



Impact of rubella vaccination strategy on the occurrence of congenital rubella syndrome

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Abstract

Objective: Routine rubella vaccination was introduced in Paraíba, northeastern Brazil, through a catch-up campaign targeting children aged 1-11 years, in 1998. A campaign among women of childbearing age was conducted in 2001. We describe the epidemiology of rubella and congenital rubella syndrome (CRS) in the state of Paraíba between 1999 and 2005.

Methods: Rubella and CRS surveillance data for the 1999-2005 period were analyzed. Suspected cases of rubella were confirmed by laboratory findings, epidemiological link, or clinical data. International standardized CRS definitions were used.

Results: Of 5,924 suspected cases of rubella between 1999 and 2005, 1,266 (21%) were confirmed, 766 (61%) by laboratory findings. During a rubella epidemic in 2000 (18.8/100,000), the incidence among individuals aged 14-19 years (42/100,000) had a fourfold increase relative to children aged 1-13 years (95% confidence interval = 3.2-5.1). The overall rubella incidence was 0.9/100,000 in 2005. Of 177 suspected cases of CRS between 1999 and 2005, 167 (94%) were tested for IgM. Of 14 (8%) laboratory confirmed cases of CRS, 12 (86%) were born in 2001, with an incidence of 0.2/100,000 children aged less than 1 year.

Conclusions: The 1998 rubella vaccination campaign was insufficient to prevent an outbreak among young adults in 2000, with a high CRS incidence in 2001. Between 2002 and 2005 the incidence of rubella and CRS decreased; however, high routine vaccination coverage and high-quality surveillance remain critically important to achieve CRS elimination by 2010.

J Pediatr (Rio J). 2007;83(5):415-421: Rubella, outbreaks, congenital rubella syndrome, vaccination, Brazil.

Introduction

Rubella is usually a mild childhood rash disease, with development of subclinical infections in 25-50% of cases. The most important consequences of rubella result from rubella infection in early pregnancy and include abortions, miscarriages, stillbirths, and fetal anomalies. Up to 80% of infants born to women who acquire rubella during the first trimester of gestation may be affected. The most commonly described anomalies associated with congenital rubella syndrome (CRS) are ophthalmologic, cardiac, auditory and neurologic ones. Although moderate and severe cases of CRS may be readily

recognizable at birth, mild cases may not be detected for months or even years after birth.¹

The objective of rubella immunization programs is to prevent fetal infection and consequent CRS. Although the disease is on the verge of elimination in many developed countries, an estimated 100,000 infants are born with CRS annually.² In Brazil, rubella vaccination was introduced in a phased manner by states during the 1992-2000 period.³ Rubella and CRS have been reportable diseases in Brazil since 1996,⁴ however surveillance for rubella became more sensitive and representative only after 1999, when it was integrated with measles surveillance.⁵ Between 1999 and 2000,

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Financial support: Brazilian Ministry of Health.

Suggested citation: Lanzieri TM, Pinto D, Prevots DR. Impact of rubella vaccination strategy on the occurrence of congenital rubella syndrome. *J Pediatr (Rio J)*. 2007;83(5):415-421.

Manuscript received May 25 2007, accepted for publication Jul 6 2007.

doi 10.2223/JPED.1692

large outbreaks of rubella were reported in almost every state, with different age distribution patterns across states, probably resulting from the gradual introduction of the vaccine. As rubella cases began to be detected among pregnant women, a CRS surveillance system was implemented in 2000⁴ and postpartum vaccination was initiated. To accelerate CRS control, a two-phased vaccination campaign targeted at women of childbearing age was conducted nationally during 2001 and 2002.⁶ Additionally, in 2003, Brazil supported the Pan American Health Organization resolution to achieve the goal of eliminating rubella and CRS from the region by 2010.⁷

In the state of Paraíba, in northeastern Brazil, rubella vaccination was introduced in August 1998, through a mass campaign using measles-mumps rubella (MMR) vaccine targeted at children aged 1 to 11 years, with coverage levels ranging from 49 to 100% throughout the 224 municipalities of Paraíba. The campaign was followed by the introduction of MMR in the childhood vaccination schedule. The current schedule includes a first dose of MMR given at age 12 months and a second dose at age 4 to 6 years. Rubella surveillance was initiated in the state of Paraíba in late 1998 as part of intensified measles elimination activities. A large rubella outbreak including numerous cases among pregnant women was reported during 2000. A statewide campaign targeted at non-pregnant women aged 15 to 29 years was held in November 2001, with coverage levels ranging from 62 to 100% across municipalities. In this study, we describe the epidemiology of rubella and CRS in the state of Paraíba during the 1999-2005 period, and the impact of rubella vaccination strategies.

Methods

Rubella surveillance

Rubella surveillance is integrated with measles surveillance and includes: (1) stimulated passive surveillance among healthcare providers for immediate notification of suspected cases of measles and rubella, (2) immediate case reporting and investigation of suspected cases, with blood collection for specific diagnosis using laboratory tests. Individual data are collected using a standardized measles-rubella case investigation form and include demographic information, clinical manifestations, vaccination history (upon review of vaccination records), pregnancy status, laboratory results and control measures. These data are entered in the National Notifiable Disease Information System (NNIDS) at the municipal or regional level, transferred to the next reporting level, and finally to the national level in the Ministry of Health.

A suspected rubella case is defined as a person of any age presenting with fever, rash, and cervical, occipital or postauricular lymphadenopathy; or any person for whom a healthcare professional suspects rubella. Suspected cases are confirmed (1) by laboratory, if rubella-specific IgM antibodies are detected by enzyme immune assay (Behringwerke AG Diagnostica); (2) by epidemiological link, if exposure to a

laboratory confirmed rubella case occurred between 12-23 days before the onset of symptoms; or (3) clinically, when the suspected case has fever, rash and lymphadenopathy, lacks laboratory testing or epidemiological link and cannot be discarded based upon epidemiological link to another rash illness (e.g. dengue) or by temporal association with the administration of rubella-containing vaccine.

To describe the epidemiology of rubella in Paraíba from 1999 to 2005, we analyzed data from the NNIDS using Epi Info version 6.04b. We calculated the annual rubella incidence per 100,000 individuals using the number of confirmed cases of rubella as a numerator and the annual population census estimates as a denominator. The chi-square test was used to compare incidence across age groups and proportions.

CRS surveillance

CRS surveillance was initiated in 2000 through (a) follow-up of pregnant women with rubella and (b) reporting of infants with suspected CRS. For all suspected CRS cases, patient medical charts were reviewed and hospital or household case investigations were conducted with completion of a standardized questionnaire and collection of a blood sample for rubella-specific IgM and IgG detection, had such testing not been performed at birth. In 2001, active sentinel CRS surveillance was established at a maternity hospital in the capital city, João Pessoa, which serves as a referral service for the state.

A suspected case of CRS was defined as 1) an infant whose mother reported confirmed rubella infection during pregnancy; or 2) an infant with manifestations compatible with CRS. Suspected CRS cases were classified according to the World Health Organization standardized case definitions as laboratory confirmed, clinically compatible or congenital rubella infection (CRI).⁸ Pregnancies with unknown outcome or infants who were not evaluated for CRS-compatible manifestations were considered lost to follow-up.

Data from CRS case reports were entered in the NNIDS and analyzed using Epi Info version 6.04b. CRS incidence was calculated using the total number of infants with confirmed or compatible CRS as a numerator and the annual census estimates of the population < 1 year old as a denominator.

Results

Rubella epidemiology

Between 1999 and 2005, 5,954 suspected rubella cases were reported in Paraíba; 1,391 (23%) suspected cases were unclassified because clinical, epidemiological and laboratory data were insufficient or inconsistent. Of the remainder, a total of 1,266 (21%) cases were confirmed, 766 (61%) by laboratory, 323 (25%) by an epidemiological link and 177 (14%) clinically. Among the 3,297 (55%) discarded cases, 2,022 (61%) had negative IgM antibody tests for rubella and 749

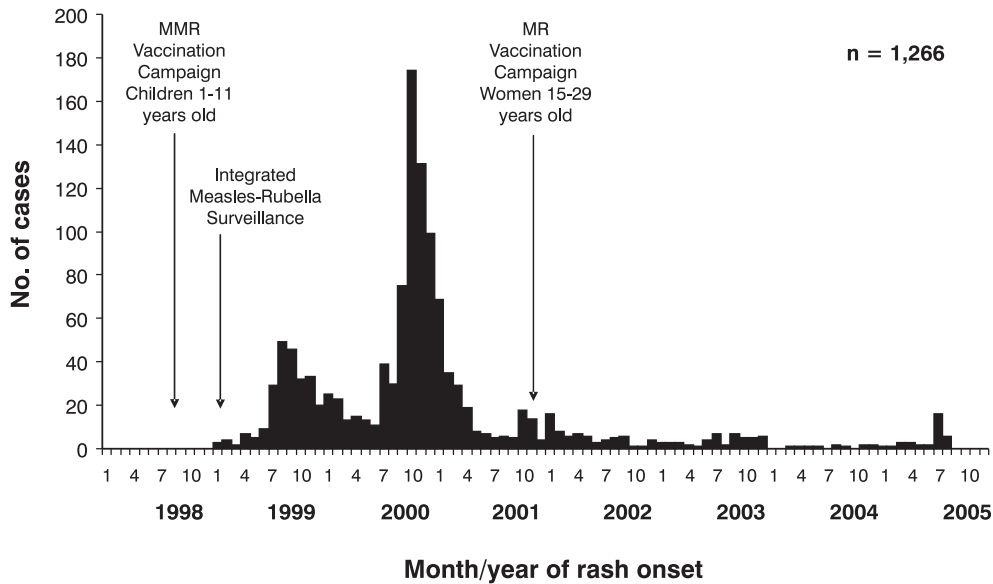


Figure 1 - Confirmed rubella cases by month of rash onset, state of Paraíba, Brazil, 1999-2005

(23%) had negative IgM antibody tests for measles. The median interval between onset of symptoms and date of sample collection was 5 days among laboratory confirmed cases (n = 630; range: 0-248 days) and 5 days among discarded cases (n = 1,894; range: 0-278 days). The diagnosis was missing for 1,259 (38%) of discarded cases and unknown for 672 (20%); 903 (27%) presented with unspecified rash illness, 425 (13%) with dengue, 22 (1%) with exanthema subitum, nine (0.03%) with vaccine adverse reactions, three with scarlet fever, two with erythema infectiosum and two with enteroviral infection.

Of 1,266 confirmed cases, 239 (19%) occurred in 1999, 648 (51%) in 2000, 219 (17%) in 2001 and the remaining

160 (13%) cases between 2002 and 2005. The number of confirmed cases peaked in October 2000 (n = 174) (Figure 1). The incidence of rubella declined from 18.8 per 100,000 individuals in 2000 to 0.9 in 2005 (Table 1).

The median age among case patients was 17.5 years in 1999 (range: 0-53) and decreased to 8 years in 2002 (range: 0-75) and to 2 years in 2005 (range: 0-42). Overall, 749 (59%) case patients were female and 372 (29%) were women aged 15 to 29 years; the proportion of women aged 15 to 29 years among case patients decreased from 32% in 1999-2001 to 13% in 2002-2005 (p < 0.01). Confirmed rubella was reported among 64 pregnant women; of these, confirmation was by laboratory tests in 50 (78%), by epidemiologic link in 12

Table 1 - Distribution of confirmed rubella cases by age group, gender and pregnancy status, state of Paraíba, Brazil, 1999-2005

Variables	Number of cases (%)						
	1999	2000	2001	2002	2003	2004	2005
Age group (years)							
< 1	12 (5)	31 (5)	20 (9)	10 (15)	18 (38)	2 (18)	11 (32)
1-13	45 (19)	98 (15)	58 (26)	30 (45)	21 (44)	7 (64)	18 (53)
14-19	81 (34)	197 (30)	43 (20)	5 (7)	4 (8)	1 (9)	1 (3)
20-29	48 (20)	200 (31)	68 (31)	11 (16)	2 (4)	0 (0)	2 (6)
> 30	32 (13)	103 (16)	30 (14)	11 (16)	3 (6)	1 (9)	2 (6)
Total*	239	648	219	67	48	11	34
Gender (female)	136 (57)	392 (61)	129 (59)	45 (67)	22 (46)	4 (36)	23 (68)
Women aged 15-29 years	66 (28)	223 (34)	64 (29)	12 (18)	5 (10)	0 (0)	3 (9)
Pregnant women	4 (2)	43 (7)	11 (5)	5 (8)	1 (2)	0 (0)	0 (0)

* 21 cases with missing data for age in 1999 and 19 in 2000.

Table 2 - Pregnancy outcome among women with confirmed rubella and classification of infants with suspected congenital rubella syndrome, state of Paraíba, Brazil, 1999-2005

Number of individuals	Type of entry in the CRS* surveillance system		Total
	Follow-up of pregnant women with confirmed rubella	Infants with suspected CRS identified at maternity hospitals	
Initial cohort	64	141	205
Lost to follow-up	24	6	30
Abortion	3	-	3
Stillbirth	1	-	1
Infants			
Investigated	36	135	171
Tested for IgM	33	134	167
IgM-positive	9	9	18
Laboratory confirmed CRS	5	9	14
Clinically compatible CRS	1	1	2
CRI [†]	4	0	4
Discarded	26	125	151

* Congenital rubella syndrome

† Congenital rubella infection.

(19%), and by clinical data in two (3%). All pregnant case patients were reported between 1999 and 2003, of which 43 (67%) had illness in 2000. The median age of pregnant case patients was 22 years, ranging from 14 to 40 years (n = 63).

In 2000, considered an epidemic year, 397 (61%) confirmed rubella cases were among adolescents and young adults aged 14 to 29 years, with a male:female ratio of 2:3. The highest incidence of rubella was among children aged < 1 year (47/100,000) followed by persons aged 14 to 19 years (42/100,000) and 20 to 29 years (34/100,000) (Table 1). Relative to children aged 1 to 13 years (10/100,000), the targeted age group during the 1998 MMR campaign, the incidence of rubella increased 4.5 times among children < 1 year old (95%CI 3.0-6.8), 4.0 times among persons aged 14 to 19 years (95%CI 3.2-5.1) and 3.3 times among persons aged 20 to 29 years (95%CI 2.6-4.2).

CRS epidemiology

Rubella was confirmed in 64 pregnant women between 1999 and 2003. Of these, 24 (38%) were lost to follow-up; 12 (50%) cases were reported between 1999 and 2000, six (25%) in 2000, five (21%) in 2002 and one (4%) in 2003. Of the remainder 40 (72%) pregnant women, three (5%) had spontaneous abortions, one (2%) had a stillbirth and 36 (56%) delivered liveborn infants (Table 2). An additional 141 infants with suspected CRS were reported between 1999 and 2005, and six were lost to follow-up. A total of 171 suspected CRS cases were investigated, 167 (98%) were tested for IgM and 18 (11%) were positive; 154 (92%) had blood samples collected within 6 months of age. Fourteen (8%) infants were

classified as laboratory confirmed CRS cases, two (1%) were clinically compatible, four (2%) had CRI, and 151 (88%) were discarded. Of discarded cases, 133 (88%) had a negative anti-rubella IgM test in a sample collected within 6 months of age.

CRS incidence per 1,000 children < 1 year old was 0.01 in 1999 (n = 1), 0.03 in 2000 (n = 2) and 0.20 in 2001 (n = 13). During 2002 and 2005, no cases of CRS were confirmed, compatible or classified as CRI. Confirmed or compatible cases of CRS born in 2001 were from eight (4%) of 224 municipalities, with CRS incidence ranging from 1 to 16 cases per 1,000 children < 1 year old in these municipalities.

Of 16 infants with CRS born during 1999 and 2001, nine (56%) had congenital heart disease, eight (50%) had hearing impairment, as the sole CRS manifestation in five (31%), and six (38%) had cataracts. One (6%) infant presented with those three manifestations and five (31%) had two of them. Six (38%) infants had purpura, four (25%) had jaundice, two (13%) had hepatosplenomegaly and one (6%) had mental retardation. Three (19%) infants were born before 37 weeks of gestation and 11 (69%) had birth weights lower than 2,500 g. Five (31%) infants with confirmed CRS had fatal outcomes within 3 months of birth, four (80%) in the first month. All of them had birth weights lower than 2,500 g, congenital heart disease, and purpura.

Of 63 suspected CRS cases with maternal rubella during pregnancy, 14 had laboratory confirmed CRS, one had clinically compatible CRS, four had CRI, 42 were discarded and two were lost to follow-up. Of 22 suspected CRS cases with maternal rubella during the first trimester of pregnancy, 12

(55%) had laboratory confirmed CRS, three (14%) had CRI and seven were discarded. The median age of mothers having infants with confirmed CRS was 26 years, ranging from 23 to 27 years ($n = 5$); none had been previously vaccinated.

Discussion

In this study, we documented the epidemiology of rubella and CRS in the state of Paraíba between 2000 and 2005. The 1998 rubella vaccination targeting children aged 1 to 11 years was not sufficient to prevent an outbreak among susceptible young adults in 2000, with a consequent high incidence of CRS in 2001. Nonetheless, the outbreak was not likely due only to suboptimal vaccination coverage, but also to a high intensity of transmission and a substantial susceptible pool in the young adult population outside the age group targeted for vaccination.

Active prospective surveillance in maternity hospitals and complete follow-up of pregnant rubella case patients were critical to documenting the CRS disease burden in 2001 and the impact of vaccination strategies on reducing this burden in the following years. Despite enhanced surveillance, the true CRS burden is likely to be underestimated for several reasons, including: 1) lack of patients seeking medical care due to the usual clinical presentation of rubella as a mild rash illness; 2) underreporting of pregnancy status on rubella case reports, 3) loss to follow-up of a great number of pregnant rubella case patients and infants with suspected CRS, 4) lack of information regarding signs and symptoms on medical records of suspected CRS case patients, 5) lack of hearing impairment evaluation for all suspected CRS cases, and 6) lack of follow-up of CRI cases who may manifest CRS-related sequelae later in life.

The proportion of CRS cases diagnosed with cardiopathy was comparable to that found in other studies with complete case ascertainment, in which approximately 40-50% of children with CRS had cardiopathy.⁹ Only half of our CRS cases had hearing impairment identified, although in some series up to 60 to 90% of CRS case patients are affected.⁹⁻¹¹ One third of infants with CRS had a fatal outcome within the first 3 months of life and a high proportion of suspected CRS cases had been tested for anti-rubella IgM antibodies in a timely manner. However, we may have missed cases with early fatal outcomes or who presented with fewer predictive signs of CRS and were not screened for hearing impairment early in life.

The annual incidence of CRS was estimated at 0.2 per 1,000 children < 1 year old in the state of Paraíba during 2001, lower than the incidence reported in other studies both in Brazil and elsewhere following rubella outbreaks in non-vaccinated populations.^{3,12,13} In Brazil, incidences of 0.6 and 0.9 per 1,000 live births were documented by prospective and retrospective studies following rubella outbreaks during the 1999-2001 period.^{3,12} In other developing countries, rates of CRS per 1,000 live births following rubella outbreaks varied

from 0.4 in Jamaica during 1995 to 2.2 in Panama during the 1986-1987 period.¹³ However, this statewide annualized incidence in Paraíba masked an incidence 2.5 times higher (0.5 per 1,000 children < 1 year old) during May-August 2001, 7 to 10 months after the rubella peak month, and in certain municipalities in which incidence was 5 to 80 times higher than the statewide incidence. The lack of follow-up of 38% of pregnant women reported with confirmed rubella between 1999 and 2003 may also have limited our CRS incidence estimates, although the trends would have been similar if all of such women had infants with CRS, since most of them had been reported during 2000.

We observed that during the epidemic year, incidence of rubella was higher among children < 1 year old, adolescents and young adults; the median age at infection was 19 years in 2000. Before the introduction of the rubella vaccine, rubella was a common childhood disease in Brazil, with an average age at infection of 6 years, and epidemics occurring approximately every 6 to 9 years in urban areas.^{14,15} Unfortunately, rubella surveillance data for the state of Paraíba were not available for years prior to 1999 for comparison to affirm there was a shift in the age distribution of cases resulting from the vaccination campaign in 1998. A change in the average age of first infection is an important indirect effect of mass immunization, resulting in longer inter-epidemic periods. Such period of low incidence during the shift from the prevaccination to the postvaccination age distribution of susceptibles, termed the honeymoon period, may be followed by a rebound in the number of cases.¹⁶ Continued endemic-epidemic transmission among adults has been observed following implementation of routine childhood vaccination in several countries, even those with relatively high coverage levels, due mainly to an increased risk of rubella infection among susceptible young adults.¹⁷⁻²² To prevent CRS, many countries have introduced rubella vaccination of schoolgirls and women of childbearing age following or concurrent with its introduction into the routine childhood vaccination schedule.

This study provides population-based data documenting rubella and CRS incidence in the state of Paraíba, Brazil, between 2000 and 2005. The increased incidence of rubella among adults during the 1999-2000 period and the increased detection of CRS cases, both in Paraíba and in the rest of Brazil, led to intensified efforts to vaccinate women of childbearing age. Although a low rubella incidence is expected in the years following outbreaks, the marked decrease in rubella and CRS incidence observed after 2001, despite intensive surveillance efforts to detect suspected cases, reflects the low positive predictive value of surveillance of both diseases and demonstrates the effectiveness of the implemented vaccination strategies. The vaccination campaign among women of childbearing age in 2001 following the outbreak likely reduced the number of remaining susceptibles in this group. However, young adult males, who have not been targeted for vaccination, may play an important role in rubella transmission in the

future. Nonetheless, as successive cohorts of children age into adulthood, including both boys and girls, the risk of rubella transmission will be further reduced.

Additionally, some municipalities did not reach the recommended 95% vaccination coverage in the previous campaigns or in the routine childhood schedule, increasing the risk of outbreaks in the future. High routine rubella vaccination coverage at the state, municipal, and local level together with a high-quality surveillance system will be critical to achieving the elimination goal in Brazil by 2010. In populations with sub-optimal vaccination coverage, and even in partially vaccinated populations, when vaccine is available only through the private sectors, future increases in the incidence of CRS may occur.²³ Fortunately, in Brazil, the vaccine is offered through the public health service. However, coverage or protection levels below the minimum recommended have resulted in outbreaks of rubella, as exemplified in the state of Paraíba. Therefore, we recommend monitoring routine rubella coverage to identify areas and subgroups at higher risk, targeting intensified vaccination efforts towards low coverage areas as well as conducting ongoing analysis of rubella surveillance data to identify and investigate clusters of suspected rubella cases, with timely adoption of control measures to prevent CRS. Finally, to document the impact of rubella vaccination strategies, efforts should focus on maintaining high sensitivity of rubella and CRS surveillance in a period of low incidence of both diseases.

Acknowledgements

We acknowledge the effort put in by Dr. Shamyia Lewis Saad Rached, neonatologist from Instituto Cândida Vargas, in establishing sentinel CRS surveillance and her dedication in detecting and reporting CRS suspected cases; we also thank the personnel at the Central Public Health State Laboratory of Paraíba for the management of blood samples and antibody testing; all members of the municipal and state surveillance and immunization services of the state of Paraíba, especially from the state capital, João Pessoa, for their intensive efforts in disease surveillance and rubella vaccination; and Henry Walke and Douglas L. Hatch for their careful review of the manuscript.

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