Approach to Verify the Status of Measles, Rubella, and Congenital Rubella Syndrome Elimination in Costa Rica

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Costa Rica introduced the measles-mumps-rubella (MMR) vaccine in 1986. The Ministry of Health adopted the goal of eliminating endemic measles in 1991 by achieving and maintaining high vaccine coverage through routine delivery, mass campaigns and outreach activities, and the strengthening of expanded program on immunization (EPI) surveillance. Measles and rubella immunization strategies shifted susceptibility to older age groups, leading to the introduction of MMR2 in 1992, administered at age 7 years. In 2000, the goal of accelerated rubella control and congenital rubella syndrome prevention was established, and a nationwide vaccination campaign targeting men and women aged 15–39 was implemented to immunize the population of reproductive age. The last endemic case of measles was confirmed in 1999, and at the end of 2001 Costa Rica reported the last endemic cases of rubella and congenital rubella syndrome. Imported cases of measles and rubella were detected in 2003 and 2005, with no secondary cases detected. In 2008, Costa Rica established a National Committee of Experts, supported by technical teams, to collect the evidence required to verify the interruption of endemic transmission of the measles and rubella viruses. The evidence includes information on trends and epidemiologic analysis, molecular epidemiology, population immunity, the quality of surveillance, and the sustainability of the EPI program.

Costa Rica is an upper-middle-income country located in Central America with a population of 4.5 million. Since the mid-1950s this nation has prioritized public social investment to achieve high social standards and universal access to health services [1]. Vaccination is a cornerstone of public health strategies.

The measles and rubella vaccines were introduced in 1967 and 1972, respectively. Use of the measles-mumps-rubella vaccine (MMR) began in 1986 administered to children aged 15 months, with a second dose added in 1992 when they started school. The country did not initially adopt a complementary strategy to immunize groups of reproductive age, which over the years led to a shift in susceptible groups toward adolescent and adult populations.

In 2000 the country set the goal of eliminating rubella and congenital rubella syndrome (CRS) and, with this, the strengthening of measles elimination [2]. A national vaccination campaign was carried out targeting men and women aged 15 to 39 years with measles-rubella (MR) vaccine and vaccinating women who had been pregnant during the campaign in the immediate postpartum period [3].

In 2003, the region of the Americas set the goal of eliminating rubella and CRS by 2010 [4]. Available epidemiological information in Costa Rica suggested that the vaccination strategies implemented to date had successfully interrupted the circulation of endemic rubella and measles viruses. The country therefore began the documentation and verification process and formed a National Committee of Experts supported by technical teams to gather the evidence required to document that it had met the goal of elimination.
The process combined an analysis of incidence trends and changes in the epidemiological pattern of rubella, measles, and CRS; the search for laboratory alternatives to improve knowledge about the rubella or measles genotypes that had been circulating; the estimation of population immunity levels by calculating coverage of vaccinated population cohorts, complemented by seroprevalence surveys available in the country; and evaluation of the quality of the surveillance system, including indicator analysis and retrospective rubella, measles, and CRS case searches, and using various methodologies and information sources to determine the consistency, validity, and representativeness of the surveillance data. This article describes the methodological approach, results obtained, and future challenges.

**METHODOLOGY**

Documentation began in May 2007 with a visit by a team of experts from the Pan American Health Organization (PAHO) and the Centers for Disease Control and Prevention (CDC) to Costa Rica. Working with a national team comprised of epidemiologists, clinicians, and people in charge of immunization and laboratory analysis, the team analyzed the available information and prepared a work plan for compiling the data needed to document measles, rubella, and CRS elimination, defined as “interruption of endemic transmission of the rubella and measles viruses for more than 12 months and the absence of CRS cases associated with endemic transmission, in the presence of high-quality surveillance” [5]. Table 1 describes the components and criteria used to document the elimination.

**National Immunization Program**

The National Immunization Program’s development, structure, and operations were examined, with special emphasis on the flow of information from institutions participating in decision making, vaccination services, epidemiological surveillance, and laboratory capabilities in serological diagnosis and viral detection/isolation.

**Trends and Changes in the Epidemiological Pattern**

Data from the national epidemiological surveillance system were used to analyze the changes in the trends and demographics of measles, rubella, and CRS cases, applying the epidemiological criteria used by the United States to confirm rubella elimination [6, 7]: an absence of or few confirmed cases in the presence of systematic reporting of a suspected case; when cases occur, they do so in an isolated manner, with no temporal or geographical association among them; loss of the seasonal pattern and cyclicity; changes in the demographic characteristics of the cases; any confirmed cases are imported, with few or no secondary cases; and no confirmed cases of CRS with systematic reporting of suspected cases.

**Laboratory Surveillance and Molecular Epidemiology**

The data from the integrated national surveillance system for febrile illnesses were analyzed. They include suspected measles and rubella cases reported through compulsory notification of the Ministry of Health, epidemiological data on samples sent to the National Virology Reference Center of the Costa Rican Institute for Nutrition and Health Research and Education (INCIENSA), and final classification of the cases. To increase the sensitivity of the system, the laboratory uses algorithms to determine the type of laboratory test to use for each sample; in this way, not only are cases with a presumptive diagnosis of rubella processed, but all those with clinical and epidemiological characteristics that meet the definition of a suspected case (fever and maculopapular skin rash). A case is classified as confirmed if it tests positive for rubella immunoglobulin M (IgM) antibodies, seroconversion is demonstrated, the virus can be isolated and genotyped, or it is epidemiologically linked with a laboratory-confirmed case.

Given the importance of having information on circulating genotypes before and after implementation of the vaccination strategies, in the absence of viral isolation in the country an attempt was made to identify serum samples from the acute phase of the last rubella outbreak (1998–1999), which could prove useful in detecting rubella by means of polymerase chain reaction methodology.

**Quality of Surveillance**

Attainment of the indicators for quality of epidemiological surveillance was analyzed: percentage of sites reporting, percentage of cases adequately investigated, percentage of cases with adequate samples, percentage of samples that reached the laboratory in ≤5 days, and percentage of results reported in ≤4 days. In order to identify cases not detected through passive surveillance, retrospective case-finding methodologies were applied using a variety of data sources, based on the identification of areas at greater risk for circulation of the rubella or measles virus.

During the period 1986–2001, a retrospective study was conducted to identify CRS cases seen at the National Children’s Hospital (HNN) [8], and the database of the National Registry Center for Congenital Diseases (CREC) was analyzed to identify cases from the International Classification of Diseases, Ninth Revision (ICD-9) compatible with CRS. In order to detect CRS cases not captured by surveillance, a new retrospective search for suspected cases was conducted for the period 2002–2007, using the following data sources: hospital registries of ICD codes compatible with CRS defects, the results of rubella IgM serology in infants <6 months of age at the HNN, congenital cataract surgeries, and the CREC database.

**Population Immunity**

Population cohorts vaccinated since 1986, the year the MMR vaccine was introduced in the routine schedule, were analyzed.
The proportion of the 1- to 40-year-old population in 2007 that had been vaccinated was estimated for both sexes. The source of the data was the Ministry of Health report on administrative coverage of the various immunization strategies, by year of birth and target group, including the routine schedule (aged 1 year, beginning in 1996); the catch-up campaign (aged 1–14, in 1993); mop-up campaigns (aged 1–4, in 1994, 1997, and 2002); the campaign to vaccinate adolescents and adults (aged 15–39, in 2001); and postpartum vaccination (pregnant women aged 15–39, May 2001 to February 2002).

The quality of the administrative coverage data for the routine program was confirmed by analyzing consistency both with the results of vaccination coverage surveys conducted in 2002, 2006, and 2010, through the inclusion of a module in the National Multipurpose Household Survey, and with seroprevalence studies reported in the country [9].

Another source of information used to evaluate vaccination coverage was the vaccination registry maintained by the Costa Rican Social Security Fund; unvaccinated children can be identified by associating the universally issued birth identification number with records of the doses of MR/MMR administered. To verify the rubella seroimmunity level in the population aged 10–24 years, we processed the serum samples taken in this group of age during 2008–2009 for the National Nutritional Household Survey in Costa Rica.

**Integrated Evidence Analysis**

In order to document elimination, an interinstitutional work team was formed to begin collecting and analyzing the data using the above-mentioned criteria. First, the country’s status was presented and, with the support of a team of external advisers from PAHO and the CDC, potential information sources and methodologies for evaluating surveillance quality were identified. In May 2008 a National Expert Committee was formed by Executive Decree as a consultative and advisory body, with members designated by the President of the Republic and the Minister of Health. Once the information has been gathered and analyzed, the Committee will determine whether the data are valid, complete, representative, and consistent among the different information sources.

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**Table 1. Components and Criteria Used to Verify the Status of Rubella, Measles, and CRS Elimination**

<table>
<thead>
<tr>
<th>Components</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1. Capacity and sustainability of the National Immunization Program</td>
<td>Legal underpinnings, organization, and sustainable operation</td>
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<td>Universal coverage and access to vaccination services</td>
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<td>Integrated information and epidemiological surveillance system</td>
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<td>2. Trends and changes in the epidemiological pattern of measles, rubella, and CRS</td>
<td>Reduction in the incidence of rubella, measles, and CRS cases</td>
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<td>Loss of temporal and spatial association</td>
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<td>Loss of seasonality and cyclicity</td>
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<td>Change in the case incidence pattern by sex, age group, and specific population (migrants, indigenous population, others)</td>
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<td>Detection of imported cases does not reestablish endemic transmission.</td>
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<td>No confirmed cases of CRS with systematic reporting of suspected cases.</td>
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<td>3. Rubella or measles genotypes that have circulated</td>
<td>Genotypes detected are not consistent with endemic genotypes</td>
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<td>4. Level of population immunity</td>
<td>Analysis of vaccinated cohorts indicates that the population immunity level impedes endemic transmission</td>
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<td>Consistency between administrative coverage and surveys</td>
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<td>Analysis of seroimmunity studies and consistency with coverage analysis</td>
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<td>5. Quality of rubella, measles, and CRS surveillance</td>
<td>Indicators of the timeliness, sensitivity, and specificity of surveillance, such as percentage of weekly reporting, percentage of cases adequately investigated, percentage of cases with a good sample, percentage of cases with blood samples</td>
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<td>Retrospective measles and rubella case finding by the surveillance system detects no unreported cases</td>
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<td></td>
<td>Retrospective CRS case finding by the surveillance system detects no unreported cases</td>
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<tr>
<td>6. Integrated analysis of the evidence</td>
<td>The information compiled from the epidemiological analysis, circulation of genotypes, population immunity level, and quality of surveillance is:</td>
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<td>Valid</td>
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<td>Representative</td>
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Abbreviation: CRS, congenital rubella syndrome.
RESULTS

Immunization Strategies
In the mid-1970s, Costa Rica began administering the rubella vaccine. However, it was not until 1986, with the inclusion of the MMR triple viral vaccine in the official vaccination series, that 80% coverage was reached (Figure 1).

In 1992, Costa Rica added the administration of a second MMR dose to children entering the school system, the schedule currently used by the country. Within the framework of the international commitments aimed at eradicating measles, a catch-up campaign was conducted in 1993 (coverage: 93%), followed by mop-up campaigns with the MR vaccine in 1994 (coverage: 81%), 1997 (coverage: 87%), and 2002 (coverage: 86%). The last follow-up campaign targeted children aged 1–9 years and was conducted in May 2011.

The national campaign targeting adults (May 2001) vaccinated men and women aged 15–39 years (42% of the total population). The final coverage was 98% (99% of men and 97% of women). Every province in the country met the vaccination goal. Rapid monitoring was useful in identifying cases and ratios of unvaccinated persons and confirmed that all cantons or municipalities had achieved >95% coverage [10]. Following the campaign, women who had been pregnant were vaccinated, achieving 98% coverage in postpartum vaccination.

Reduction in the Incidence of Rubella and Measles Cases
In the 1970s and 1980s, measles outbreaks exhibited a high incidence (n = 6389 cases, rate = 285.9 per 100 000 population in 1979), cyclicity every 3 to 5 years, and extended duration, as seen in the outbreaks of 1986 (n = 4470) and 1987 (n = 3870). With the introduction of the MMR vaccine for 1-year-olds in 1986, measles and rubella rapidly declined (Figure 2).

However, in 1991 Costa Rica was once again faced with a measles outbreak, with 6323 cases (rate = 202.6 per 100 000 population), displaying a shift in susceptibility toward the adolescent population. In light of this in 1992 the country initiated the administration of a second MR/MMR dose when children entered school to provide birth cohorts with a second vaccination opportunity.

During the period 1977–2001, endemic rubella virus was circulating in the country with epidemic periods every 5 to 7 years. There were 4 outbreaks in the 1980s and 1990s, with an incidence rate of 14.1 per 100 000 population in 1982 (n = 345 cases) and a rate of 11.8 per 100 000 population in 1993 (n = 393 cases). The outbreaks of 1987 and 1999 had higher incidence rates, with figures of 38.5 and 39.1 per 100 000 population, reporting 1079 and 1505 cases, respectively. With the 2001 vaccination campaign targeting adolescents and adults, in 1 year, the country went from 117 cases of measles and 32 cases of rubella to zero confirmed cases of endemic transmission for the 2 diseases in 2002.

Change in the Susceptibility Pattern
Figure 3 shows the change in rubella incidence by age group. In the 1970s, cases were most frequent in children <5 years. The figures gradually began to fall in that age group, only to rise in the population aged 15–24 years (94 per 100 000 population), followed by the population aged 25–34 years (43 per 100 000 population) beginning in 1987. The last rubella outbreak in
Costa Rica, which began in late 1998, revealed a substantial shift in susceptibility, with a higher incidence in the population aged 25–34 years (80 per 100,000 population), followed by the group aged 15–24 years (26 per 100,000 population).

The frequency distribution of rubella outbreaks by age and sex indicates that 42.8% of reported rubella cases in 1992 were children <5 years. During the 1999 outbreak, the age of the affected groups increased: 75.4% of the rubella cases were in individuals between the ages of 15 and 45 years. The distribution of cases by sex has been similar in men and women across the 3 decades, both in endemic and epidemic periods.

**Importation of Cases Has Not Reestablished Endemic Circulation**

During the period 2007–2010, the National Reference Laboratory processed an average of 354 (range, 319–403) samples

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**Figure 2.** Reported cases of measles and rubella, Costa Rica, 1975–2010. CRS, congenital rubella syndrome. Source: Ministry of Health, Department of Statistics and Epidemiology, Costa Rica.

**Figure 3.** Reported incidence of rubella (rate per 100,000) by age group, Costa Rica, 1977–2010. Source: Ministry of Health, Department of Statistics and Epidemiology.
for measles and rubella IgM annually, a figure that corresponds to an average national rate of 7.9 per 100 000 population (range, 7.1–8.8 per 100 000 population). During the period 2007–2010, 91 cases positive for measles and/or rubella IgM were detected. A thorough analysis of these “hot cases” indicated that 30 of them were cross-reactions to parvovirus B19 and 7 to dengue; 4 were postvaccination reactions to MMR, and 50 were associated to infectious diseases as herpesvirus 6 or coxsackie B4, resulting in all 91 cases discarded for measles and rubella.

The last confirmed cases of endemic rubella were detected in 2001. In 2003, a case of febrile rash illness entered the country from India that was serologically confirmed as a measles case. The virus could not be isolated. Epidemiological investigation and active case searches found no case secondary to the imported case. In 2005, a rubella case that had arrived from Colombia and Venezuela was reported. The source of infection could not be identified, and no cases secondary to the imported case were found.

**CRS Incidence**

In 2001, Costa Rica began to develop a specific CRS surveillance protocol and created the Congenital Infections Clinic at the HNN for the referral and assessment of suspected cases from all over the country. CRS should be suspected if the patient is a child <1 year of age with 1 or more of the manifestations indicated in the clinical description of CRS (cataracts, congenital glaucoma, congenital heart disease [primarily, the persistence of ductus arteriosus or peripheral stenosis of the pulmonary artery], hearing impairment, purpura) or if the child’s mother had a suspected or confirmed rubella infection during pregnancy. A CRS diagnosis in newborns is confirmed by the presence of rubella-specific IgM antibodies and/or isolation of the virus in the cell culture of nasopharyngeal or urine specimens before the age of 6 months.

Passive surveillance has been complemented with retrospective CRS case searches at the HNN. From 1996 to 2001, 577 cases were reviewed, 45 of which were confirmed as CRS and 4 identified as congenital infection [11]. CRS surveillance intensified after the 2001 campaign. Of the 38 cases assessed at the HNN in 2001, only 1 was confirmed as CRS. This case was diagnosed in November 2001 in a preterm newborn who was rubella IgM–positive and displayed alterations in liver function and the persistence of ductus arteriosus. This was the child of a woman who had not been vaccinated because she was pregnant at the time of the May campaign.

Retrospective case searches from 2002 to 2007 yielded 403 cases that had some of the manifestations associated with CRS. Of these, 102 cases met the definition of a suspected case and all were discarded as they involved cardiac abnormalities associated with prematurity, various chromosomal syndromes, or other congenital TORCH infections.

**Quality of Surveillance**

From 2007 to 2010, the percentage of adequate samples that reached the laboratory was the indicator with the best performance (range, 90%–100%), with reporting of results in ≤5 days holding steady at close to 80%. However, the speed with which samples reach the laboratory (range, 69%–81%), the timeliness of the reporting of suspected cases, and the proportion of cases that are adequately investigated need improvement.

**Vaccinated Population Cohorts**

Figure 4 shows that >95% of the population aged 20–40 years is vaccinated against measles and rubella. In the 16–19-year age group, administration of a second MR dose during the catch-up campaign raised the percentage of the vaccinated population to 93%, a figure higher than the MMR coverage reported by the regular program.

However, the figures for routine MMR coverage following the 2001 campaign targeting adolescents and adults were <95% at the national level, and 72% (n = 58 of 81) of the country’s cantons reported coverage of <95% in 2007. The mop-up campaigns of 1994, 1997, and 2002 also recorded coverage of <95%. A National Household Survey performed in 2008–2009 showed a seroimmunity level of 98.6% in the population aged 10–24 years. To assure appropriate immunity protection in children <10 years of age, Costa Rica implemented a national follow-up campaign in May 2011.

**DISCUSSION**

The evidence to date indicates that the vaccination strategies implemented in Costa Rica succeeded in interrupting endemic transmission of the rubella and measles viruses. Key elements of that analysis are the change in the cyclicity of the disease, the demographics of the affected population during the outbreaks occurring over the past 3 decades, and the characteristics of the last measles and rubella cases detected in the country. Furthermore, the absence of cases secondary to importation of the rubella or measles virus indicates that the level of population immunity impedes the reestablishment of endemic transmission.

It cannot be stated for certain that epidemiological surveillance is sensitive and specific enough to ensure that no cases have gone undetected by the system. The indicators established for timeliness and surveillance quality are necessary but must be complemented with retrospective case searches to rule out the possibility of unreported cases. Another prerequisite is to continue collecting specimens for the detection, isolation, and molecular typing of the virus in every suspected case. The ability to identify the source of infection and characterize the transmission mechanism of rubella and measles cases will depend on this, given the risk of imported rubella and measles cases from endemic countries in countries where there is no circulation of the virus.
Given the variety of clinical manifestations of CRS, for surveillance to meet the quality criteria required to confirm the elimination of the syndrome, timely clinical and laboratory diagnosis must be ensured, along with referral systems that guarantee the detection and classification of suspected cases and investigations to determine whether the case is endemic or imported. In addition to reducing the incidence of CRS, the rubella elimination strategy offered opportunities to improve access and the quality of care for congenital disabilities. One example of this was the creation of the neonatal deafness program [12], which permits early detection of hearing impairments in newborns and, thus, early interventions. The basic purpose of this program, in addition to its being a CRS surveillance tool, is to improve the quality of life for hearing-impaired children through new diagnostic technologies, educational interventions, and effective rehabilitation.

Maintaining homogeneous ≥95% MR/MMR2 coverage is the essential strategy for protecting achievements, especially due to the existence of areas with high migration flows and neglected groups, where pockets of susceptibles can accumulate. Thus, having vaccination information systems that identify the people vaccinated, complemented with timely, practical methodologies for identifying and immunizing unvaccinated people at the local level, is essential. Examples of such methodologies are systematic monitoring and periodic use of vaccination coverage surveys [13].

Major challenges lie ahead. In an epidemiological scenario where no endemic cases are being detected but the risk of importation from other countries and regions of the world persists, health and surveillance services cannot lower their guard. The foundation for surveillance will always be a detailed clinical assessment of suspected cases, accompanied by appropriate epidemiological investigation and timely control measures. Thus, it is necessary to improve knowledge at the clinical level of what constitutes a suspected case and heighten efforts and integrated surveillance of febrile rash illnesses—among them, dengue, which poses a challenge as one of the principal differential diagnoses for measles and rubella.

Acknowledgments

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