Elimination of Endemic Measles, Rubella, and Congenital Rubella Syndrome From the Western Hemisphere: The US Experience

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IMPORTANCE To verify the elimination of endemic measles, rubella, and congenital rubella syndrome (CRS) from the Western hemisphere, the Pan American Health Organization requested each member country to compile a national elimination report. The United States documented the elimination of endemic measles in 2000 and of endemic rubella and CRS in 2004. In December 2011, the Centers for Disease Control and Prevention convened an external expert panel to review the evidence and determine whether elimination of endemic measles, rubella, and CRS had been sustained.

OBJECTIVE To review the evidence for sustained elimination of endemic measles, rubella, and CRS from the United States through 2011.

DESIGN, SETTING, AND PARTICIPANTS Review of data for measles from 2001 to 2011 and for rubella and CRS from 2004 to 2011 covering the US resident population and international visitors, including disease epidemiology, importation status of cases, molecular epidemiology, adequacy of surveillance, and population immunity as estimated by national vaccination coverage and serologic surveys.

MAIN OUTCOMES AND MEASURES Annual numbers of measles, rubella, and CRS cases, by importation status, outbreak size, and distribution; proportions of US population seropositive for measles and rubella; and measles-mumps-rubella vaccination coverage levels.

RESULTS Since 2001, US reported measles incidence has remained below 1 case per 1 000 000 population. Since 2004, rubella incidence has been below 1 case per 10 000 000 population, and CRS incidence has been below 1 case per 5 000 000 births. Eighty-eight percent of measles cases and 54% of rubella cases were internationally imported or epidemiologically or virologically linked to importation. The few cases not linked to importation were insufficient to represent endemic transmission. Molecular epidemiology indicated no endemic genotypes. The US surveillance system is adequate to detect endemic measles or rubella. Seroprevalence and vaccination coverage data indicate high levels of population immunity to measles and rubella.

CONCLUSIONS AND RELEVANCE The external expert panel concluded that the elimination of endemic measles, rubella, and CRS from the United States was sustained through 2011. However, international importation continues, and health care providers should suspect measles or rubella in patients with febrile rash illness, especially when associated with international travel or international visitors, and should report suspected cases to the local health department.
Measles, Rubella, and Congenital Rubella Syndrome

Methods

Review of Disease Surveillance Data
In every state, health care providers (eg, physicians, nurses) are required to report measles, rubella, and CRS cases to their respective local health departments. State health departments report cases to the CDC directly by telephone or e-mail to the National Center for Immunization and Respiratory Diseases and electronically to the National Notifiable Diseases Surveillance System. Cases are classified according to standard case definitions and classifications published by the Council of State and Territorial Epidemiologists. We reviewed the available information on all confirmed cases of measles (from 2001) and rubella and CRS (from 2004) through 2011. We focused on the case importation status classifications, which are critical to assessing elimination of endemic disease. An internationally imported case was defined as a case in which measles or rubella results from exposure to measles or rubella virus outside the United States. As evidence of importation, the case patient must have spent at least some of the exposure period (7-21 days before rash onset for measles or 12-23 days before rash onset for rubella) outside the United States and had rash onset occurring within 21 days (measles) or 23 days (rubella) of entering the United States, with no known exposure to measles or rubella in the United States during that time. All other cases are considered US-acquired cases. For a CRS case to be classified as internationally imported, the infant’s mother must have acquired rubella infection outside the United States, or in the absence of documented rubella infection, the mother must have been outside the United States during at least some of the period from 21 days before conception through the first 24 weeks of pregnancy. The study is a review of disease surveillance data and compiled data from other studies, for which the CDC did not require ethical review and approval.

United States–acquired cases are subclassified into 4 mutually exclusive groups, import-linked, imported-virus, unknown source, and endemic cases. An import-linked case is any case in a chain of transmission that is epidemiologically linked to an internationally imported case. An imported-virus case is any case in a chain of transmission for which an epidemiologic link to an internationally imported case was not identified, but for which viral genetic evidence indicates an imported measles or rubella genotype. Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases. Any case for which an epidemiologic or virologic link to importation or to endemic transmission within the United States cannot be established after a thorough investigation is considered an unknown source case. Finally, endemic cases are those for which epidemiologic or virologic evidence indicates an endemic chain of transmission.

Review of Molecular Epidemiology
Genotype information was analyzed from viruses associated with chains of transmission in the United States to determine whether any genotype was endemic. Cases in a single chain of transmission of measles or rubella share the same genotype and have nearly identical nucleotide sequences. A genotype would be considered endemic if sequence information showed that a chain of transmission was present for greater than 12 consecutive months. However, multiple importations of viruses with identical sequences from the same international source can occur for over several years. Therefore, it is important to show that the epidemiologic characteristics of the cases are consistent with endemic transmission before a genotype is designated as endemic.

Evaluation of Surveillance Adequacy
Verification of the elimination of endemic measles, rubella, and CRS requires documentation that surveillance is adequate to detect endemic disease. For the initial documentation of the eli-
nation of measles, rubella, and CRS, multiple detailed studies of the adequacy of surveillance were conducted and published.9-11,15,20-25 For this follow-up evaluation, we did not repeat these studies but compiled data on 3 factors indicative of sustained surveillance adequacy. These factors were the detection of imported cases, the detection of small chains of transmission, and the reference laboratory testing volumes at the CDC.

Assessing Population Immunity to Measles and Rubella
To assess population immunity to measles and rubella, we compiled data from national immunization coverage surveys and reviewed published data on vaccine exemption and measles and rubella seroprevalence from the National Health and Nutrition Examination Survey.26 Measles-mumps-rubella vaccine (MMR) coverage data were obtained from the National Immunization Survey (NIS), the National Immunization Survey-Teen (NIS-Teen), and kindergarten immunization surveys conducted by the states. The NIS and the NIS-Teen are annual nationally representative telephone surveys that obtain provider-verified vaccination histories.27

Results
Disease Surveillance Data
Measles Epidemiology
From 2001 to 2011, a total of 911 cases of measles were reported (annual median number, 61 cases [range, 37-220 cases]). The annual measles incidence remained below 1 case per 1 000 000 population (Figure 1). The highest average annual incidence occurred in infants 6 to 11 months of age (4.1 cases per 1 000 000 population) followed by children 12 to 15 months of age (3.6 cases per 1 000 000 population). For all other age groups, the incidence was below 1 case per 1 000 000 population every year. Most measles cases were unvaccinated (65%) or had unknown vaccination status (20%).

From 2001 to 2011, there were 372 (41%) imported measles cases; 215 (58%) occurred in US residents returning from international travel, and 157 (42%) occurred in foreign visitors. Measles importations were associated with travel from 57 countries. China, Japan, India, Italy, the Philippines, and the United Kingdom were each associated with 20 or more imported cases. On average, 34 imported measles cases were reported each year (with a maximum of 80 cases in 2011). Of the imported cases, 83% did not result in any additional reported cases, 8% were transmitted to only 1 reported case, and only 9% resulted in outbreaks (defined as 3 or more linked cases). Import-linked cases accounted for 239 cases (26%) and imported-virus cases accounted for 190 cases (21%) (Figure 2). In total, 801 reported measles cases (88%) were import-associated cases.

A total of 110 unknown source cases (12%) were reported (annual median number, 6 cases [range, 2-25 cases]). Among US counties, 3063 (98%) reported no unknown source cases; 49 counties reported only 1 unknown source case, and 18 coun-
ties reported more than 1 unknown source case (with a maximum of 9 cases) (Table 1).

Outbreak-related cases comprised 478 (52%) of total measles cases, and 66 measles outbreaks were reported (range, 2-16 outbreaks per year). The median outbreak size was 6 cases (with a maximum of 34 cases). The longest outbreak lasted 11 weeks. Sixteen outbreaks included 10 or more measles cases. Of these outbreaks, 13 (81%) had an imported case as the index case, and 3 (19%) had genotype information that indicated an imported measles virus (Table 2). Measles outbreaks occurred in multiple settings, predominantly in unvaccinated communities that object to vaccination.

### Rubella and CRS Epidemiology

Final data on rubella cases for this report included the 72 cases reported to the National Notifiable Diseases Surveillance System from 2004 to 2011, minus 2 cases determined to be vaccine related after reporting. Also included were 7 cases reported through National Center for Immunization and Respiratory Diseases programs, giving a total of 77 rubella cases for this period. The annual median number was 10 cases (range, 4-18 cases); incidence remained below 1 case per 10 000 000 population (Figure 1). Cases were reported from 57 counties, with no county reporting more than 4 total cases. Cases were reported in 63 weeks (15% of weeks during this period). The median age was 29 years (range, 5 months-61 years); 60% of rubella cases occurred among adults 20 to 49 years of age. Eighty-eight percent of rubella cases were unvaccinated (34 cases [44%]) or had unknown vaccination status (34 cases [44%]). Among the cases for which country of birth was known, most (33 cases [58%]) were born overseas.

There were 31 imported rubella cases (40%), 4 import-linked cases (5%), 7 imported-virus cases (9%), and 35 unknown source cases (45%). Overall, 42 rubella cases (54%) were import-associated cases (Figure 2). Importations occurred from 18 countries; the most common being India (6 importations). Overall, 86% of imported cases did not result in any additional reported cases, and 14% resulted in transmission to only 1 reported case.

From 2004 to 2011, 35 unknown source rubella cases (45%) were reported (annual median number, 6 cases [range, 0-9 cases]). No unknown source cases were reported from 99% of US counties, 31 counties each reported 1 unknown source case, and 2 counties each reported 2 unknown source cases. From 2004 to 2011, 2 rubella outbreaks were reported, each consisting of 3 cases. No imported source of exposure was identified for either outbreak. One outbreak was associated with imported virus genotype 2B, and the other was an unknown source outbreak. Eight rubella cases occurred in 4 chains of transmission of 2 cases each. The remaining 63 cases (82%) were isolated cases.

A total of 4 CRS cases were reported, with 2 cases born in 2008 and 1 each born in 2003 and 2004. The average annual reported CRS incidence was less than 1 case per 5 000 000 births. Three CRS cases (75%) were imported, with maternal exposures occurring in Nigeria, Côte d’Ivoire, and India. The mothers of these 3 children were born outside the United States or had an unknown country of birth and had unknown vaccination statuses. The fourth case was an unknown source case of a child whose mother was born in the United States, had no history of international travel or exposure to foreign visitors or to rubella, and had documented receipt of 1 dose of MMR vaccine.

### Table 1. Unknown Source Cases of Measles by County by Year, United States, 2001-2011*

<table>
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<tr>
<th>County, State</th>
<th>2001</th>
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<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<tr>
<td>Island, WA</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Year total</td>
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<td>3</td>
<td>6</td>
<td>3</td>
<td>1</td>
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<td>1</td>
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</tr>
</tbody>
</table>

* Counties with more than 1 unknown source case.
Measles genotype information was obtained from 31% of isolated cases, 52% of 2-case chains, 68% of outbreaks with 3 to 5 cases, and 93% of larger outbreaks. Elevendifferentmeaslesvirus genotypes (of 24 recognized genotypes) were identified with 3 to 6 different genotypes detected each year (Table 3). The most frequently detected genotypes varied from year to year; however, between 2008 and 2011, there were multiple imported-virus cases in which genotype D4 was detected. Thenumberofimportedorimport-linkedcaseswithgenotype D4 increased from 4 in 2010 to 47 in 2011, reflecting the widespread transmission of genotype D4 measles viruses in Europe during 2011. The number of imported or import-linked cases with genotype D4 increased from 4 in 2010 to 47 in 2011, reflecting the widespread transmission of genotype D4 measles viruses in Europe during 2011. The parallel increase in imported-virus cases with genotype D4 from 3 in 2010 to 43 in 2011 suggested that these cases resulted from transmission from undetected imported cases or from an undetected link to reported imported cases. The longest chain of transmission associated with a genotype D4 virus that was not linked to importation lasted 10 weeks during May, June, and July 2009 (Table 2). In the 9-month period before and after this outbreak, only 1 case with a genotype D4 virus not linked to importation was detected. In addition, analysis of the distribution of genotype D4 cases across space and time indicated that the imported-virus genotype D4 cases did not occur in a continuous or focused pattern suggestive of an endemic chain of transmission.

Rubella Viruses in the United States
The absence of endemic rubella viruses from the United States from 2004 to 2007 has been documented in previous publications. From 2008 to 2011, a total of 33 rubella cases were reported to the CDC (18 imported cases). Genotype information was available for 13 cases, and 4 different genotypes (1E, 1G, 1J, and 2B) were identified. Nine imported cases had genotypes consistent with the known source country. Two imported-virus cases were identified among cruise ship crews, and association with source countries was not possible. Analysis of nucleotide sequences from imported-virus cases showed no linkages between cases, and no genotype occurred in a pattern suggesting that it was endemic.

Evaluation of Surveillance Adequacy
Measles, Rubella, and CRS Surveillance and Outbreak Response
Surveillance for measles, rubella, and CRS in the United States is a passive but rapidly responsive system and has been described and evaluated in detail. Once a case is reported, an active investigation is initiated to identify the patient's contacts in order to determine the source of exposure,
Measles, Rubella, and Congenital Rubella Syndrome

Original Investigation Research

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ahigh level of investigation of suspected cases. ber of tests performed was much higher, which demonstrates CR S cases investigated in the United States. The actual number of tests performed was much higher, which demonstrates a high level of investigation of suspected cases.

Table 3. Distribution of Sizes of Measles Chains of Transmission and Detection of Measles Genotypes, United States, 2001-2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases, Total No.</th>
<th>Isolated Cases Genotyped, No. (%)</th>
<th>2-Case Chains Genotyped, No. (%)</th>
<th>Outbreaks With 3-5 Cases Genotyped, No. (%)</th>
<th>Outbreaks With &gt;5 Cases Genotyped, No. (%)</th>
<th>All Chains of Transmission With ≥2 Cases Genotyped, No. (%)</th>
<th>Genotypes Detected</th>
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<tbody>
<tr>
<td>2001</td>
<td>116</td>
<td>44 (14)</td>
<td>7 (457)</td>
<td>7 (57)</td>
<td>3 (267)</td>
<td>17 (59)</td>
<td>D3, D4, D5, D7, H1</td>
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<tr>
<td>2002</td>
<td>44</td>
<td>21 (29)</td>
<td>2 (0)</td>
<td>1 (100)</td>
<td>5 (240)</td>
<td>B3, D3, D4, D7, D8</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>56</td>
<td>23 (52)</td>
<td>3 (0)</td>
<td>2 (100)</td>
<td>2 (33)</td>
<td>D4, D6, D7, H1</td>
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<tr>
<td>2004</td>
<td>37</td>
<td>14 (29)</td>
<td>5 (2)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>D3, D8, H1</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>66</td>
<td>18 (44)</td>
<td>2 (50)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>D3, D4, D6, D8, D9</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>55</td>
<td>26 (42)</td>
<td>1 (100)</td>
<td>3 (33)</td>
<td>1 (100)</td>
<td>B3, D4, D5, D6, D8, H1</td>
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<tr>
<td>2007</td>
<td>43</td>
<td>21 (14)</td>
<td>2 (50)</td>
<td>3 (67)</td>
<td>1 (100)</td>
<td>D4, D5, D9</td>
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<tr>
<td>2008</td>
<td>140</td>
<td>27 (19)</td>
<td>3 (133)</td>
<td>3 (100)</td>
<td>6 (100)</td>
<td>D4, D5, H1</td>
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<tr>
<td>2009</td>
<td>71</td>
<td>17 (41)</td>
<td>3 (133)</td>
<td>4 (75)</td>
<td>4 (75)</td>
<td>D4, D8, H1</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>63</td>
<td>39 (44)</td>
<td>5 (240)</td>
<td>4 (75)</td>
<td>0 (0)</td>
<td>B3, D4, D8, D9, H1</td>
<td></td>
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<tr>
<td>2011</td>
<td>220</td>
<td>86 (42)</td>
<td>11 (82)</td>
<td>7 (100)</td>
<td>9 (100)</td>
<td>B3, D4, D8, H1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>911</td>
<td>336 (32)</td>
<td>46 (52)</td>
<td>37 (68)</td>
<td>29 (93)</td>
<td>112 (68)</td>
<td>B3, D3, D4, D5, D6, D7, D8, D9, H1, H2, G3</td>
</tr>
</tbody>
</table>

identify additional cases, and prevent further transmission by vaccinating contacts who lack evidence of immunity.

To verify elimination, a surveillance system must be capable of detecting endemic transmission. United States surveillance capacity to detect a chain of transmission that continues for 12 months or longer is clearly demonstrated by the consistent detection of small chains of transmission and isolated imported cases. Of the 448 chains of measles transmission reported, 306 (68%) had import sources, and 382 (85%) were isolated cases or 2-case chains (Table 3). All reported rubella cases either were isolated cases or occurred in 2-case chains with only 2 small outbreaks.

The CDC measles and rubella laboratories provide confirmatory serologic testing, specialized serologic tests, and molecular diagnostics and virus genotyping. In the last 6 years, the CDC measles laboratory has performed confirmatory measles IgM testing on more than 1000 serum samples and has performed virological testing on more than 1500 specimens. For fiscal years 2006 through 2011 (October 1, 2005-September 30, 2011), the testing volume in the CDC rubella laboratory remained relatively constant, with a total of 410 confirmatory IgM tests performed. These testing volumes represent only a fraction of the suspected measles, rubella, and CRS cases investigated in the United States. The actual number of tests performed was much higher, which demonstrates a high level of investigation of suspected cases.

Population Immunity to Measles and Rubella

Vaccination Coverage Data

The US federal government spends $4 billion annually to support vaccine purchase, as well as to support critical state immunization infrastructure and operational costs. National-level 1-dose MMR coverage among children 19 to 35 months of age has remained high over the last decade at 90% or higher. State coverage estimates ranged from 85.1% to 97.8% in 2010. The NIS-Teen vaccination coverage data for adolescents 13 to 17 years of age have only been available since 2008. In 2010, a total of 90.5% of adolescents had evidence of 2 MMR vaccine doses. State 2-dose adolescent MMR coverage ranged from 79.7% to 98.4%. Kindergarten coverage data showed that a total of 94.8% of children entering kindergarten had evidence of 2 MMR doses in 2010.

The percentage of students who claim exemption to school immunization requirements ranged from less than 0.1% in Mississippi to 6.2% in Washington. Vaccine exemptors tend to cluster geographically. For example, the 2010-2011 county-level nonmedical-exemption rates in Washington ranged from 1.3% to 27.5%. There is some evidence of an increase in vaccine exemption in the United States in recent years.

Measles and Rubella Seroprevalence

National Health and Nutrition Examination Survey data from persons in the US population 6 to 49 years of age in 1999-2004 showed a measles antibody seroprevalence of 95.9% and a rubella antibody seroprevalence of 91.3%. Measles seropositivity was above 92% in all assessed birth cohorts (born 1949-1998).

Discussion

Collectively, the very low disease incidences, the high proportions of importation-associated cases, the absence of endemic genotypes, the adequate surveillance, and the high levels of population immunity all indicate that the elimination of endemic measles, rubella, and CRS has been sustained in the United States.
United States. However, because measles and rubella remain endemic in many parts of the world, importations will continue to occur. To respond to this challenge, the CDC spent approximately $438.9 million from 2001 to 2011 on global measles control activities,42–43 purchasing more than 200 million doses of measles vaccine and providing technical support for developing countries.42

Health care providers in the private and public health sectors must work together to prevent imported cases from transmitting measles and rubella in the United States and potentially reestablishing endemic transmission. The first task is to maintain high levels of vaccination coverage across the population and minimize demographic pockets of susceptibility due to high rates of vaccine exemption. Second, interruption of transmission of imported measles and rubella viruses requires detecting, reporting, and investigating potential cases. Physicians and other health care providers should suspect measles and rubella in patients with fever and generalized nonvesicular rash illnesses, especially in association with international travel. Immediate reporting of suspected cases to local health departments will enable rapid intervention, including the coordination of the collection of appropriate specimens, laboratory confirmation and identification, and vaccination of susceptible contacts.

Conclusion

The expert panel that reviewed these compiled data concluded that the elimination of endemic measles, rubella, and CRS has been sustained in the United States. The keys to ongoing success will be sustaining high levels of immunity throughout the US population through vaccination, maintaining strong US surveillance and public health response capacity, and supporting other countries in efforts to control and eliminate measles, rubella, and CRS and, hopefully in the future, to achieve the goal of a world without measles, rubella, and CRS.4

REFERENCES

14. Centers for Disease Control and Prevention. Documentation and verification of measles, rubella
Measles, Rubella, and Congenital Rubella Syndrome

Original Investigation Research

Overview.


