up of infants born to susceptible mothers (see Definitions below). The protocols were developed in consultation with the Congenital Malformations in Latin America Collaborative Study, the Pan American Health Organization, and the United States Centers for Disease Control and Prevention (CDC). The protocols included the latest CDC recommendations that reduced from 90 to 28 days the interval for women to avoid conception following rubella vaccination [10]. Prior to implementation, the surveillance protocol was approved by the Brazilian Council of Medicine and by national societies of gynecologists, obstetricians, pediatricians, and neonatologists, which disseminated the protocol through networks of private and public health care practitioners. Preparation for the mass campaign included social mobilization activities that promoted vaccination among women of childbearing age and advised pregnant women to defer vaccination until after giving birth. Women receiving vaccination were advised not to conceive for 1 month (28 days) [10, 13].

The objectives of the surveillance system were to identify susceptible women vaccinated during pregnancy or the month prior to conception and to monitor pregnancy outcomes. Surveillance for rubella vaccination during pregnancy was incorporated into surveillance for adverse events following vaccination in each state. Prior to implementation, surveillance protocols were reviewed by state coordinators for immunizations, obstetrics and gynecology, and communicable disease surveillance. A description of required notification and follow-up of women vaccinated during pregnancy was included in the national immunization handbook distributed to >25 000 posts throughout the country.

Women vaccinated during pregnancy or within 28 days of the estimated date of conception were reported by a health professional to the surveillance system. Notification forms included age, address, date of last menstrual period, date of vaccination, gestational age (in weeks) at vaccination, and estimated date of delivery. Serum specimens were collected and sent with notification forms to public health laboratories for rubella serological testing. Results of serological testing were recorded on notification forms and weekly laboratory reports sent to state surveillance coordinators, in addition to being returned to primary health care facilities.

Women vaccinated during or preceding pregnancy were informed of the possibility of fetal infection with rubella vaccine virus; women who were susceptible to rubella infection at the time of vaccination were followed through delivery. One state (Rio de Janeiro) included women with indeterminate rubella serological testing in follow-up. Stickers were placed on women's vaccination cards to facilitate identification upon presentation for delivery. State surveillance coordinators maintained lists of expected delivery dates for follow-up of pregnant women.

Congenital rubella infection and CRS in children born to susceptible women were the primary surveillance outcomes. Miscarriage and stillbirth were secondary outcomes reported from 5 of the 7 states that conducted active follow-up. Live-born

children of vaccinated mothers, regardless of serologic result, were examined for signs of CRS, visible cataracts, and normal responses to otoacoustic wave emissions. Serum specimens were collected for live births to susceptible women for rubella serological testing. For immunoglobulin (Ig) M–seropositive infants, swab samples of oropharyngeal secretions (or urine specimens in São Paulo state) were collected for viral isolation. Infants with suspected CRS and IgM-seropositive infants were referred to tertiary referral hospitals for evaluation by pediatric specialists (neurologists, cardiologists, ophthalmologists, and otolaryngologists). Infected infants were followed through 12 months of age. In several states, specialized medical evaluations and testing were made possible through the support of nongovernmental organizations, such as the Brazilian Association of Parents and Friends of Exceptional Children.

Active follow-up of notifications was conducted in 7 states (Bahia, Goiás, Minas Gerais, Pernambuco, Rio de Janeiro, Rio Grande do Sul, and São Paulo), comprising 62% of the Brazilian population. These states had contributed additional resources to assign dedicated surveillance coordinators at state health departments and identified tertiary care referral hospitals where suspected CRS cases could be evaluated by specialists. The São Paulo State Health Department conducted additional laboratory testing (avidity testing for anti-rubella antibody) not included in the national protocol.

Laboratory Methods

Serologic testing for anti-rubella IgM- and IgG-specific antibodies was conducted at state health laboratories using commercial enzyme immunoassay kits (Dade Behring) according to the manufacturer's instructions. Viral testing of oropharyngeal secretions from neonates was conducted at the National Measles/Rubella Laboratory, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil. For the state of São Paulo, urine specimens were tested for the presence of rubella virus at the Adolfo Lutz Institute of the São Paulo State Health Department. Tests performed included reverse-transcriptase polymerase chain reaction to detect the presence of rubella virus RNA using 3 different protocols [14–16].

Definitions

Pregnant women who tested positive for anti-rubella IgM antibodies in serum samples collected after vaccination were classified as susceptible to rubella infection at the time of vaccination, and follow-up procedures were initiated. Pregnant women who tested IgG seropositive and IgM seronegative within 30 days after vaccination were classified as immune at the time of vaccination, and no follow-up was performed, whereas those who tested IgG seropositive and IgM seronegative in specimens collected >30 days after vaccination were classified as having indeterminate serological test results, and follow-up occurred at the discretion of the state surveillance coordinator. Women who tested IgM and IgG seronegative in specimens collected >30 days after vaccination were classified as nonresponders.

Congenital infection with rubella vaccine virus was defined as positive anti-rubella IgM immunoassay in a child born to a vaccinated mother. Infants with congenital rubella infection were evaluated for CRS using World Health Organization criteria [17]. We classified vaccination 6 or fewer days after reported date of last menstrual period as having occurred before conception. Miscarriage was defined as loss of a fetus of <500 g in weight or at <22 weeks gestation; prematurity was dichotomized as <37 weeks of gestation, and low birth weight was dichotomized as <2500 g.

Analysis

Vaccination coverage data were obtained from the National Information System for Immunizations. Data from notifications of women vaccinated during or preceding pregnancy were collected by state health departments and entered into spreadsheets or EpiInfo databases. EpiInfo, version 6.04d (CDC) was used for data management and analysis.

Ethical Considerations

Surveillance for potential adverse events caused by rubella vaccination of unknowingly pregnant women was an ethical imperative of the Ministry of Health, considering the large number of childbearing-age women to be vaccinated. Surveillance data were analyzed without identifiers. Informed consent was not required for specimen collection.

RESULTS

In 2001 and 2002, >26 million women between the ages of 12 and 39 years were vaccinated against measles and rubella in 24 Brazilian states (Table 1), representing 95.6% of the target female population in this age category. The 7 states that conducted active follow-up of notifications accounted for 62.3% (16 435 776 of 26 361 761) of the vaccine doses administered (Figure 1). Three states vaccinated women of childbearing age prior to 2001.

The surveillance system received 22 708 notifications of women vaccinated during pregnancy or prior to becoming pregnant. Variations in the notification rate reflected differences in surveillance capacity among states (Table 1). In 7 states with active follow-up, the rate ranged from 0.50 notifications per 1000 doses administered in Pernambuco to 2.37 notifications per 1000 doses administered in Rio Grande do Sul.

Results of serological testing were available for 91% of notifications from the 7 participating states. Specimens were collected a median of 63 days after vaccination (range, 0–333 days). In the states of Bahia and Rio de Janeiro, 29% (1036 of 3530) and 69% (1576 of 2292) of the serum samples, respectively, were collected >30 days after vaccination. The serological

Table 1. Numbers of Doses of Measles-Rubella Vaccine Administered to Women of Childbearing Age During Campaigns in 2001 and 2002 and Incidence of Notifications of Women Vaccinated During or Preceding Pregnancy, Brazil

State	Year of campaign	Number of doses administered to women aged 12–39 years[a]	Number of episodes notified	Rate of notification (per 1000 doses administered)
Acre	2001	124 947	7	0.06
Alagoas	2001	487 445	…	
Amazonas	2001	459 002	104	0.23
Amapá	2002	123 851	88	0.71
Bahia[a]	2002	3 071 038	3530	1.15
Ceará	2002	1 631 947	133	0.08
Distrito Federal[b]	1993	N/A	N/A	N/A
Espirito Santo	2001	335 884	121	0.36
Goiás[a]	2001	877 120	610	0.70
Maranhão	2001	901 925	16	0.02
Minas Gerais[a]	2001	2 766 046	2008	0.73
Mato Grosso do Sul	2002	460 998	702	1.52
Mato Grosso	2002	593 430	373	0.63
Pará	2002	1 614 719	…	
Paraíba	2001	469 469	292	0.62
Pernambuco[a]	2001	1 750 595	879	0.50
Piauí	2002	634 432	…	
Paraná	1998	N/A	N/A	N/A
Rio de Janeiro[a]	2001	1 464 950	2665	1.82
Rio Grande do Norte	2000	N/A	N/A	N/A
Rio Grande do Sul[a]	2002	1 885 877	4371	2.32
Rondônia	2001	277 310	156	0.56
Roraima	2001	79 503	47	0.59
Santa Catarina	2002	1 142 455	…	
Sergipe	2001	312 893	133	0.43
São Paulo[a]	2001	4 620 150	6473	1.40
Tocantins	2002	275 730	…	
Total		26 361 761	22 708	0.86

NOTE. Data provided by the National Immunization Program, Ministry of Health, Brazil. N/A, not available.

[a] Indicates states that participated in evaluation of the surveillance system for women vaccinated against rubella during pregnancy and their offspring.

[b] The Federal District began routine vaccination of women of childbearing age in 1993 and did not conduct a campaign to vaccinate women of childbearing age.

[c] N/A not applicable; …, not available

classification of rubella susceptibility among women vaccinated during pregnancy is shown in Table 2. The percentage of susceptible women at the time of vaccination varied little by state and was consistent with national estimates of ~10% susceptibility among women of childbearing age prior to the immunization campaigns. Data on previous vaccination were available from 4 states (Goiás, Minas Gerais, Pernambuco, and Rio de Janeiro). Among 2644 women in these 4 states for which prior vaccination status was reported, 1719 (65%) had never been vaccinated, and 198 (7%) reported previous vaccination against rubella, whereas 727 (27%) did not know their prior vaccination history. Gestational age at the time of vaccination was reported for 3098 women from 6 states (excluding São Paulo state). Vaccination occurred prior to estimated date of conception in 437 (14%) of 3098 women, within 4 weeks of conception in 2015 (65%), and 4 weeks or later in 646 (21%).

Pregnancy outcomes among susceptible women are summarized in Table 3. Six states evaluated rates of miscarriage and still births as secondary outcomes. Among these, the overall prevalence of miscarriage was 5.8% and of stillbirth was 0.8%.

Results of serologic testing were available for all 1647 infants recorded as live births; 67 (4.1%) tested positive for anti-rubella IgM antibodies, which was indicative of congenital infection with rubella virus (Tables 1, 4). The incidence of congenital infection with rubella vaccine virus was estimated to be 4.1 congenital infections per 100 susceptible women vaccinated during pregnancy (95% confidence interval, 3.2–5.1 infections per 100 susceptible women).

None of the 67 IgM-seropositive infants born to susceptible mothers was reported as having signs of CRS following initial physical examination and auditory response testing. Complete data on gestational age, birthweight, and clinical findings were

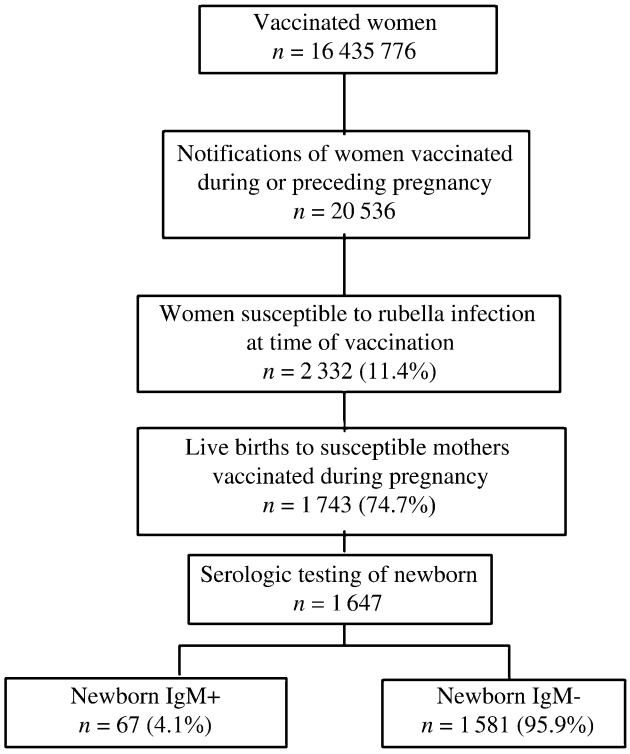

Figure 1. Number of vaccinated women, notifications of women vaccinated during or preceding pregnancy, and follow-up of pregnancy outcomes following vaccination campaign. Surveillance data from 7 states, Brazil, 2001–2002.

available for 47 IgM-seropositive infants. Nine (19.1%) of 47 were premature births (gestational age <37 weeks), and 9 (19.1%) of the infants weighed <2500 g at birth. One infant of a susceptible mother vaccinated during pregnancy was born prematurely and presented malformations compatible with CRS at birth (purpura, arterial communication, hepatosplenomegaly, and auditory impairment). Wild-type rubella virus (type 1G) was detected in nasopharyngeal secretions collected on the day of birth. One infant was born with a congenital malformation of the heart, diagnosed as an interatrial communication not related to maternal rubella vaccination. In another IgM-seropositive infant, a systolic heart murmur was detected at 35 days of age, with no major clinical signs of congenital rubella infection. Clinical examinations and follow-up of IgM seropositive infants identified no cases of CRS associated with vaccine virus. Rubella vaccine virus was not detected in oropharyngeal swab specimens tested from IgM-seropositive infants.

DISCUSSION

Surveillance for cases of rubella vaccination during or preceding pregnancy was effectively implemented in Brazil. More than 20 000 women vaccinated during pregnancy or during the month prior to conception were identified, and their serologic status was determined. Women received information about their serologic status and the potential for transmission of rubella vaccine virus to the fetus. This facilitated serologic testing of newborns and clinical evaluation of infants who were seropositive for rubella IgM antibodies. No cases of CRS in infants were associated with maternal rubella vaccination; 1 infant with CRS who was born to a mother vaccinated during pregnancy was infected with wild-type rubella virus. Data from the surveillance system contribute to the scientific literature on the safety of rubella vaccine during pregnancy.

Rubella serological testing was completed for 91% of notifications and for 94% of live births among susceptible mothers with complete follow-up in 7 states. Data from these states provide an estimate of 4.0 congenital infections with rubella vaccine virus per 100 susceptible women vaccinated during pregnancy. Limited data on gestational age at time of vaccination indicated that 90% of these women were vaccinated during the first 4 weeks of pregnancy. This estimate of the incidence of

Table 2. Susceptibility to Rubella Infection at the Time of Vaccination Among Pregnant Women Vaccinated With Measles-Rubella Vaccine, Surveillance Data From 7 States, Brazil, 2001–2002

State	Notifications	Number (%) of women with serologic result	Classification of susceptibility to rubella infection at time of vaccination, according to serology[a], Number (%) of women with serologic result			
			Susceptible	Immune	Indeterminate	Nonresponders
BA	3530	3530 (100)	402 (11.4)	2947 (83.5)	181 (5.1)	0
GO	610	504 (82.6)	71 (14.1)	55 (10.9)	378 (75.0)	0
MG	2008	1916 (95.4)	236 (12.3)	997 (52.0)	675 (35.2)	8 (0.4)
PE	879	879 (100)	99 (11.3)	64 (7.3)	716 (81.4)	0
RJ	2665	2203 (82.7)	288 (10.8)	316 (13.8)	1576 (68.8)	23 (1.0)
RS	4371	3973 (90.9)	425 (10.7)	970 (24.4)	2561 (64.5)	17 (0.4)
SP	6473	5580 (86.2)	811 (12.5)	2135 (38.2)	2607 (46.7)	27 (0.5)
Total	20 536	18 585 (90.5)	2332 (12.5)	7484 (40.3)	8694 (46.8)	75 (0.4)

NOTE. BA, Bahia; GO, Goiás; MG, Minas Gerais; PE, Pernambuco; RJ, Rio de Janeiro; RS, Rio Grande do Sul; SP, São Paulo.

[a] For definitions of serological classification, see Methods.

Table 3. Results of Follow-up of Women Vaccinated During or Preceding Pregnancy, Surveillance Data From 7 States, Brazil, 2001–2002

State	Number of susceptible women identified[a]	Number (%) of women with follow-up data	Pregnancy outcome		
			Live birth	Miscarriage	Still birth
			Number (%)[b]		
BA	402	338 (84.1)	323 (95.6)	11 (3.2)	4 (1.2)
GO	71	65 (91.5)	55 (84.6)	10 (15.4)	0
MG	236	234 (99.2)	212 (90.6)	19 (8.1)	3 (1.3)
PE	99	90 (90.9)	90 (100)	…	…
RJ	288	217 (75.3)	205 (94.5)[c]	10 (4.6)	2 (0.9)
RS	425	272 (64.0)	250 (91.9)	19 (7.0)	3 (1.1)
SP	811	644 (79.4)	608 (94.4)	34 (5.2)	2 (0.5)
Total	2332	1860 (79.8)	1743 (93.7)	103 (5.8)[d]	14 (0.8)[d]

NOTE. BA, Bahia; GO, Goiás; MG, Minas Gerais; PE, Pernambuco; RJ, Rio de Janeiro; RS, Rio Grande do Sul; SP, São Paulo.

[a] Includes only women with laboratory evidence of susceptibility to rubella infection (see Methods) for whom follow-up was initiated.

[b] Percentages of birth outcomes include only susceptible women with follow-up data on birth outcome recorded on notification form.

[c] Includes 1 child born to a susceptible mother with wild-type rubella virus detected in nasopharyngeal secretions.

[d] Percentage based on surveillance for these outcomes in 6 states (excluding PE).

congenital rubella infection following fetal exposure to rubella vaccine virus is at the higher range of previous reports [10, 18, 19]. The observed incidence may have been influenced by factors specific to this population, including maternal age, parity, and gestational age at vaccination. Alternatively, higher sensitivity of the serologic assay used in this surveillance system, compared with laboratory tests used previously, may have improved detection of congenital rubella infections. A single commercial assay and standard protocol was used in this surveillance system, which should facilitate comparison to results from other settings. Although rubella vaccine virus was not detected in samples from children with evidence of congenital rubella infection, the presence of anti-rubella IgG antibodies in specimens collected at birth or within the first year of life supported the diagnosis of congenital rubella infection based on IgM seropositivity [20]. Secretion of rubella vaccine virus is less common than shedding of wild-type virus by congenitally infected infants (J. Icenogle, S. Katow [CDC], and L Jin [Health Protection Agency, London], personal communication).

Table 4. Incidence of Congenital Rubella Infection Among Infants Born to Susceptible Women Vaccinated During or Preceding Pregnancy, Surveillance Data From 7 States, Brazil, 2001–2002

State	Results of Serological Testing Performed at State Laboratory			
	Number of infants tested[a]	Number of IgM-positive newborns	Incidence[b] of congenital rubella infection	95% CI
BA	272	4	1.5	.3–3.0
GO	39	0	0	0–9.0
MG	212	12	4.5	3.0–9.7
PE	90	5	5.5	1.8–12.5
RJ	204	4	2.0	.5–4.9
RS	250	15	6.0	3.4–9.7
SP	580	27	4.6	3.1–6.7
Total	1647	67	4.1	3.2–5.1

NOTE. BA, Bahia; CI, confidence interval; GO, Goiás; Ig, immunoglobulin; MG, Minas Gerais; PE, Pernambuco; RJ, Rio de Janeiro; RS, Rio Grande do Sul; SP, São Paulo.

[a] Includes only live births to women with laboratory evidence of susceptibility to rubella infection (see Methods) for whom follow-up was initiated.

[b] Incidence of congenital rubella infection expressed per 100 live births to susceptible, vaccinated women.

Because of the publicity associated with the vaccination campaign, there was a high level of awareness among health professionals of the potential risk associated with rubella vaccination during pregnancy. This increased the chance of detection by the public health system of a child with CRS born to a vaccinated mother. The recommendations for pregnant women to defer vaccination until after giving birth and for vaccinated women to avoid conception for 1 month following receipt of rubella vaccine were publicized at vaccination posts. Recommendations were disseminated in writing to health professionals by national societies. The surveillance protocol was presented during trainings at all levels of the public health system (national, state, and local). Infants born with CRS during the surveillance period were investigated to determine whether the mother had received rubella vaccine during pregnancy, and specimens were sent to the national reference laboratory to confirm that infants born with CRS had been infected with wild-type rubella viruses. The collection of samples and isolation of wild-type rubella virus from a child with signs of CRS born to a vaccinated mother demonstrated the importance of the surveillance system. A rubella outbreak (caused by genotype 1G) had occurred prior to the rubella campaign in the community where the

mother resided, in the western part of the city of Rio de Janeiro. The mother's infection with wild-type rubella had not been detected prior to the child's birth. The investigation of this single case was important to rule out an association between CRS and the mother's rubella vaccination during the rubella campaign.

The experience in Brazil demonstrates the practical challenges of avoiding vaccination of pregnant women during mass immunization of women of childbearing age. However, the accumulated experience with rubella immunization campaigns among women of childbearing age in numerous countries supports the findings of this analysis [19, 21]. These results, however, do not support indiscriminate vaccination of pregnant women. In Brazil, the potential for vaccination of pregnant women made it an imperative for the Ministry of Health to conduct surveillance for potential adverse effects on the fetus. The implementation of this surveillance system strengthened cooperation between state public health laboratories and epidemiologic surveillance and demonstrated the role of a reporting system for adverse events after vaccination.

The data from this surveillance system have several limitations. The national protocol was designed to identify major malformations characteristic of CRS among infants born to mothers vaccinated during pregnancy. The system was not designed to investigate associations between congenital rubella infection and outcomes besides CRS, including any impairment that may present later in life. Infants with evidence of congenital rubella infection were followed for 12 months. Second, the evaluation of the surveillance system did not include a comparison population for the incidence of stillbirths and miscarriage among women who did not receive rubella vaccine. The incidence of miscarriage and stillbirth in the states that evaluated these outcomes were similar to rates reported from a follow-up study involving women who received yellow fever vaccine while unknowingly pregnant [22], and the prevalence of stillbirth was lower than estimates based on pregnancy-related hospitalizations in 1995 in the 6 states, which ranged from 9.7 to 17.7 fetal deaths for every 1000 live births [23]. Incidence rates and confidence intervals were based on notifications with complete follow-up, which may not be representative of all women of childbearing age vaccinated during pregnancy. Because notification rates were highest in states with a greater capacity to conduct surveillance, it is likely that the number of women vaccinated during pregnancy was substantially underreported. Areas with limited public health infrastructure experienced many difficulties conducting surveillance for women vaccinated during pregnancy, including transportation of serum specimens, timeliness of feedback and follow-up, and transport of children born with evidence of congenital rubella infection for medical examinations by specialists. Last, rates of miscarriage, stillbirth, and low birth weight were considered secondary outcomes and were estimated on the basis of passive surveillance.

In Brazil, mass immunization of women of childbearing age was conducted to prevent cases of CRS that were occurring as a result of ongoing circulation of rubella virus among the susceptible population. Although childhood immunization against rubella was phased in throughout Brazil from 1992 through 2000, an accumulation of susceptible individuals among adolescents and adults was sustaining transmission of rubella and resulting in several large rubella outbreaks. The alternative to mass vaccination of women of childbearing age would have been to wait several decades until cohorts vaccinated in childhood reached adulthood [24, 25]. As countries in other regions of the world pursue rubella elimination and decide upon vaccination strategies, these data provide evidence for the safety of rubella vaccination among women of childbearing age. The strategy of mass vaccination to accelerate the elimination of rubella and CRS depends upon high public confidence in vaccine safety.

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