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Background. Rubella during pregnancy can cause serious fetal abnormalities and death. Peru has had integrated measles/rubella surveillance since 2000 but did not implement congenital rubella syndrome (CRS) surveillance until 2004, in accordance with the Pan American Health Organization recommendations for rubella elimination. The article describes the experience from the CRS sentinel surveillance system in Peru.

Methods. Peru has maintained a national sentinel surveillance system for reporting confirmed and suspected CRS cases since 2004. A surveillance protocol was implemented with standardized case definitions and instruments in the selected sentinel sites. Each sentinel site completes their case investigations and report forms and sends the reports to the Health Region Epidemiology Department, which forwards the data to the national Epidemiology Department. CRS surveillance data were analyzed for the period 2004–2007.

Results. During the period 2004–2007, 16 health facilities, which are located in 9 of the 33 health regions, representing the 3 main geographical areas (coast, mountain, and jungle), were included as sentinel sites for the CRS surveillance. A total of 2061 suspected CRS cases were reported to the system. Of these, 11 were classified as CRS and 23 as congenital rubella infection. Factors significantly associated with rubella vertical transmission were: (1) in the mother, maternal history of rash during pregnancy (odds ratio [OR], 12.0; 95% confidence interval [CI], 3.8–37.8); (2) and in the infant, pigmentary retinopathy (OR, 18.4; 95% CI, 3.2–104.6), purpura (OR, 14.7; 95% CI, 2.8–78.3), and developmental delay (OR, 4.4; 95% CI, 1.75–11.1).

Conclusions. The surveillance system has been able to identify rubella vertical transmission, reinforcing the evidence that rubella was a public health problem in Peru. This system may serve as a platform to implement surveillance for other congenital infections in Peru.

Rubella is usually a benign viral disease, but during pregnancy it can cause serious fetal damage, including abortion, stillbirth, and a pattern of birth defects known as congenital rubella syndrome (CRS). Intrauterine rubella infection can also cause mental retardation and autism [1].

In Peru, rubella is an endemic disease, with outbreaks every 4–6 years. Infection is seasonal, with the highest incidence in spring and the lowest in winter. The mean annual reported incidence in endemic years is 5 cases per 100,000 persons, increasing to 13–25 cases per 100,000 persons during an epidemic year [2].

A recently published study found that, in 2003, 12.8% of postpartum women in Peru were susceptible to rubella [3], despite large epidemics in 2000–2001. Another study estimated that, on average, 16,000 infants were born each year with CRS in Latin America and the Caribbean [4]. The same authors estimated the annual burden of CRS cases for Peru ranged from 350 to 660 cases. Using a simple mathematical model, the Dirección General de Epidemiología—Ministerio de Salud del Perú estimated that the annual number of CRS cases in Peru varied from 356 in an endemic year to 752 in an epidemic year (unpublished data) (Figure 1). The impact of CRS in the life and economy of the
countries of the Americas was high; therefore, it became necessary to accelerate control and, ultimately, eliminate rubella virus transmission. The Caribbean English-speaking countries estimated that the CRS elimination program costs were about only 7% of the total direct costs of treatment and long-term care of CRS cases, with a benefit-cost ratio of 13.3–1[5].

Because of the major public health importance of CRS, the Pan-American Health Organization (PAHO) recommended the implementation of a plan of action to eliminate rubella and CRS by the year 2010 [6]. This initiative focuses on rapidly reducing the number of rubella-susceptible persons, including women of reproductive age; developing integrated measles-rubella surveillance systems; and developing a CRS surveillance system [7].

To that end, the measles-mumps-rubella vaccine was introduced in the National Immunization Schedule in 2003, and a mass vaccination campaign against measles and rubella was conducted, targeting all persons aged 2–39 years, in 2006. In 2004, the Ministry of Health from Peru, with the technical and financial support of the World Health Organization and PAHO, implemented the Congenital Rubella Syndrome Sentinel Surveillance system through the National Epidemiology Department (Dirección General de Epidemiología [DGE]) and the National Institute of Health (Instituto Nacional de Salud [INS]).

The objective of this article is to describe the experience from the CRS sentinel surveillance system in Peru.

METHODS

The CRS sentinel surveillance system was implemented in April 2004. The population at risk was infants born to mothers with rubella exposure during pregnancy. The information sources include the mother, the medical files of the mother and infant, information from the attending physicians, and laboratory results.

Case Definition

**CRS Suspected Case.** a. A child aged <1 year with ≥1 of the following signs: cataracts/congenital glaucoma, hepatosplenomegaly, pigmentary retinopathy, congenital heart disease, microcephaly, microphthalmia, purpura, thrombocytopenia, hearing impairment, radiolucent bones; or

b. confirmed maternal rubella during the pregnancy or known exposure to a febrile rash illness; or

c. newborn with probable diagnosis of TORCHS (i.e, toxoplasmosis, other infections, rubella, cytomegalovirus infection, herpes simplex virus infection, and syphilis).

The protocol also indicated that low-birth-weight infants should be examined particularly carefully for any of the anomalies mentioned in point a above.

In the sentinel sites located in Cusco and Junín, low weight for the gestational age and jaundice in the first 24 hours of life, were added to the case definition.

**CRS Confirmed Case.** Suspected case laboratory-confirmed by rubella-specific enzyme-linked immunosorbent assay for immunoglobulin (Ig) M.

**CRS Compatible Case.** Suspected case without laboratory testing.

**Congenital Rubella Infection (CRI).** Cases of positive rubella-specific IgM but without clinical signs of CRS. The diagnosis of CRI is definitive only after ruling out sensorineural hearing loss by testing by either otoacoustic emissions or brainstem auditory evoked potentials.
**CRS Discarded Case**  Probable cases with serum test results negative for rubella-specific IgM.

**CRS Surveillance Information Flow**

Suspected cases should be reported within the first 24 hours after identification. Every case is investigated within 48 hours after its identification.

The physician who identified the case is responsible for completing the surveillance case report form. The hospital epidemiology staff is responsible for reporting the case to the next level, performing quality control of the surveillance case report forms, entering the data in an Excel database sheet (Microsoft), and sending the information to the next level weekly in accordance with the routine disease notification procedures. The laboratory personnel are responsible for the serum sample collection and shipment to the INS, accredited as part of the regional laboratory network for measles and rubella of the Americas, for the rubella-specific ELISA IgM testing.

In Peru, there are 3 levels in the information flow for surveillance data: the national level, the regional level, and the local level (health facilities). Every level has its own responsibilities and functions. To strengthen the surveillance work, a national surveillance working team was formed, with participation of epidemiologists and virologists, and duplicated at the regional level and sentinel sites.

**Sentinel Surveillance Site Selection**

The selection of the sentinel sites was based on the following factors: health facilities had the capability to have adequate neonatal and infant clinical and laboratory diagnosis and management; are referral centers for patient treatment in their regions; represented the largest urban areas/cities in different geographic regions of the country; and had well-functioning surveillance for other diseases.

In total, 16 health facilities, located in 9 of the 33 health regions but representing the main geographical areas of coast, mountain, and jungle, were included as sentinel sites.

**Surveillance Implementation**

Surveillance implementation was initiated in every sentinel establishment by the National Working Team. Before arrival of the Working Team, each hospital had to create a technical team formed by health professionals from the different areas involved in the CRS surveillance: pediatrics, neonatology, gynecology and obstetrics, ophthalmology, otolaryngology, cardiology, neurology, nursery, and laboratory. This was intended to allow ≥1 professional in every critical area for the case identification, because the CRS cases are identified by clinical examination or by the pregnancy history.

The National Working Team had meetings with the Regional Office of Epidemiology and the Regional Reference Laboratory (regional level), the health facility director, the Epidemiology Unit surveillance team, and all health professionals working in priority areas at the facility. The objective of these meetings was to sensitize the authorities and health personnel about CRS surveillance. The initial meetings were documented with signed notes for the record to document procedures, terms of reference, and expected products.

The first hospital to begin the CRS surveillance was San Bartolomé Mother-Child Hospital in the capital city of Lima. It served as a pilot for the surveillance system. By July 2006, the surveillance system included another 15 health facilities (13 national and regional hospitals and 2 major health centers). All of the sentinel establishments are located in the capital of the region and serve as the health facilities for patient reference from the region. The hospitals in Lima serve as health establishments for patient reference in the country.

**Supervision and Evaluation Procedures**

The first supervision was made 2–3 months after surveillance implementation. The objective of this first visit was to solve any problems affecting the proper functioning of surveillance and to maintain and increase the health personnel interest in case detection and investigation. These sessions included the authorities, the surveillance team, and the health personnel of the areas included in the surveillance.

Supervision visits continued every 4–6 months in the first 2 years, and every 12 months thereafter, always with the objective of evaluating the system and stimulating the health personnel participation in the CRS surveillance.

To perform the supervision, the National Working Team designed guidelines to standardize site visits. The findings from these visits were discussed and documented with reports, copies of which were distributed to the sentinel establishment and to the regional level. These reports were filed at the national level. Every year, during the national surveillance evaluation in Lima, every sentinel site and Health Regional Department presents their surveillance indicators and their identified strengths and weaknesses. They are also required to plan for the year to come, in order to correct deficiencies.

The surveillance analysis was made from 2 perspectives: the examination of the characteristics of CRS cases detected by the system and the review of the surveillance performance indicators.

To identify factors associated with a positive IgM test result, multivariable analysis using a logistic regression model was performed using SPSS software, version 13.0 (SPSS Inc). The variables included in the analysis were as follows: (1) in mothers, age, maternal history of rubella vaccination, rash illness in the mother during pregnancy, rubella in pregnancy, contact of the mother with rubella in pregnancy, and travel during pregnancy; and (2) in children, age, sex, birth weight, APGAR score, prematurity, and presence of cataracts, glaucoma, pigmentary retinopathy, microphthalmia, patent ductus arteriosus, pulmonary stenosis, other cardiac defects, hearing impairment, thrombocytopenia,
anemia, intrauterine growth retardation, microcephaly, purpura, developmental delay, hepatomegaly, splenomegaly, bone radiolucency, meningoencephalitis, and jaundice.

Finally, to assess the quality of the CRS surveillance system, a series of indicators and targets were defined in the topics of case notification, investigation, laboratory investigation, and follow-up of the children (Table 1).

No ethics clearance was needed because the cases were being identified as part of the routine clinical practices and national surveillance procedures.

### RESULTS

From April 2004 to December 2007, 2061 suspected cases of CRS were notified to the system (Table 2). Of these, 34 (11 CRS cases and 23 CRI cases) were confirmed by rubella-specific IgM testing. Among the 34 subjects with confirmed cases, 21 were female and 13 were male. The median age at the time of sample collection for the IgM-positive children was 5 days (third quartile, 21 days), and for the negative cases, it was 3 days (third quartile, 7 days). The mothers’ median age was 29 years for those

<table>
<thead>
<tr>
<th>Sentinel health establishment</th>
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<th>2005</th>
<th>2006</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Suspected</td>
<td>IgM +</td>
<td>Suspected</td>
<td>IgM +</td>
</tr>
<tr>
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<td>2</td>
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<td>23</td>
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<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Hospital de Apoyo Iquitos</td>
<td>21</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Centro de Salud San Juan–Iquitos</td>
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<td>1</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Hospital María Auxiliadora–Lima</td>
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<td>1</td>
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<tr>
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<td>4</td>
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<tr>
<td>Hospital Belén de La Libertad</td>
<td>53</td>
<td>3(1)</td>
<td>495</td>
<td>17(7)</td>
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**NOTE.** Data are from Dirección General de Epidemiología—RENACE—Ministerio de Salud del Perú. +, Positive.
with IgM-positive cases (third quartile, 8 years) and 26 years for those with IgM-negative cases (third quartile, 12 days).

The 3 regional facilities using the suspected CRS case definition including low weight for the gestational age and jaundice in the first 24 hours of life accounted for 66.9% of the total cases notified to the system, for 24 (70.6%) of the 34 IgM positive cases, and for 6 (54.5%) of the 11 CRS cases (Table 2). Of the 34 rubella IgM-positive cases, 11 cases met the case definition criteria and were classified as CRS cases. The extended case definition criteria resulted in the identification of all 23 CRI cases. Thus, the use of extended case definitions identified 67.6% of all IgM-positive cases.

A comparison between the number of probable cases identified with the extended case definition and the original one suggested that the original case definition would have only identified 23.1% of the total cases notified. By using the case definition recommended by PAHO [8], the number of cases reported to the system would have been 10.5% of the total number of cases notified by the extended case definition (~216 cases), and the number of IgM-positive cases identified would have been only 5.

Clinical characteristics of reported cases were diverse and varied (Table 3). Six (17.65%) of 34 children had 0 birth defects; 15 (44.12%) had 1 defect; 9 (26.47%) had 2 defects; and 4 (11.76%) had ≥3 defects. Intrauterine growth retardation and prematurity occurred more frequently among patients with confirmed cases. The variables found to be significantly associated with a positive IgM result were as follows: in mothers, a history of rash illness during pregnancy (odds ratio [OR], 11.99; 95% confidence interval [CI], 3.80–37.83); and in infants, pigmentary retinopathy (OR, 18.40; 95% CI, 3.24–104.57), purpura (OR, 14.73; 95% CI, 2.77–78.26), and developmental delay (OR, 4.40; 95% CI, 1.75–11.06) (Table 4).

Surveillance indicators covering case notification, investigation, laboratory investigation, and follow-up were used to evaluate the quality of the surveillance. The areas of laboratory results timeliness and infant follow-up scored the lowest (Table 1).

**DISCUSSION**

The CRS sentinel surveillance system provided useful documenting vertical transmission from mother to child of rubella virus in Peru during the years 2004–2007. The CRS/CRI case number peaked in 2005 and 2006, probably because of a large rubella epidemic that occurred in the country in 2004–2005 [9, 10]. The marked decrease in rubella and CRS cases in 2007 resulted from the nationwide rubella campaign that was conducted in October 2006, with the goal of eliminating rubella and CRS from Peru. Nearly 20 million people aged 2–39 years were vaccinated with a rubella virus-containing vaccine, with a vaccine coverage rate of 98% [11]. Nevertheless, CRS cases were still expected to be reported to the system until 9 months after the end of the vaccination campaign because during the campaign, some pregnant women could still be exposed to the wild rubella virus. Moreover, because some CRS cases are not detected at birth, the system allows for delayed reporting through the age of 12 months. Therefore, case identification was still possible until 21 months after the vaccination campaign. This explains why 2 cases were reported in the first 4 months of 2007. From April 2007 to December 2008, no confirmed cases of CRS/CRI were reported to the system. Furthermore, since January 2007, there have not been confirmed rubella cases reported to the measles-rubella surveillance system [2, 9, 10]. Thus, elimination of CRS/
CRI and rubella may be achieved through a national mass campaign and consistent high measles-mumps-rubella vaccine coverage in children aged <5 years [12].

The use of extended case definitions in Cusco and Junín resulted in a more sensitive surveillance system, particularly for identification of CRI cases. CRI cases may play an important role as virus shredders and in the continuation of rubella transmission in the community. Therefore, identifying them to prevent further rubella transmission is also important in the context of rubella elimination. A more specific case definition may be preferred in a context in which control measures have not been implemented and the rubella incidence is high. However, the use of a more specific case definition might underestimate the number of CRI cases and, therefore, their role in rubella persistence and transmission in the population. Nevertheless, using a more sensitive case definition will not only increase the probability of identifying positive cases but also will increase the costs of the system, mainly in association with laboratory testing. Therefore, the case definition must be carefully considered before one decides to use a more sensitive case definition.

There are a number of lessons learned from the experience in Peru. First, it is important to have a multidisciplinary group of persons in charge of developing the guidelines for the surveillance. In Peru, staff from the Epidemiology and Laboratory Departments at the Ministry of Health played a critical function. Also, it is crucial to have a person at the national level in charge of implementing, maintaining, and supervising the surveillance. In the sentinel health facilities, the formation of surveillance working teams was also critical, with teams including personnel from the neonatology service. The commitment of a senior physician is important. A main challenge is to maintain the motivation of local staff. One way to ensure commitment and participation was to hold national evaluation meetings at which the surveillance teams presented the results of their work during the year. Feedback of the results to regional and local levels was also essential to improve the quality of the work. Newborn eyescreening training at a national reference neonatology hospital was particularly welcomed by local teams.

Peru has good evidence to suggest that rubella endemic transmission has been interrupted. Nevertheless, rubella is still endemic in many parts of the world; therefore, it is important to maintain the surveillance system in place in order to document the sustained absence of CRS and to maintain high vaccine coverage. The current challenge is to expand this surveillance system to include diagnosis of toxoplasmosis, cytomegalovirus infection, and herpes in the system. This will provide a broader vision of the communicable diseases affecting Peru’s newborn population.

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### References


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**Table 4. Logistic Regression Results for Variables Associated with Rubella IgM Positive Results in Infants, Peru, CRS Surveillance 2004–2007**

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point estimate</td>
<td>Standard error</td>
<td>P</td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Rash in the mother during pregnancy</td>
<td>2.485</td>
<td>0.586</td>
<td>&lt;.001</td>
<td>11.996 (3.804–37.828)</td>
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<tr>
<td>Pigmentary retinopathy</td>
<td>2.912</td>
<td>0.887</td>
<td>.001</td>
<td>18.398 (2.237–104.568)</td>
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<tr>
<td>Purpura</td>
<td>2.690</td>
<td>0.852</td>
<td>.002</td>
<td>14.730 (2.772–78.261)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>1.481</td>
<td>0.471</td>
<td>.002</td>
<td>4.397 (1.748–11.059)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from Dirección General de Epidemiología—RENACE—Ministerio de Salud. CI, confidence interval; OR, odds ratio.