Rubella Outbreaks Following Virus Importations: The Experience of Chile

Doris Gallegos,1 Andrea Olea,1 Viviana Sotomayor,1 Claudia González,1 Juan Carlos Muñoz,2 Mónica Ramos,3 M. Cecilia Espinoza,2 Gladys Mendoza,2 Graciela Torres,4 Emilio Espineira,4 Winston Andrade, 4 Jorge Fernández,5 and Rodrigo Fasce4

1Department of Epidemiology, Ministry of Health, 2Regional Health Secretariat (SEREMI) for the Valparaíso Region, 3Regional Health Secretariat (SEREMI) for the Metropolitan Region, 4Subdepartment of Viral Diseases, and 5Molecular Genetics Section, Biomedical Laboratory Department, Institute of Public Health, Santiago, Chile

Background. Strategies for accelerated control of rubella and congenital rubella syndrome (CRS) in Chile included mass vaccination of women of childbearing age in 1999 but did not include vaccination of adult men.

Methods. We reviewed data from Chile’s integrated surveillance system for measles, rubella, and CRS from 2004 through 2009 and describe the epidemiology of rubella outbreaks and implementation of control measures in 2005 and 2007 following mass vaccination of women. Population estimates from census data were used to calculate rubella incidence rates. The age distribution of rubella cases during 2007 was compared with rubella vaccination opportunities by birth cohort to orient mass vaccination of adult men.

Results. In 2005, an institutional outbreak of rubella occurred among male naval recruits 18–22 years of age, with 46 confirmed cases over a 5-month period. Beginning in March 2007, rubella outbreaks among young adults in the capital of Santiago spread throughout Chile, resulting in >4000 confirmed rubella cases. Delayed control measures and rapid dissemination among young adults led to widespread transmission. From 2007 through 2009, rubella incidence was highest among adult men not included in previous vaccination strategies. Mass vaccination of men 19–29 years of age was conducted in November 2007 to interrupt rubella transmission.

Conclusions. Chile’s experience suggests that vaccination strategies for rubella and CRS elimination need to include both men and women.

Following on the success of measles elimination in the Americas in 2002 [1], Chile adopted the goal of rubella and congenital rubella syndrome (CRS) elimination by 2010 with the other countries of the World Health Organization Region of the Americas. Prior to 1990, rubella cases had been steadily increasing in Chile, with epidemics occurring in cycles. In 1990, the Chilean national immunization program introduced routine immunization of children at 12 months of age with combined measles-mumps-rubella (MMR) vaccine, followed in 1991 by a recommendation for a second dose of vaccine at school entry. From 1990 through 1996, the incidence of rubella decreased rapidly (Figure 1), principally among children <10 years old [2]. During 1997 and 1998, Chile experienced a resurgence of rubella cases throughout the country and a shift in the age distribution, with 70% of reported cases occurring among persons 10–29 years of age. Eighteen cases of CRS were identified following the rubella resurgence in 1997 and 1998.

To prevent additional cases of CRS, the Chilean Ministry of Health conducted a mass vaccination campaign targeting women 10–29 years of age in 1999, prior to implementation of a national plan for accelerated rubella control [3]. The campaign reached an estimated 99% of the target female population. Incidence of rubella and CRS cases decreased after the campaign. Rubella incidence was reduced from 31 cases per 100000 population in 1998 to 11 cases per 100000 population in 1999, followed by gradual decrease to 1.9 cases per 100000 population in 2002 (a reduction of 94%
compared with the incidence in 1998). In 2002, 68% of rubella cases occurred among children <5 years of age. In 2003, only 128 confirmed rubella cases were identified in the country, for an incidence of 0.8 cases per 100,000 population, followed by 3 isolated rubella cases identified in 2004. In the same year, Chile integrated measles and rubella surveillance, and serum specimens from all suspected cases were tested at the national reference laboratory for evidence of measles and rubella virus infection.

Susceptibility to rubella persisted among groups of individuals, especially young male adults excluded from the mass vaccination campaign in 1999. From January through May 2005, an institutional outbreak of rubella (genotype 1C) was identified among naval recruits for a total of 46 cases. Then in March 2007, outbreaks caused by genotype 2B spread throughout Chile, resulting in >4000 cases over a 12-month period. This article describes the rubella outbreaks in 2005 and 2007 that affected the susceptible population, as well as the measures implemented in response to the outbreaks.

**METHODS**

**Integrated Measles/Rubella Surveillance in Chile**

Measles, rubella, and CRS are subject to mandatory notification according to national legislation (DS no. 158 of 2004 and DS no. 55 of 2008). A suspected case of measles was defined as a person presenting with fever, rash, and 1 respiratory symptom (cough, coryza, or conjunctivitis); suspicion of rubella was based on the clinician’s criteria. When a patient presents for medical attention with symptoms compatible with suspected measles or rubella, the attending physician at the public or private health facility is responsible for immediately notifying the regional and national public health authorities of the suspected case, following established procedures. Until the first semester of 2003, >90% of reported cases were classified on the basis of clinical criteria. Subsequently, all notified cases with compatible clinical presentation were actively investigated and classified according to laboratory criteria, which became standard practice for integrated measles/rubella surveillance. In accordance with regional measles and rubella elimination goals, all samples from suspect cases are tested for measles and rubella in the Institute of Public Health (ISP), Chile’s national reference laboratory. Laboratory testing at ISP includes measles immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA; Dade Behring; Siemens) and indirect immunofluorescence imaging for measles immunoglobulin G antibody, and rubella IgM ELISA (Dade Behring; Siemens).

Surveillance for CRS cases has been conducted in Chile since 1999, the same year as the first mass vaccination campaign against rubella, and notification of suspected CRS cases has been mandatory since 2004. A suspected case of CRS was defined as an infant who presents with 1 or more compatible clinical findings, including cataracts, congenital glaucoma, cardiac malformations (intraventricular communication, persistent arterial ductus, or pulmonary arterial stenosis), or deafness (classified as group A); or thrombocytopenic purpura, hepatomegaly, splenomegaly, microcephaly, meningoencephalitis, mental retardation, or translucent bone disease (classified as group B). Clinically compatible cases with positive serological test results for anti-rubella IgM antibodies or laboratory evidence of rubella virus infection are classified as laboratory-confirmed cases. Laboratory testing for rubella is also performed as part of screening for TORCH pathogens (Toxoplasma gondii, rubella virus, cytomegalovirus, human simplex virus, and others [including syphilis]) among infants with congenital malformations. The national reference laboratory receives ~180 specimens from suspected CRS cases annually.

**Figure 1.** Rubella incidence in Chile, 1990–2009. MMR, measles-mumps-rubella vaccine.
representing a notification rate of 1 suspected case per 1000 live births.

Data from integrated measles/rubella notification forms were entered into the Measles Elimination Surveillance System (MESS; Pan American Health Organization, Washington, DC). Due to the rapid and unexpected increase in rubella cases during outbreaks in 2007, surveillance officers were unable to enter all cases in the MESS system created by the Pan American Health Organization for routine surveillance. During the outbreak period, spreadsheets were created in Microsoft Excel 2007 with the minimum number of variables sent by regional health departments to the central level.

**Modified Surveillance Guidelines During 2007 Rubella Outbreaks**

Following notification of the first suspected rubella cases in each outbreak, surveillance officers conducted active searches for additional rubella cases among contacts and vaccinated all of those without documented vaccination, including all contacts in academic or work settings. Serum specimens were collected from the first case patients identified in each outbreak setting or region, as the epidemic spread throughout Chile. Once 10% of the suspected rubella cases in each outbreak setting were confirmed by serological testing, collection of serum specimens was no longer recommended. Procedures for interpretation of serological test results followed the same algorithm used for integrated measles/rubella surveillance. In addition, at the beginning of the outbreak, nasopharyngeal aspirates were collected from suspected cases and inoculated in Vero cells for viral isolation and genotyping. Infection of Vero cells was confirmed using indirect immunofluorescence with rubella-specific monoclonal antibodies. Genotyping and nucleotide sequencing was performed at the ISP reference laboratory.

**Case Definitions Used in 2007 Rubella Outbreaks**

During rubella outbreaks from March through December 2007, a probable rubella case definition was adapted for surveillance purposes, defined as men ≥19 years old without recent history of travel outside Chile presenting with diffuse rash of acute onset and 1–3 days duration, with or without fever, and 1 or more of the following symptoms: arthralgia, arthritis, lymphadenopathy, or conjunctivitis. Regional health departments were instructed to test ~10% of probable cases for laboratory evidence of rubella virus infection. Laboratory confirmation was required for all suspected cases of rubella in male or female individuals ≥18 years of age and in women ≥19 years of age. Epidemiological linkage was defined as exposure to a confirmed rubella case during the case patient’s contagious period, defined as the 7 days before and after the date of rash onset. In institutional settings, the at-risk population was defined as men 19–29 years of age and women without documented rubella vaccination.

**Analysis of Susceptible Birth Cohorts**

Prior to the beginning of the rubella epidemic in 2007, the Department of Epidemiology in the Ministry of Health conducted a study of vaccination opportunities for male individuals according to year of birth to establish the target population for vaccination. The methodology used was similar to analyses conducted prior to the mass vaccination of women in 1999. The percentage of the population considered unprotected in each birth cohort was estimated as 100% minus the estimated vaccination coverage multiplied by the seroconversion rate (95%) for a single dose of vaccine. Cohorts that received 2 doses were assumed to be effectively immunized. To account for natural immunity as a result of infection among individuals <30 years old, we calculated age-specific rubella incidence rates for the period 1990–2006 and subtracted from the unprotected population the number of rubella cases in each birth cohort. We assumed that 50% of rubella virus infections were asymptomatic and doubled the number of persons in each birth cohort assumed to have acquired national immunity. We assumed that 85% of adult men and women had naturally acquired rubella-specific antibodies and considered all infants susceptible during their first year of life.

**RESULTS**

In 2005, 6 years after mass vaccination of women of childbearing age, a rubella outbreak was identified at the naval academy in Valparaiso, a city of 1.7 million inhabitants that receives large numbers of tourists situated to the north of the metropolitan region of Santiago. A total of 46 confirmed rubella cases were identified during the outbreak, all in men 18–22 years of age, 43 of whom were recruits at the naval academy and 3 of whom were university students with no epidemiologic link to the naval academy. Of the 46 confirmed cases, 35 (77%) were laboratory-confirmed (including all 3 university students), whereas 11 (23%) were classified on the basis of clinical and epidemiologic criteria. Rubella virus genotype 1C was isolated from 2 case patients. Prompt notification of the first suspected rubella cases among naval recruits allowed rapid implementation of control measures at the naval academy; all recruits were vaccinated within 48 hours following confirmation of the outbreak. Additional measures included voluntary isolation of suspected cases during the contagious period and vaccination at other affected institutions. No additional cases were identified in the region or in other parts of Chile following the outbreak.

From March 2007 through February 2008, rubella outbreaks first detected in the metropolitan region of Santiago spread throughout Chile. A total of 4275 probable and confirmed rubella cases were reported (26 cases per 100 000 population). Among reported cases, 96% occurred in men with a median age of 23 years (range, 8 months–74 years). Incidence was highest among men 19–24 years old (259 cases per 100 000 population)
Table 1. Number and Incidence of Confirmed Rubella Episodes by Age Group and Sex, Chile, 2007

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1–18</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>19–24</td>
<td>856</td>
<td>137.8</td>
<td>887</td>
</tr>
<tr>
<td>25–29</td>
<td>31</td>
<td>0.6</td>
<td>34</td>
</tr>
<tr>
<td>$\geq 30$</td>
<td>875</td>
<td>71.1</td>
<td>887</td>
</tr>
</tbody>
</table>

**NOTE.** Confirmed rubella episodes for which the age of patient was not reported were excluded.

*Confirmed rubella episodes per 100 000 population.

(Table 1). The epidemic curve demonstrates the rapid increase of rubella cases after epidemiologic week 25 (Figure 2), corresponding to the beginning of the winter period in Chile. The number of cases peaked during weeks 35–37 at the end of the winter period (late August to early September), with ~300 new rubella cases reported weekly.

Rubella virus genotype 2B was isolated from nasopharyngeal samples submitted from 2 case patients in 2007. Nucleotide sequencing identified 99.8% similarity between rubella virus isolates in Chile and rubella genotype 2B viruses isolated from patients in Brazil and several European countries in 2007, suggesting probable importation into Chile of the genotype 2B rubella virus.

Rubella cases were reported from 14 of Chile’s 15 regional departments. Cases were initially concentrated in the Santiago metropolitan region and Valparaíso (region V), but by week 23 cases were reported from Araucanía in the south and by week 27 from Antofagasta in the north of the country. Incidence of probable and confirmed rubella cases in the male population was highest in Antofagasta (68 cases per 100 000 male residents), Valparaíso (43 cases per 100 000 male residents), and the Santiago metropolitan region (41 cases per 100 000 male residents) (Figure 3). The only regional department that did not report cases was Aisén, possibly due to its geographic isolation and distance from Santiago. In addition, regional health authorities in Aisén received early warning of the rubella outbreaks in other regions.

Three children born with laboratory-confirmed CRS were identified in 2008; these were the first CRS cases identified in Chile since 2000. In only 1 case, the mother had been diagnosed with rubella during pregnancy, although the public health authorities had not been notified of the mother’s infection at the time.

**Description of Initial Cases and Control Measures**

The first rubella case identified in 2007 occurred in a 23-year-old male postgraduate student residing in the metropolitan region with reported onset of rash, lymphadenopathy, and arthralgia on 21 March 2007; initial clinical suspicion was of an allergic reaction. Approximately 10 days later, the patient sought care for persistent symptoms at a second private health facility and serological testing for rubella was requested. Only after confirmation of rubella virus infection was the regional health secretariat notified by the private laboratory of the rubella case, at which time serum was sent to the national reference laboratory. On 13 April, 3 weeks after the case patient’s onset of rash, the case was confirmed by the virology laboratory at the Public Health Institute. Contact tracing did not identify the case patient’s source of infection. The case patient had traveled for vacation during the month of January to Brazil, where rubella outbreaks were reported in several states.

*Figure 2. Confirmed rubella cases according to administrative region of occurrence, March 2007 through January 2008.*
By the time the index case had been notified to the surveillance system, a second rubella case was reported in a 24-year-old male resident in the metropolitan region; no epidemiologic link to the index case was established. This was followed by 2 additional cases in students (both male, 21 and 22 years old) at the same university although in different class years. Vaccination of students at the university was initiated for outbreak control. Clusters of rubella cases were subsequently reported from other institutions of higher education. At the end of May 2007, the first cases outside the metropolitan region were reported from Valparaiso (region V). Although contact tracing did not establish an epidemiologic link between the index case and subsequent cases, the epidemic curve suggests that initial cases occurred in 3 generations prior to widespread transmission (Figure 2).

During case investigations and follow-up of the first rubella cases reported in the Santiago metropolitan region, vaccination with combined measles-rubella (MR) vaccine was offered to contacts as well as all persons working or studying in the same institution as suspected case patients. To improve early recognition and diagnosis of rubella for timely implementation of control measures, health alerts were sent through the surveillance departments to public and private health care facilities. Health professionals were reminded to notify the authorities of all suspected cases and collect serum samples and respiratory secretions for confirmatory testing. Surveillance personnel were instructed to thoroughly investigate confirmed cases to identify probable sources of infection and vaccinate contacts with MR vaccine. In regions that had not reported rubella cases, active case searches were conducted. By the peak of the outbreak in late August, a total of 350 confirmed rubella cases had been identified and >20 000 MR doses had been administered for outbreak control, increasing to 50 000 doses prior to initiation of a mass vaccination campaign targeted at men 19–29 years of age.

A study of rubella incidence and vaccination opportunities by birth cohort conducted in February 2007 identified the highest percentage of unprotected individuals (84%) among men 19–29 years of age. Age-specific incidence rates during the 2007 rubella epidemic supported the results of the birth cohort analysis. On the basis of this information, the Ministry of Health conducted in December 2007 a mass vaccination campaign among men 19–29 years of age, reaching an estimated 92.3% coverage in the target population. The number of confirmed rubella cases continued to decrease after the campaign until transmission of rubella was interrupted. The last confirmed case of rubella in Chile occurred in July 2008 and was classified as an importation from Argentina. Chile has reported no rubella cases since July 2008.

**DISCUSSION**

Persistence of susceptibility to rubella among young adult men created the conditions for a rubella outbreak and a rubella epidemic several years after mass vaccination of women of childbearing age in 1999. The rubella outbreak in 2005 mainly affected recruits at a naval academy and resulted in a limited number of cases. The rubella epidemic in 2007 resulted in a large number of cases, predominantly among men, and was characterized by rapid community and institutional dissemination from the capital of Santiago throughout the country.
In the 2005 rubella outbreak among naval recruits, timely notification and implementation of control measures may have limited transmission and helped control the outbreak. Vaccination of contacts was initiated a short time after exposure to infectious cases, reducing transmission inside the naval academy as well as in the community. However, the identification of 3 cases among university students not associated with the naval academy suggests that community transmission did occur and might have resulted in a much larger outbreak. In contrast, delayed diagnosis and laboratory confirmation of the index case in 2007 may have contributed to community transmission prior to implementation of control measures, with rapid dissemination among susceptible young adults. Ring vaccination of contacts in the community and institutions was ineffective in preventing the rubella epidemic. In contrast to the outbreak among naval recruits, other control measures such as voluntary quarantine during the infectious period were not feasible and young adults with rubella circulated widely.

Prior to the outbreak, control activities, including vaccination of contacts, were not initiated until after rubella was confirmed as the cause of illness. Despite the integration of measles and rubella surveillance, vaccination with MR vaccine was only recommended after notification of suspected measles cases, whereas for suspected rubella cases, laboratory confirmation was required. As of 2010, ring vaccination with MR vaccine was initiated upon notification of suspected rubella or measles.

A tragic consequence of the rubella epidemic was the occurrence of 3 cases of CRS in children born to women presumably infected during the beginning of their pregnancies. This not only was a setback for Chile’s CRS elimination goals but also indicated susceptibility to rubella infection among some percentage, however small, of women of childbearing age. This observation served as additional justification for the implementation of the mass vaccination of adult male individuals to achieve elimination goals for rubella and CRS in Chile [4].

Chile maintains a network of epidemiologic surveillance at all levels in the health system, including public and private institutions. Delayed diagnosis and notification of febrile rash illnesses may result from low indices of suspicion for diseases in phases of elimination such as measles and rubella. On the other hand, the national reference laboratory at the Public Health Institute has gained experience with viral isolation from clinical specimens and genotyping, first with measles viruses and more recently with rubella viruses, which will be needed for characterization of imported cases. Characterization of rubella virus isolates worldwide is still limited. In Chile, only 3 rubella virus genotypes have been identified: 1E (during an outbreak in 1998–1999), 1C (2005 outbreak), and 2B (2007 epidemic). Genotype 2B was not detected in the Americas prior to 2006 and, based on sequence information, may represent an importation from Europe, which is considered to be endemic for the genotype [5]. The detection of genotype 2B in Chile coincided with rubella outbreaks in Brazil and Argentina from 2006 through 2009. Notably, all 3 countries had conducted mass vaccination of women of childbearing age to accelerate control of CRS but had not vaccinated adult men, which suggests that vaccination strategies for rubella elimination should include male and female individuals. The last cases of infection with genotype 2B rubella virus were identified in northern Argentina in the first semester of 2009 and represented the last endemic cases of rubella in the Region of the Americas.

Chile is preparing documentation to verify the elimination of endemic measles, rubella, and CRS by 2012. To maintain the elimination of measles and rubella in Chile, as well as throughout the region, high routine coverage with MMR vaccine needs to be maintained and imported cases need to be detected and notified promptly to prevent secondary transmission. Maintaining sensitivity of integrated surveillance for measles and rubella and laboratory expertise to rapidly characterize imported viruses are essential due to the constant risk of importation from endemic regions.

**Funding**

This work was supported by the Ministry of Health, Chile.

**Acknowledgments**

We thank the epidemiologic surveillance teams in the regional health departments and the professionals at health centers throughout Chile, who participated actively in the investigation and control of the rubella outbreak.

**References**