Evidence Used to Support the Achievement and Maintenance of Elimination of Rubella and Congenital Rubella Syndrome in the United States

Susan E. Reef,¹ Susan B. Redd,² Emily Abernathy,² Preeta Kutty,² and Joseph P. Icenogle²

¹Global Immunization Division, ²Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

On 29 October 2004, an expert panel was convened to review the status of elimination of rubella and congenital rubella syndrome (CRS) in the United States. Primarily based on 5 types of information presented—epidemiology of reported cases, molecular epidemiology, seroprevalence, vaccine coverage, and adequacy of surveillance—the panel unanimously agreed that rubella virus is no longer endemic in the United States. Since 2004, new data continue to support the conclusion that elimination has been achieved and maintained. In documenting elimination in the United States, each of the 5 types of data provided evidence for elimination and collectively provided much stronger evidence than any one type could individually. As countries document the elimination of rubella and CRS, many sources and types of data will likely be necessary. Rigorous data evaluation must be conducted to look for inconsistencies among the available data. To maintain elimination, countries should maintain high vaccine coverage, adequate surveillance, and rapid response to outbreaks.

SUMMARY OF DATA THAT SUPPORTED ELIMINATION OF RUBELLA AND CRS IN THE UNITED STATES

Data from several different subject areas were used to support the elimination of rubella and CRS in the United States, including epidemiology, molecular epidemiology, vaccine coverage, seroprevalence, and adequacy of surveillance.

Epidemiological characteristics for elimination as described previously [2] included: low incidence (rates) of rubella disease (<0.1/100,000 population), temporal and spatial separation of cases, absence of disease seasonality, changing demographics of cases, increase in the percentage of imported cases from median 7% (2%–7%) during 1998–2000 as compared with a median of 22% (14%–50%) during 2001–2004, 1 outbreak reported during 2001–2004 as compared with 24 outbreaks reported during 1998–2000, and 5 CRS cases born during 2001–2004 as compared with 23 cases of
CRS born during 1998–2000. During 2001–2004, the molecular epidemiological profile of rubella and CRS showed a pattern of virus genotypes consistent with virus originating outside the United States. Prior to elimination of rubella, between 1996 and 2000, of the 55 rubella viruses genotyped, 37 (67%) were 1C; however, from 2001 to 2004, of the 2 rubella viruses genotyped, no genotype 1C was identified [3].

The population immunity was evaluated by 2 independent sources: population-based vaccine coverage [4] and seroprevalence studies [5]. In both sources, the immunity to rubella was above the threshold to eliminate [6]. For vaccine coverage, 3 independent sources were the Biologics Surveillance, the National Immunization Survey (NIS), and state surveys of school entrants. The Biologics Surveillance data show that the net number of rubella vaccine doses sold was at least equivalent to the number of children born each year during 1970–2004. The average coverage for school-entrant surveys among reporting states was >95% for 1980–2004. National coverage among children 19–35 months of age was >90% overall for each year during 1995–2004.

Two nationwide seroprevalence studies were conducted through the population-based National Health and Nutrition Examination Survey [5]. Sera were tested for rubella immunoglobulin G antibodies during 1988–1994 and 1999–2004. In 1999–2004, the overall age-adjusted rubella seropositivity in the US population 6–49 years of age was 91.3%, which was a statistically significant increase from 88.1% in 1988–1994. Further subgroup analyses were conducted to identify any demographic groups that may be at risk. These analyses showed that seroprevalence either remained at the same level or higher for the groups (ie, children of both sexes, women of childbearing age) that were targeted for vaccination.

In 2004, to evaluate the adequacy of surveillance, 5 different sources were reviewed [7]. These included (1) data reported to the national surveillance system during 2002–2004, (2) a survey of health department and public health laboratories on rubella investigations between 2002 and 2004, (3) enhanced rubella activities in California between 2000 and 2004 and in New York City between 1999 and 2004, (4) sentinel surveillance between 1999 and 2004 along the US-Mexico border, and (5) a health maintenance organization (HMO) database. Evaluation of the national surveillance system revealed no additional cases of rubella or CRS that had been reported to the state or local health departments or laboratories. The survey of the national, state, city, and county public health departments and laboratories documented that rubella cases were being aggressively investigated and that there was little spread to the surrounding communities. With an enhanced surveillance survey including retrospective search for infants with CRS, we focused on sites (ie, New York City, California) with recent rubella disease and outbreaks, large immigrant populations, and many foreign visitors. In these areas, the survey and study results showed no additional cases of rubella or CRS. The last source was a large HMO that provided insight into the reporting practices of the primary care providers. No additional CRS or rubella cases were identified through that review.

**DATA FROM 2005 TO 2007**

**Methods**

**Definition of Elimination.** Elimination is defined as the absence of endemic rubella virus transmission. Endemic transmission is defined as a chain of rubella virus transmission continuous for ≥12 months within the United States [2].

**Epidemiology of Rubella and CRS.** The data we included in the analysis were number of cases, demographics, clinical presentation, and exposure and vaccination histories of reported cases of rubella and CRS.

**Case Definitions and Classifications.** Rubella and CRS cases were classified using the US Council of State and Territorial Epidemiologists (CSTE) case definitions [8]. Since the previously published descriptive epidemiology, the case classifications for rubella and CRS have been modified and approved by the CSTE to include a case classification for “endemic” disease [9]. Previously, endemic transmission was defined separately from the other US-acquired source classifications: import-linked, imported virus, and unknown source. With this change in the case classification, all possible scenarios of transmission are included in the classification system, but it does not impact the analyses conducted nor the panel’s conclusion (Table).

**Rubella.** Rubella cases classified as confirmed according to the CSTE case definition were included in the analyses; all cases classified as being of unknown case status because of a lack of information for making a determination on the case classification were also included [2].

**Rubella Outbreak.** An outbreak was defined as ≥3 epidemiologically related cases. For outbreaks with cases in ≥1 setting (eg, school, worksite), the outbreak setting was classified as community-wide. Outbreaks were classified by the year in which the first case was identified.

**Data Sources**

**Rubella Cases.** We analyzed data regarding confirmed and unknown rubella cases reported from 2005 to 2007 to the National Notifiable Diseases Surveillance System. For each case, demographic information, including age, sex, race/ethnicity, case classification, relationship to an outbreak, clinical information, vaccination history, and pregnancy information, as well as source of exposure and the site of transmission are collected. The National Center for Immunization and Respiratory Diseases also collected country of origin and length of US residence for cases, and country of exposure for internationally imported cases.

To supplement case reports, we obtained additional information from state and local health departments on outbreak investigations and control measures.
Congenital Rubella Syndrome continues to be developed as more viruses are discovered [11, 12]. Since 2006, the nomenclature for wild-type rubella viruses determining rubella virus genotypes has not changed substantially. These genotypes are classified by year of birth. The National Congenital Rubella Syndrome Registry (NCRSR) collects clinical and demographic data about infants with CRS and their mothers, including mother’s country of birth and country of exposure. CRS cases are classified epidemiologically as internationally imported or US acquired, according to the source of the infection in the mother, using the definitions below, which are parallel to the classifications for rubella cases [4].

### Import Status
- **Internationally imported case:** To be classified as an internationally imported CRS case, the mother must have acquired rubella virus infection outside the United States or in the absence of documented rubella virus infection, the mother was outside the United States during the period when she may have had exposure to rubella that affected her pregnancy (i.e., from 21 days before conception and all through the first 24 weeks of pregnancy).
- **Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.
- **Imported-virus case:** A case for which an epidemiologic link to an internationally imported case was not identified but for which viral genetic evidence indicates an imported rubella genotype, (i.e., a genotype that is not occurring within the United States in a pattern indicative of endemic transmission). An endemic genotype is a genotype of any rubella virus that occurs in an endemic chain of transmission (i.e., lasting ≥12 months). Any genotype that is found repeatedly in US-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.
- **Endemic case:** A case for which epidemiological or virological evidence indicates a chain of rubella virus transmission continuous for ≥12 months within the United States.
- **Unknown source case:** A case for which an epidemiological or virological link to importation or to endemic transmission within the United States cannot be established after a thorough investigation.

### US-acquired case
A US-acquired case is defined as a case in which the patient had not been outside the United States during the 23 days before the rash onset or was known to have been exposed to rubella within the United States. US-acquired cases are subclassified into 4 mutually exclusive groups:

- **Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.
- **Imported-virus case:** A case for which an epidemiologic link to an internationally imported case was not identified but for which viral genetic evidence indicates an imported rubella genotype, (i.e., a genotype that is not occurring within the United States in a pattern indicative of endemic transmission). An endemic genotype is a genotype of any rubella virus that occurs in an endemic chain of transmission (i.e., lasting ≥12 months). Any genotype that is found repeatedly in US-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.
- **Endemic case:** A case for which epidemiological or virological evidence indicates a chain of rubella virus transmission continuous for ≥12 months within the United States.
- **Unknown source case:** A case for which an epidemiological or virological link to importation or to endemic transmission within the United States cannot be established after a thorough investigation.

#### NOTE.
Cases were classified epidemiologically according to the source of infection [9].

### CRS Cases
We analyzed data on CRS cases reported from 2005 to 2007 to the National Congenital Rubella Syndrome Registry (NCRSR). The NCRSR collects clinical and demographic data about infants with CRS and their mothers, including mother’s country of birth and country of exposure. CRS cases are classified by year of birth.

#### Molecular Epidemiology
We analyzed data on molecular epidemiology obtained from 2005 to 2007. Wild-type rubella virus obtained in the United States between 2005 and 2007 was analyzed and sequenced using the same methodology as described elsewhere [3, 10]. Even though the methodology for determining rubella virus genotypes has not changed substantially since 2006, the nomenclature for wild-type rubella viruses continues to be developed as more viruses are discovered [11, 12].

#### Vaccination Coverage
The 3 data sources previously used for documentation for elimination were the Biologics Surveillance, state school entry immunization surveys, and the NIS [4]. More recent data were available and reviewed using the same methodology as previously described.

### RESULTS

#### Rubella
Since the achievement of rubella and CRS elimination, the incidence of rubella and CRS has remained low. The annual incidence of rubella was 0.005/100,000 population during 2005–2007. Annually from 2005 to 2007, the median number of reported cases was 11 (range, 11–12) (Figure 1). During 2005–2007, 1 major city reported 4 cases, and 16 states reported 1–5 cases each.

During 2005–2007, reported cases were separated temporally and geographically with persistent absence of seasonality. During 2005–2007, cases of rubella were reported in only 30 (19%) of the 156 weeks. When the weeks with only internationally imported cases or import-associated cases were excluded for 2005–2007, rubella cases classified as unknown source were reported in 17 (11%) weeks. As previously described, since 2001, no seasonality was evident during 2005–2007.

During 2005–2007, a total of 31 (91%) of the 34 cases were among adults aged 15 years and older; however, the incidence for both persons aged 0–14 years and 15–45 years of age was <0.001/100,000 population. Annual rubella incidence among Hispanic persons during 2005–2007 was <0.1/100,000 population.

During 2005–2007, of cases with known country of origin, a total of 13 (57%) were born outside the United States. Of these cases, 1 (8%) was from the World Health Organization (WHO) Region of the Americas (Mexico); 4 (33%) were from the WHO European Region (France, 1 case; Ireland, 1 case; Spain, 1 case; and Russia, 1 case); 3 (25%) were from the WHO Southeast Asian Region (India, 2 cases and Bangladesh, 1 case); and 5 (42%) were from the WHO Western Pacific Region (Philippines, 2 cases; Malaysia, 1 case; Vietnam, 1 case; and Japan, 1 case).
The percentage of imported cases was a median of 25% (18%–45%) during 2005–2007. Of the 10 (29%) cases classified as internationally imported during the period 2005–2007, 1 (10%) had source of exposure in the WHO Region of the Americas (Brazil, 1 case); 3 (30%) were exposed in the WHO European Region (France, 2 cases and Russia, 1 case); 1 (10%) was exposed in the WHO African Region (Uganda, 1 case); 3 (30%) were exposed in the WHO Western Pacific Region (Philippines, 2 cases and Malaysia, 1 case); and 2 (20%) were exposed in the WHO Southeast Asian Region (Bangladesh, 2 cases). During 2005–2007, 4 additional cases were classified as import associated: 1 was exposed to a parent who was exposed in France, and 3 of the cases who were linked had no identified source of exposure; however, molecular genotyping identified a 2B virus.

During 2005–2007, 2 outbreaks were reported. In 2005, a single outbreak consisted of a total of 3 cases, of which 2 attended a conference in the United States. Subsequently, the spouse of a conference attendee was infected. In 2007, a single outbreak occurred among 3 foreign-born college students; molecular genotyping identified a 2B virus as mentioned above. No source of exposure was identified for either outbreak.

**Congenital Rubella Syndrome**

During 2005–2007, 2 infants with CRS were reported to the NCRSR. One infant was born in 2003 and classified as an imported case from Nigeria, and the second infant was born in 2004 and classified as an imported case from Cote d’Ivoire [13]. Neither CRS cases were born during 2005–2007.

Both mothers of infants with CRS were born outside the United States. Their countries of birth were Nigeria and Liberia.

**Molecular Epidemiology**

Between 2005 and 2007, 6 wild-type rubella viruses were detected in the United States and sequenced. Two sequences were determined to be from genotype 1G viruses, and both were identified as African importations: a CRS case in which the Liberian mother was infected in the Cote d’Ivoire [13] and a rubella case contracted during travel to Uganda. One sequence was determined to be genotype 1E, and the case was identified as an importation from Malaysia. Three identical sequences from the 2007 outbreak among foreign-born students were determined to be genotype 2B. Because nonimported 2B viruses have never been found in the United States, the source of this virus, although unidentified, was likely an importation. Thus, between 2005 and 2007, there was no evidence of indigenous circulation of any genotype; specifically, there is no evidence of 1C viruses circulating in the United States [14].

**Vaccination Coverage**

During 2005 and 2006, data from the Biologics Surveillance showed that 10,559,745 and 11,522,254 doses of rubella-containing vaccine were distributed in the United States, respectively.

Data from the school survey coverage estimates suggest that 1- or 2-dose rubella coverage among kindergarten and/or first-grade school entrants during 2005–2007 was consistently >95% for reporting states. During these years, only 4 states (Colorado, Delaware, Idaho, and Iowa) reported annual rubella coverage <90% (range, 80.9%–88.5%).

Data from the NIS show estimated rubella vaccine coverage among children 19–35 months of age was >90% nationally in each year of the survey including 2005, 2006, and 2007 [15–17]. However, 26 states (2005), 27 states (2006), 6 states (2007), and selected urban and county areas reported coverage between 80% and 89.9%, but none reported coverage below 80%.

**DISCUSSION**

Data from a variety of sources provide continued evidence that endemic rubella elimination, achieved in 2001, has been maintained, including (1) an epidemiological profile of rubella and CRS that showed a continued low reported incidence of rubella (<0.1/100,000 population) with no geographic and temporal association among the cases, 2 outbreaks with 3 cases in each outbreak, and no reported cases of CRS born during 2005–2007; (2) a molecular epidemiological profile of rubella and CRS that showed a pattern of virus genotypes consistent with virus originating outside the United States; and (3) continued very high (>90%) rubella vaccination coverage for the United States. These data are consistent with the data that were used to support elimination in the United States.

**Evidence for Elimination of Rubella and CRS**

For countries preparing for documentation of elimination, several important data issues must be considered, including (1) availability of supporting data to validate findings, and (2) consistency between the different types of data from multiple sources. For example, the adequacy of the rubella and CRS surveillance systems in the United States allowed analysis and
interpretation of rubella and CRS epidemiologic data and molecular virology data. If the quality of the data from the rubella and CRS surveillance systems had been questionable, then the rubella and CRS epidemiologic data would have been difficult or impossible to interpret. Data sources should also be compared with each other for inconsistencies. For US data, no inconsistencies were identified that would affect the conclusion that elimination has been achieved. For example, coverage data documented sustained high coverage, which was also documented by seroprevalence data, and no cases were seen in the US resident population as predicted by the seroprevalence and coverage data. In addition, when the ethnicity of rubella cases underwent a dramatic shift away from Hispanics after 2000, the genotypes of virus recovered shifted from 1C, a genotype only found in Latin America.

As countries in the Americas prepare for documenting elimination of rubella and CRS, many sources and types of data should be explored. No single type of data is likely to be sufficient to convincingly document elimination. Although the data available in each country may be different, the types of data used in the United States and other countries to document rubella elimination should be reviewed and included in the documentation process to the extent possible. There will likely be countries where types of data other than those used in the United States will contribute significantly to the documentation of elimination. After reviewing the available data, additional studies or surveys may need to be conducted. For example, as part of the US process of documenting elimination, additional studies on the adequacy of surveillance were needed. These studies were critical to interpreting US epidemiological data.

Information from surrounding countries may be important in the documentation process. For the United States, accelerated rubella control in the Western Hemisphere had a direct impact on the epidemiology of rubella in the United States [18]. In the late 1990s, most of the US cases were among persons born either in Mexico or other parts of Latin America, and the predominant genotype was 1C, found only in the Americas. As rubella control improved in other countries in the Americas, there has been a significant change in demographics of rubella cases. Cases occurring after 2000 among foreign-born adults were almost all from the other 5 WHO regions outside the WHO Region of the Americas.

The fact that rubella is endemic in many parts of the world ensures that the risk of importation into the United States remains even after rubella elimination is documented. To maintain elimination, countries must maintain high vaccination rates among children and ensure vaccination among women of childbearing age, particularly women born outside the United States. Good surveillance for both rubella and CRS must also be maintained with rapid response to outbreaks.

References