Historical Analysis of Birth Cohorts Not Vaccinated Against Rubella Prior to National Rubella Vaccination Campaign, Brazil

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Background. Brazil conducted mass rubella vaccination campaigns to meet disease elimination goals by 2010. An analysis of rubella vaccination opportunities was conducted to target population groups with concentrations of unvaccinated individuals.

Methods. Rubella vaccination strategies for all 27 states were reviewed between 1992 and 2006. Yearly vaccination coverage was calculated by dividing number of doses of measles-rubella or measles-mumps-rubella vaccines administered by census estimates of target populations. For annual birth cohorts (1967–2005), percentages of persons not vaccinated prior to 2007 were estimated by subtracting the highest coverage obtained in any vaccination strategy (routine or campaign) from 100%. Cohort analysis results were compared with rubella incidence by population group.

Results. An estimated 28.9 million males and 7.7 million females aged 2–40 years in 2007 remained unvaccinated against rubella, corresponding to 43.0% of males and 11.5% of females of these ages in Brazil. The highest percentages of unvaccinated birth cohorts (93.6%–98.1%) were identified among males aged 26–40 years. In rubella outbreaks reported during 2007, the highest disease incidence (22 cases per 100000 population) occurred among males aged 20–29 years.

Conclusions. Analysis of rubella vaccination opportunities identified concentrations of unvaccinated adults and adolescents for targeting mass vaccination to eliminate rubella and congenital rubella syndrome in Brazil.

In the Americas, the substantial burden of rubella disease and congenital rubella syndrome was largely hidden until the implementation of enhanced surveillance for measles in the early 1990s [1]. Rubella control strategies gained momentum as countries in the region pursued measles elimination goals [2]. In 2003, member states of the Pan American Health Organization, including Brazil, set a goal of eliminating transmission of rubella and congenital rubella syndrome by 2010 [3]. The strategy adopted to achieve this goal, based on the successful approach to measles elimination [4], includes conducting surveillance for rubella and congenital rubella syndrome, routine childhood immunization against rubella using the combined measles-mumps-rubella (MMR) vaccine, periodic follow-up campaigns to vaccinate all children younger than 5 years of age with MMR, and mass vaccination of adolescents and adults with measles-rubella (MR) vaccine [5]. According to the Pan American Health Organization, all strategies should reach 95% of the target population in order to avoid leaving pockets of susceptible individuals who can maintain transmission of rubella or allow reestablishment of measles transmission [4].
In Brazil, rubella vaccine became available in private clinics in the early 1970s. However, rubella vaccination did not become widespread until the introduction of MMR vaccine into the routine childhood immunization schedule state by state between 1992 and 2000. The implementation of vaccination strategies rapidly changed the epidemiological characteristics of rubella in Brazil. During 1997 and 1998, children 1–9 years of age experienced the highest incidence of rubella, with 15 cases per 100000 children. During 1998 and 1999, peak incidence had shifted to the 15–29 year age group, with 13 cases per 100000 adolescents and adults of both sexes [6]. Follow-up MMR campaigns for children 1–4 years of age were conducted in 2000 and 2004, and mass vaccination of women of childbearing age (age groups ranging between 12 and 39 years depending on state) with MR vaccine was conducted between 2001 and 2002 in most states to prevent cases of congenital rubella syndrome [7]. These strategies reduced rubella incidence in the population to a low of 1 case per 100000 population in 2006. However, as a result of an accumulation of unvaccinated cohorts of individuals and continuous transmission of rubella virus throughout Brazil, rubella outbreaks were recognized in 2006 and spread throughout Brazil in 2007 [6, 8]. By 2006, rubella cases were occurring mainly among adolescent and adult men, while pools of susceptible individuals in all age groups sustained viral circulation. To reach the 2010 goal of rubella elimination, the government of Brazil planned mass vaccination of adults for 2008. Several approaches were used to define the ideal age range to target in order to vaccinate the largest percentage of unvaccinated individuals.

This article describes a retrospective analysis of rubella vaccination opportunities by birth cohort, sex, and state of residence performed to identify population groups with high proportions of unvaccinated individuals. We compared the results of the analysis of nonvaccinated cohorts with the age- and sex-specific incidence of rubella during widespread outbreaks of rubella throughout Brazil in 2007. These data informed the selection by the Brazilian Ministry of Health of target population groups, considering age and sex, in preparation for the 2008 national vaccination campaign against rubella.

METHODS

Brazil, the largest country in Latin America and the fifth largest country in the world, has tremendous geographic and socioeconomic diversity. The population of 191.8 million (2000 census) is distributed in 26 states and 1 Federal District, with 85.2% living in urban areas [9].

Surveillance

Brazil has conducted integrated surveillance for measles and rubella through its national surveillance system for rash illness since 1999 (Figure 1) [10]. Individuals presenting with rash, fever, and lymphadenopathy to public or private health centers are notified through the National Notifiable Disease System (SINAN) as having suspect cases of measles or rubella [6]. Suspect cases are investigated by epidemiologic surveillance units in healthcare facilities or at the municipal or district level. Control measures to prevent secondary cases, including ring vaccination of contacts of patients with suspect cases, are instituted as rapidly as possible after notification of patients with suspect cases. Serum specimens collected from patients with suspect cases are sent to state health department laboratories (LACEN) for measles and rubella serological analysis. Specimens from patients with suspect rubella cases are tested for anti-rubella IgM antibodies. Specimens from patients with suspect measles cases are first tested for measles IgM antibodies and, if seronegative, are tested for rubella IgM antibody. Following the interruption of endemic measles transmission in Brazil in 2000
For each state, all rubella vaccination strategies from 1992 to 2006 were arranged in spreadsheets (Excel, version 2003, Microsoft) according to sex and age group of the target population. Opportunities for vaccination against rubella were then “mapped” to birth cohorts considering the age group targeted by vaccination. For example, individuals born in 1990 would have been “exposed” to immunization campaigns targeting children 1–11 years of age in 2000. Considering that the life expectancy at birth in Brazil was 72.4 years [9], cohorts born in 1967 (aged 39 years in 2006) through 2005 (aged 1 year in 2006) were considered in this analysis. Persons born prior to 1967 were unlikely to ever have been vaccinated against rubella (results not presented). Persons aged >40 years were assumed to have acquired immunity to rubella through natural infection, because rubella infection was widespread prior to introduction of vaccination strategies.

A total of 6 vaccination strategies were included: (1) vaccination campaigns with MR or MMR vaccines among children 1–11 years of age conducted from 1992 to 2000 (Figure 1), (2) routine childhood MMR vaccination among children 1 year of age from 1992 to 2006, (3) catch-up campaigns with MMR vaccine among children aged 1–4 years conducted in 2000 and 2004, (4) vaccination campaigns with MR vaccine among women of childbearing age conducted from 1998 to 2002, (5) routine MMR vaccination among women of childbearing age beginning in 1993 in the Federal District, and (6) routine MR or MMR vaccination of adolescents and previously unvaccinated adults aged 12 years and older from 2004 to 2006. Routine MR or MMR vaccination of adolescents from 12 years of age and previously unvaccinated adults was implemented in state immunization programs beginning in 2004.

The number of MR and MMR doses administered per calendar year by sex and age category was obtained for each vaccination strategy. Strategies were analyzed separately for each of the 26 states and Federal District. For 1992–1994, prior to the implementation of a national information system, MMR doses given to children 1 year of age in routine immunization activities were obtained from spreadsheets provided by state immunization programs. For 1995 through 2005, vaccine doses applied in routine activities were obtained from the national information system. Doses of MMR vaccine administered to children older than 1 year of age, and doses registered as second doses for all ages were excluded from analysis. Doses administered during campaigns among children aged 1–11 years and women of childbearing age were summarized by age category. Because both MMR and MR vaccines were used for childhood vaccination campaigns, doses of MMR and MR vaccines administered in the same vaccination activity were added together. For adults, doses of MR or MMR vaccine administered during routine immunization visits were recorded in the national information system beginning in 2004, excluding vaccination of women in the postpartum period.

The proportion of the target population covered by each vaccination strategy was estimated by dividing the number of vaccine doses administered by the target population. Population estimates were obtained from the Brazilian Institute of Geography and Statistics and were based on census counts and intercensal projections [12]. Age- and sex-specific vaccine coverage rates were calculated according to state and year. When the number of doses administered was not available by sex or year of age, we assumed that males and females in birth cohorts included in the target population had the same probability of being vaccinated.

**Statistical Methods**

For each birth cohort, the probability of having ever been vaccinated against rubella was considered to be equal to the highest vaccination coverage for any rubella immunization strategy, by state. Effects of migration on individual probabilities of vaccination against rubella were ignored. When the number of doses administered exceeded the estimated target population, the probability of vaccination was equal to 1.0. The Statistical Program for the Social Sciences (SPSS, version 15) was used for data analysis.

The number of persons in each birth cohort that had not been vaccinated against rubella was calculated as (1 – highest estimated rubella vaccination coverage) multiplied by the number of individuals in that birth cohort alive in 2006. Because routine vaccination of adults is considered a selective strategy, doses administered in routine immunization of adults were subtracted from the number of unvaccinated adults in 2006. Estimates of the number of unvaccinated individuals, by sex, age in 2007, and state were exported to spreadsheets in Excel (Microsoft).

**RESULTS**

Table 1 shows the years in which Brazilian states conducted MR and MMR campaigns among children 1–11 years old and among women between 12 and 39 years of age. Estimates of vaccine coverage for these campaigns were based on the number of doses administered in the target population. In the 18 states
that had introduced MMR vaccine prior to 2000, catch-up campaigns with MMR vaccine were conducted among children aged 1–4 years to provide a second opportunity for immunization of children in this age group. Campaigns to vaccinate women of childbearing age with MR vaccine were conducted in 24 of 27 states in 2001 and 2002; 1 state (Federal District) had begun routine vaccination of women of childbearing age with MMR in 1993, and 2 states conducted mass campaigns of immunization of women of childbearing age with MR vaccine in 1998 (Paraná) and 2000 (Rio Grande do Norte) following rubella outbreaks.

On the basis of the analysis of rubella vaccination strategies and proportion of each birth cohort vaccinated by state, we estimated that 28.9 million males and 7.7 million females between the ages of 2 and 40 years in 2007 had never been vaccinated against rubella, corresponding to 43.0% of the male population and 11.5% of the female population in this age group (Table 2). Among children 2–15 years of age of both sexes, the analysis predicted that only 5% of this population remained unvaccinated, reflecting high coverage with routine childhood immunizations throughout Brazil. The highest percentages of unvaccinated birth cohorts were observed among males aged 26–40 years in 2006 (Figure 2). Among persons 16–40 years of age, the analysis predicted 4 times as many unvaccinated males (27.5 million) as unvaccinated females (6.4 million), reflecting the strategy to vaccinate women of childbearing age in most Brazilian states during 2001 and 2002. However, we found a substantial percentage of unvaccinated women between the ages of 31 and 40 years, which represents a potentially susceptible population at risk of rubella infection during pregnancy and of having a child with congenital rubella syndrome.

Table 1. Immunization Campaigns With Measles-Mumps-Rubella (MMR) or Measles-Rubella (MR) Vaccines and Estimated Vaccine Coverage for Children Aged 1–11 Years and Women of Childbearing Age, by State, Brazil, 1992–2002

<table>
<thead>
<tr>
<th>State</th>
<th>Population 2007</th>
<th>Year of MMR campaign among children aged 1–11 years</th>
<th>Reported coverage of catch-up campaign, %</th>
<th>Year of MR campaign among women of childbearing age</th>
<th>Age group targeted for vaccination of women of childbearing age, years</th>
<th>Reported coverage among women of childbearing age, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>São Paulo</td>
<td>41 648 498</td>
<td>1992</td>
<td>95.8</td>
<td>2001</td>
<td>15–29</td>
<td>90.7</td>
</tr>
<tr>
<td>Federal Districta</td>
<td>2 435 984</td>
<td>1993</td>
<td>90.1</td>
<td>...</td>
<td>12–39</td>
<td>72.6</td>
</tr>
<tr>
<td>Espírito Santo</td>
<td>3 511 099</td>
<td>1995</td>
<td>95.4</td>
<td>2001</td>
<td>17–29</td>
<td>104.1</td>
</tr>
<tr>
<td>Paraná</td>
<td>10 514 261</td>
<td>1995</td>
<td>95.8</td>
<td>1998</td>
<td>12–39</td>
<td>87.4</td>
</tr>
<tr>
<td>Minas Gerais</td>
<td>19 667 932</td>
<td>1996</td>
<td>85.4</td>
<td>2001</td>
<td>12–29</td>
<td>92.6</td>
</tr>
<tr>
<td>Rio Janeiro</td>
<td>15 735 852</td>
<td>1996</td>
<td>83.6</td>
<td>2001</td>
<td>15–29</td>
<td>82.2</td>
</tr>
<tr>
<td>Santa Catarina</td>
<td>6 049 288</td>
<td>1996</td>
<td>89.6</td>
<td>2002</td>
<td>12–39</td>
<td>88.1</td>
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<tr>
<td>Bahia</td>
<td>14 028 434</td>
<td>1997</td>
<td>106.9</td>
<td>2002</td>
<td>12–39</td>
<td>87.9</td>
</tr>
<tr>
<td>Ceará</td>
<td>8 314 099</td>
<td>1997</td>
<td>115.8</td>
<td>2002</td>
<td>12–39</td>
<td>91.2</td>
</tr>
<tr>
<td>Piauí</td>
<td>3 057 541</td>
<td>1997</td>
<td>99.6</td>
<td>2002</td>
<td>12–39</td>
<td>92.6</td>
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<tr>
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<td>2 905 251</td>
<td>1998</td>
<td>71.1</td>
<td>2002</td>
<td>12–39</td>
<td>94.2</td>
</tr>
<tr>
<td>Mato Grosso Do Sul</td>
<td>2 329 367</td>
<td>1998</td>
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<td>2002</td>
<td>12–39</td>
<td>90.9</td>
</tr>
<tr>
<td>Paraiba</td>
<td>3 645 902</td>
<td>1998</td>
<td>93.1</td>
<td>2001</td>
<td>15–29</td>
<td>103.2</td>
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<tr>
<td>Rio Grande Do Norte</td>
<td>3 075 104</td>
<td>1998</td>
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<td>5 826 979</td>
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<td>2001</td>
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<td>1999</td>
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<td>Acreb</td>
<td>702 475</td>
<td>2000</td>
<td>105.6</td>
<td>2001</td>
<td>12–39</td>
<td>97.9</td>
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<tr>
<td>Alagoasb</td>
<td>3 069 387</td>
<td>2000</td>
<td>97.5</td>
<td>2001</td>
<td>12–29</td>
<td>101.9</td>
</tr>
<tr>
<td>Amazonasb</td>
<td>3 391 324</td>
<td>2000</td>
<td>95.3</td>
<td>2001</td>
<td>12–29</td>
<td>97.2</td>
</tr>
<tr>
<td>Parnaib</td>
<td>7 250 156</td>
<td>2000</td>
<td>107.9</td>
<td>2002</td>
<td>12–39</td>
<td>106.8</td>
</tr>
<tr>
<td>Pernambucoa</td>
<td>8,584 079</td>
<td>2000</td>
<td>111.0</td>
<td>2001</td>
<td>12–34</td>
<td>100.5</td>
</tr>
<tr>
<td>Rondoniab</td>
<td>1 583 198</td>
<td>2000</td>
<td>95.1</td>
<td>2001</td>
<td>12–39</td>
<td>84.0</td>
</tr>
<tr>
<td>Roraimab</td>
<td>413 113</td>
<td>2000</td>
<td>121.9</td>
<td>2002</td>
<td>12–39</td>
<td>99.0</td>
</tr>
<tr>
<td>Tocantinsb</td>
<td>1 357 735</td>
<td>2000</td>
<td>105.5</td>
<td>2002</td>
<td>12–39</td>
<td>98.5</td>
</tr>
</tbody>
</table>

NOTE. Source: National Immunization Program, Ministry of Health, Brazil.

a Coverage estimates for the Federal District are based on routine MMR vaccination among women of childbearing age implemented in 1993. The Federal District did not conduct mass immunization.

b In 2000 MR vaccine was used for childhood vaccination campaigns in 9 states because of a shortage of MMR vaccine. These states implemented routine MMR vaccination of children at 12 months of age following the campaign.
In several states, MMR vaccination campaigns among children 1–11 years of age did not reach at least 90% of the target population. In 5 of these states (Maranhao, Minas Gerais, Mato Grosso, Rio de Janeiro, and Rio Grande do Norte), the accumulation of unvaccinated adolescents as a result of this suboptimal coverage suggested the need to target the population between 12 and 19 years of age during the rubella vaccination campaign. In these 5 states, the proportion of previously unvaccinated 11–20-year-olds was 16% for males and 13% for females, versus 8% and 2%, respectively, in the remaining 21 states and federal district. In addition, the analysis identified states with accumulations of unvaccinated children ≥7 years of age as a result of low routine immunization coverage. A national “catch-up” vaccination campaign was conducted in 2011 to complete immunization of this age group.

The analysis of unvaccinated birth cohorts predicted the susceptible population that experienced the highest incidence of rubella in outbreaks throughout Brazil in 2007. Rubella cases were notified in 22 of 27 Brazilian states and 640 (11%) of 5580 municipalities, mainly in the heavily populated coastal areas (Figure 3). Males accounted for 6035 (69%) of 8751 confirmed cases. The majority (52%) of confirmed cases occurred among persons 20–29 years of age, followed by the 30–39 year (19%) and 12–19 year (11%) age categories. Occurrence of cases in men and women 40 years of age and older indicates the presence of susceptible individuals in the population assumed to be immune to rubella. The highest incidence of disease was observed among males 20–29 years of age (Figure 4), a population group that previous rubella vaccination strategies had not targeted. In the 12–19 year age group nationally, rubella incidence was higher among adolescents 15–19 years old (4.4 cases per 100 000 population) versus 12–14 years old (1.8 cases per 100 000 population). Although incidence was lower among females 11–39 years of age, compared with males, infection of susceptible women resulted in 37 confirmed cases of congenital rubella syndrome in 2007 and 2008.

### DISCUSSION

The decision by the government of Brazil to eliminate rubella and congenital rubella syndrome by 2010 required dramatic action to interrupt ongoing rubella transmission. This analysis of unvaccinated birth cohorts was conducted to inform vaccination strategies for rubella elimination. We considered the year of introduction of childhood vaccination against rubella, mass
vaccination campaigns, and routine immunization coverage as predictors of rubella vaccination opportunities by birth cohort. Analysis of rubella vaccination opportunities in Brazil was complicated by the differences between state immunization programs in the timing of vaccination strategies implemented and coverage achieved. By incorporating all available information from state immunization programs, the analysis quantified the population of adults that likely had been missed by previous immunization activities. Results showing the lowest percentages of vaccination among men 20–39 years of age were supported by surveillance data in 2007 showing the highest incidence of confirmed rubella in this age group. Birth cohorts of individuals aged 20–39 years in 2007 were born prior to the introduction of MR vaccines in most states, and adult males of this age had not been included in previous rubella control strategies. In addition, the analysis of unvaccinated birth cohorts identified important gaps in rubella vaccination among adolescents 12–19 years of age in 5 states. The analysis revealed that in the absence of mass vaccination, it might take as long as 20 years for vaccination coverage in adults to attain levels high enough to interrupt transmission [2]. Despite highly successful mass vaccination campaigns among women of childbearing age, cases of congenital rubella syndrome continue to occur among the small proportion of unvaccinated women. The results of this analysis were presented to the Brazilian government as supporting evidence of the need for mass immunization to achieve

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**Figure 3.** Confirmed rubella cases by municipality of residence, Brazil, 2007. Each dot represents 1 case ($n = 8751$ cases). Shading indicates the states in which 25% or more of the population 2–40 years of age had not been vaccinated against rubella, according to analysis of vaccination opportunities by cohort.

**Figure 4.** Incidence of confirmed rubella cases per 100 000 population by age and sex, Brazil, 2007.
rubella elimination by 2010 and provided information on priority groups to be targeted during the vaccination campaign.

Brazil’s National Immunization Program conducted a national rubella immunization campaign in the third quarter of 2008, targeting men and women aged 20–39 years in all states and the Federal District, and adolescent males and females aged 12–19 years in 5 states. The target population included 69.7 million people, 36% of the Brazilian population. Although vaccination of adults presents several challenges, Brazil and several other countries of the Americas have successfully conducted adult vaccination campaigns [5, 13]. During the campaign, all persons in the target population were vaccinated regardless of prior history of rubella vaccination or confirmed infection. Revaccination is safe and provides immunity to the small percentage of individuals that do not seroconvert after primary immunization [14]. In Brazil, “selective” vaccination strategies that target only unvaccinated individuals have resulted in low turnout. Few adults have written documentation of prior vaccination, complicating efforts to determine prior vaccination status during a campaign.

Despite relatively high vaccination coverage among women of childbearing age, the National Immunization Program decided to target women, as well as men, to prevent cases of congenital rubella syndrome from occurring among the small percentage of unvaccinated women. In addition, recruitment of adult women may improve adherence among adult men. Mass vaccination of women of childbearing age in Brazilian states between 1998 and 2002 achieved high vaccination coverage and received strong public support. Inclusion of women in the national rubella campaign was justified given the proven safety of MR and MMR vaccines [15, 16].

The objective of this analysis was to identify birth cohorts that had no prior opportunities for vaccination against rubella rather than to estimate the number of individuals with susceptibility to infection. For the latter, seroprevalence surveys are commonly used, especially among women of childbearing age. Several cross-sectional serosurveys were conducted in large Brazilian cities during the 1980s and 1990s prior to widespread vaccination [17–20], and approximately 60%–80% of adolescents and adults surveyed between the ages of 10 and 39 years were immune to rubella. With no loss of immunity over time, these earlier studies might suggest that at least 80% of the population born prior to 1980 would have acquired natural immunity to rubella infection. However, to obtain more precise estimates of rubella susceptibility in the population living in 2007, large serosurveys covering a more representative sample of Brazilian adolescents and adults would have been required. The approach used to identify birth cohorts with concentrations of unvaccinated individuals was appropriate for the purpose of selecting age groups to include in mass immunization campaigns.

Conversely, surveillance data including age- and sex-specific incidence of confirmed rubella cases could have been used to choose the target population for vaccination without the birth cohort analysis. However, the number of confirmed rubella cases during 2007 was relatively small, compared with the size of the target population for the vaccination campaign. The added contribution of the birth cohort analysis was to quantify the population that had no prior opportunity for vaccination. By showing large numbers of previously unvaccinated individuals, the National Immunization Program was better able to convince decision makers at national, state, and municipal levels of the need for mass immunization.

The data used in this analysis of vaccination opportunities by birth cohort were subject to several limitations. First, data on doses administered generally overestimate the number of persons vaccinated. Some individuals may receive >1 dose, and wasted doses may be recorded as administered. During the period of interest, Brazil did not conduct routine surveys to estimate vaccination coverage on an individual basis; such information would have been useful in this analysis. The first national immunization survey among children aged <5 years was completed in 2008. Second, we dealt with multiple opportunities for vaccination in a birth cohort by considering only the highest coverage achieved with any single strategy in a 1-year period. It is possible that different strategies reached different individuals and that actual vaccination coverage was higher than the percentage included in the final analysis. Finally, we did not account for population migration. The population residing in a state in 2007 was treated as having had opportunities for rubella vaccination based on the vaccine coverage and timing of vaccination activities in that state.

This analysis of opportunities for rubella vaccination by birth cohort demonstrated the potential use of routine (administrative) data on doses of vaccines administered compiled by state and municipal immunization programs. In addition, results for each state provided useful feedback to state immunization programs for campaign planning. The final analysis was a collaborative effort between the national immunization program and disease surveillance coordination. Comparisons between rubella surveillance data and results of the birth cohort analysis strengthened coordination between immunization and surveillance activities. Analysis of immunization data led to improvements in the information system used to record doses of vaccines applied, including recommendations for standard age categories for different vaccination strategies. Finally, analyses of MMR vaccination data in infants that showed high coverage justified postponing until 2011 a planned follow-up campaign among children aged 1–6 years to maintain high levels of protection against measles and rubella.

In conclusion, analysis of opportunities for rubella vaccination over the first 13 years of the rubella vaccination program in Brazil provided useful data to justify and plan mass vaccination of adolescents and adults to accelerate rubella elimination. This approach may be useful in other countries for estimating
numbers of unvaccinated individuals. As the member countries of the Pan American Health Organization complete strategies to eliminate rubella in the region, lessons learned and successful strategies may be applied in other regions to accelerate global elimination of rubella and congenital rubella syndrome.

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