

# Documentation and Verification of Measles, Rubella and Congenital Rubella Syndrome Elimination in the Region of the Americas

United States National Report, March 28, 2012

National Center for Immunization and Respiratory Diseases  
Division of Viral Diseases



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## I. Introduction

The World Health Organization (WHO) Region of the Americas has been a global leader in measles, rubella and congenital rubella syndrome (CRS) elimination. The Pan American Health Organization (PAHO) has coordinated the successful elimination efforts of all member countries within the Region of the Americas. Regional measles elimination has been sustained since 2002 and PAHO set an elimination goal for rubella and CRS by 2010. No endemic cases of rubella have been reported since 2009 and the last endemic CRS case in the Americas was also reported in 2009. Three other WHO regions, the European, Eastern Mediterranean and Western Pacific regions have targeted measles for elimination by 2015 or before. Other regions are focused on measles mortality reduction strategies. The WHO European Region has a rubella elimination target of 2015 and the Eastern Mediterranean and Western Pacific regions have established congenital rubella syndrome (CRS) prevention goals. The Southeast Asian and African Regions have not established goals for rubella control or elimination.

As a PAHO member country, the United States is committed to the goal of eliminating endemic measles, rubella, and CRS from the Region of the Americas, and to the documentation and verification of elimination by the end of 2011, as resolved by the 27<sup>th</sup> Pan American Sanitary Conference (CSP27.R2) in 2007. As part of this regional effort, this U.S. National Report confirms the successful, sustained elimination of endemic measles from the United States since elimination was verified in 2000 and of endemic rubella and CRS since verification of elimination in 2004. The United States has verified and documented the elimination of endemic measles and rubella in two phases.

### **Phase 1: Initial Documentation and Verification of the Elimination of Endemic Measles, Rubella and Congenital Rubella Syndrome in the United States**

#### ***Step 1: Measles elimination documentation and verification***

In the year 2000, the U.S. verified the elimination of endemic measles within its borders. In March 2000, the National Immunization Program of the Centers for Disease Control and Prevention (CDC) convened an external panel of 12 consultants to review the status of measles in the United States. The experts reviewed the U.S. strategy for elimination, which includes the following components: achieving very high coverage with 2 doses of measles-containing vaccine; sustaining adequate surveillance; responding to cases with thorough case investigation and outbreak response; and promoting measles control in other countries. The definitions of elimination, mathematical models of endemic measles transmission elimination and the population immunity required to achieve elimination were also discussed with the panel. The epidemiology of measles in the United States was presented, including the sustained extremely low incidence, the high proportion of cases that were internationally imported or import-associated, and the small and infrequent outbreaks. Also, molecular epidemiologic data were presented to the panel that showed that no endemic genotype has been detected in the United States since 1994. The quality of surveillance was reviewed in detail, including presentations by health officials from New York City, Los Angeles, and Chicago showing the various approaches to surveillance in these high-risk locations. An

overall assessment showing high population immunity to measles was presented based on National Immunization Survey coverage estimates, school entry vaccine coverage surveys and national serosurvey results. Finally, the progress made by other countries in the Americas and the positive impact this progress had on tracking the epidemiology of measles in the United States was presented. Each of the 12 consultants in the external panel concluded that measles was not endemic in the United States. The elimination of endemic measles in the United States in 2000 was documented, along with all of the evidence presented to the external consultants, in a supplement to the *Journal of Infectious Diseases*.<sup>1</sup> The Executive Summary of the panel's opinion, along with all of the data presented and published, was provided to the Phase II external review panel and will be provided to the International Expert Committee to verify and document the sustained elimination of endemic measles from the United States.

### ***Step 2: Rubella and CRS elimination documentation and verification***

In October 2004, CDC convened an independent panel of internationally recognized authorities on public health, infectious diseases, and immunization to assess progress toward elimination of rubella and CRS in the United States, which was a national health objective for 2010. The key data presented included 1) fewer than 25 reported rubella cases each year since 2001, 2) at least 95% reported vaccination coverage among school-aged children, 3) estimated 91% population immunity among persons 6-49 years of age, 4) adequate surveillance to detect rubella outbreaks, and 5) a pattern of virus genotypes consistent with virus originating in other countries. Given the available data, all panel members concluded that rubella was no longer endemic in the United States. The summary of the panel review and the key data presented were published as a supplement to *Clinical Infectious Diseases*<sup>2</sup> as well as in the *Morbidity and Mortality Weekly Report*<sup>3</sup> and in *Pediatrics*.<sup>4</sup> The meeting summary including the panel's opinion, along with all of the data published, was provided to the Phase II external review panel for the United States and will be provided to the International Expert to Committee to verify and document the sustained elimination of endemic rubella and congenital rubella syndrome from the United States.

## **Phase 2: Verifying and Documenting that Elimination of Endemic Measles, Rubella and Congenital Rubella Syndrome has been Sustained to the Present Time**

To document and verify the sustained elimination of measles, rubella and CRS, the CDC's National Center for Immunization and Respiratory Diseases (NCIRD) assembled a Phase II panel of five external experts on immunization, infectious diseases, and public health to serve as consultants to review the documentation and verification of sustained measles, rubella and CRS elimination in the United States (Section X, Expert Panel). A review of the initial verification and documentation of elimination of measles in 2000, and rubella and CRS in 2004, with relevant publications, was provided to the panel. NCIRD staff compiled the relevant information concerning measles, rubella and CRS in the United States into a detailed draft report for the Phase II Expert Panel and International Expert Committee to review. NCIRD staff met with the Phase II Expert Panel on December 16, 2011 to discuss and review the information in the draft report. Following the meeting, the report was modified according to suggestions from the expert panel and the panel's summary and conclusions were attached to the report. This final United States National Report on the Elimination of Endemic Measles, Rubella and Congenital Rubella Syndrome was approved and signed by the members of the U.S. Expert Panel in March, 2012.

## II. Surveillance of Measles, Rubella, and Congenital Rubella Syndrome

### Case Definitions

*Measles* - The following case definition for measles has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 1997 and updated in 2009.

Clinical case definition - Measles is an illness characterized by all of the following:

- A generalized maculopapular rash lasting  $\geq 3$  days
- A temperature  $\geq 101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ )
- Cough, coryza, or conjunctivitis

Laboratory criteria for diagnosis

- Positive serologic test for measles immunoglobulin M (IgM) antibody;
- Significant (generally a four-fold) rise in measles IgG antibody level by any standard serologic assay;
- Isolation of measles virus from a clinical specimen;
- Detection of measles –virus specific nucleic acid by polymerase chain reaction

*Note: Genotype identification by a WHO reference laboratory (CDC) is required to distinguish wild type from vaccine strains if the case was vaccinated within 18 days of rash onset.*

Case classification

**Suspected:** Febrile illness accompanied by generalized, maculopapular rash.

**Probable:** A case that meets the clinical case definition, has noncontributory or no serologic or virologic testing, and is not epidemiologically linked to a confirmed case.

**Confirmed:** A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed case. A laboratory-confirmed case does not need to meet the clinical case definition.

*Rubella* - The case definition for rubella has been approved by the CSTE and was published in 2009.

Clinical case definition - Rubella is an illness that has all of the following characteristics:

- Acute onset of generalized maculopapular rash
- Temperature  $>99^{\circ}\text{F}$  ( $37.2^{\circ}\text{C}$ ), if measured
- Arthralgia, arthritis, lymphadenopathy, or conjunctivitis

Laboratory criteria for diagnosis

- Isolation of rubella virus; or
- Significant rise between acute- and convalescent-phase titers in serum rubella immunoglobulin G antibody level by any standard serologic assay; or
- Positive serologic test for IgM antibody; or
- Detection of rubella-virus specific nucleic acid by polymerase chain reaction.

Case classification

**Suspected:** Any generalized rash illness of acute onset that does not meet the criteria for probable or confirmed rubella or any other illness

**Probable:** A case that meets the clinical case definition, has no or noncontributory serologic or virologic testing, and is not epidemiologically linked to a laboratory-confirmed case of rubella

**Confirmed:** A case that is laboratory confirmed (with or without symptoms) or that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case of rubella

**Importation status**

The same importation status classifications are used for measles and rubella, with a slight modification in the defined exposure periods of the diseases, and were approved by the CSTE in 2006.

**International importation:** An internationally imported case is defined as a case in which measles or rubella results from exposure to measles or rubella virus outside the United States as evidenced by at least some of the exposure period (7–21 days before rash onset for measles, 12–23 days before rash onset for rubella) occurring outside the United States and rash onset occurring within 21 days (measles) or 23 days (rubella) of entering the United States and there is no known exposure to measles/rubella in the U.S. during that time. All other cases are considered U.S.-acquired.

**U.S.-acquired case:** A U.S.-acquired case is defined as a case in which the patient had not been outside the United States during the 21 days (measles) or 23 days (rubella) before rash or was known to have been exposed to measles or rubella within the United States. U.S.-acquired cases are sub-classified into four 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 measles or 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 the genotype of any measles or rubella virus that occurs in an endemic chain of transmission (i.e., lasting  $\geq 12$  months). Any genotype that is found repeatedly in U.S.-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location. *Note- In this report, any case occurring in a chain of transmission from which viral genetic evidence indicates an imported genotype is considered an imported-virus case, even if the specimen tested is from another case in the transmission chain.*

**Endemic case:** A case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of measles or rubella virus transmission that is continuous for  $\geq 12$  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 U.S. cannot be established after a thorough investigation. These



cases must be carefully assessed epidemiologically to assure that they do not represent a sustained U.S.-acquired chain of transmission or an endemic chain of transmission within the United States.

*Note: Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases. For national reporting, cases will be classified as either internationally imported or U.S.-acquired.*

***Congenital Rubella Syndrome-*** The following case definition for congenital rubella syndrome (CRS) was approved by the CSTE in June 1999.

Clinical case definition - An illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by signs or symptoms from the following categories:

- Cataracts and congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, pigmentary retinopathy
- Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

#### Clinical description

Presence of any defect(s) or laboratory data consistent with congenital rubella infection. Infants with CRS usually present with more than one sign or symptom consistent with congenital rubella infection. However, infants may present with a single defect. Hearing impairment is the most common single defect.

#### Laboratory criteria for diagnosis

- Isolation of rubella virus, or
- Positive serologic test for rubella immunoglobulin M (IgM) antibody, or
- Infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month)
- Detection of rubella-virus specific nucleic acid by polymerase chain reaction.

#### Case classification

**Suspected:** A case with some compatible clinical findings but does not meet the criteria for a probable case.

**Probable:** A case that is not laboratory confirmed and has any two complications listed in first paragraph of the clinical case definition or one complication from the first paragraph and one from the second paragraph, and lacks evidence of any other etiology.

**Confirmed:** A clinically consistent case that is laboratory confirmed.

**Infection only:** A case that demonstrates laboratory evidence of infection, but without any clinical symptoms or signs.

**Comment:** *In probable cases, either or both of the eye-related findings (cataracts and congenital glaucoma) count as a single complication. In cases classified as infection only, if any compatible signs or symptoms (e.g., hearing impairment) are identified later, the case is reclassified as confirmed.*

Importation Status

Congenital rubella syndrome cases will be classified epidemiologically as internationally imported or U.S.-acquired, according to the source of infection in the mother, using the definitions below, which parallel the classifications for rubella cases.

Internationally imported case: To be classified as an internationally imported CRS case, the mother must have acquired rubella infection outside the United States or in the absence of documented rubella infection, the mother was outside the United States during at least some of the period when she may have had exposure to rubella that affected her pregnancy (from 21 days before conception and through the first 24 weeks of pregnancy).

U.S.-acquired case: A U.S.-acquired case is one in which the mother acquired rubella from an exposure in the United States. U.S.-acquired cases are sub-classified into four groups as described in the rubella importation status classification.

Note:

*Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases. States may also choose to classify cases as “out-of-state-imported” when imported from another state in the United States. For national reporting, however, cases will be classified as either internationally imported or U.S.-acquired.*

**Elimination of endemic disease-** Absence of endemic transmission of measles or rubella, ideally documented for at least 3 consecutive years. No endemic genotype is present.

**Outbreak:** A chain of transmission of measles or rubella including 3 or more cases.

**Timeframes:**

Phase I *initial documentation of elimination of endemic measles* - Was completed in 2000, covering the years 1997-2000.

Phase II *documentation of elimination of endemic measles* – In process, covers the years 2001-2011. Data for 2011 cover through September 30, 2011, unless otherwise noted.

Phase I *documentation of elimination of rubella and CRS* - Completed in 2004, covering the years 2001-2004.

Phase II *documentation of elimination of endemic rubella and CRS* - In process, covers the years 2004-2011. Data for 2011 cover through September 30, 2011, unless otherwise noted.

**Methods for Surveillance and Outbreak Investigation and Response**

The surveillance system for measles, rubella and CRS in the United States was described and evaluated in detail in the initial verification and documentation of elimination of endemic measles, rubella and CRS and has not changed significantly in the interim.<sup>1-4, 5</sup> Surveillance consists of four essential components: detection, reporting, case investigation and laboratory confirmation.

Surveillance for measles, rubella and CRS in the United States is passive, requiring reporting from health care providers to state and local health departments, but not actively seeking cases. In every state in the United States, health care providers are required by law to report confirmed measles, rubella and CRS cases to local or state health departments. In some states, suspected cases are reportable as well as confirmed cases. Measles, rubella and CRS cases are reported by state health departments directly to CDC/NCIRD and to the National Notifiable Disease Surveillance System.

Since documentation of measles and rubella elimination, CSTE has updated reporting guidance. State health departments are now expected to report measles and rubella (including CRS) cases to CDC/NCIRD within 24 hours of confirmation. CDC/NCIRD Division of Viral Diseases (DVD) also collects detailed real-time information directly from the state on every measles, rubella and CRS case. CDC staff participate in case investigation and response as requested by state health departments, through provision of epidemiology and laboratory technical assistance, to help ensure the maintenance of elimination.

An important component of the U.S. surveillance system for measles, rubella and CRS, is that it is a responsive system. Once a case is reported, the system changes immediately to an active investigation mode. Cases are investigated in detail to identify their source of exposure and potential contacts. Contacts of cases are identified rapidly to attempt to find additional cases. Presumptive evidence of immunity is assessed for contacts. Those who lack evidence of immunity are offered MMR vaccine, measles immune globulin, or are quarantined, as appropriate, to prevent further transmission.

### **Laboratory Surveillance Activities for Measles and Rubella in the United States**

Laboratory confirmation of measles and rubella cases is considered essential in the post elimination era and is recommended for every case. An exception to this rule may be made during an outbreak if it is not feasible to confirm every case.

The systems for laboratory diagnosis of measles and rubella in the United States are composed of a combination of private and public laboratories; no routine summaries of the numbers of laboratories conducting such tests or the numbers of test performed are available. A detailed overview of the U.S. surveillance system, including laboratory diagnostic practices was published by Guris, et al in 2004.<sup>5</sup> Private (commercial and clinical) laboratories provide the majority of initial testing of serum samples for measles and rubella IgM, especially for samples collected from suspected cases seen by private physicians. Measles and rubella testing is readily available and typically performed quickly. The quality of the tests performed is regulated, but may not be consistent across different laboratories. Reporting of positive tests by laboratories is required, but not monitored. The number of tests performed is not reported. Surveys in 1997 and 1999 each estimated private laboratories tested over 25,000 measles IgM specimens per year.<sup>6</sup> The number of tests currently being performed at commercial and clinical laboratories has not been summarized.

CDC's measles and rubella laboratory serves as the national laboratory for the United States, a regional reference laboratories for the Pan American Health Organization, and a Global Specialized Laboratory in the World Health Organization (WHO) Global Measles and Rubella Laboratory Network.<sup>7</sup> CDC's measles and rubella laboratory provides global leadership in measles and rubella diagnosis, research, and training and expert advice at the national and international level on suspect measles and rubella and CRS case classification, even when testing is not done in the CDC laboratory.

#### ***Measles laboratory surveillance activities***

CDC measles laboratory provides reference laboratory support for measles surveillance in the United States. This support consist of confirmatory serologic testing (if the diagnosis is uncertain

and the specimen is available), specialized serologic tests (e.g., IgG avidity, neutralization, IgG EIA), as well as molecular diagnostics and viral genotyping.<sup>8</sup> CDC measles laboratory staff provides protocols and test panels to the state laboratories and provides training through site-visits, in-house trainings, and webinars.

All state laboratories have the capacity to perform or access to (samples sent to private or commercial laboratory or partnership with another state laboratory) IgM serologic testing for measles. According to the American Public Health Laboratory (APHL) survey published in May of 2011, of 59 member laboratories that are performing VPD testing, 59% are performing measles IgM testing. There is no consistent laboratory test used for measles IgM serology. The number of tests performed is not routinely reported to CDC. State laboratories often perform confirmatory serology testing on specimens with positive results from private laboratories. Approximately 25 states have validated or are in the process of validating real time RT-PCR assays for measles based on CDC's protocol. Two state laboratories currently perform measles genotyping. CDC and APHL are working on a number of projects to enhance the diagnostic capacity for vaccine preventable diseases in state laboratories.

### ***Rubella laboratory surveillance activities***

Serologic testing methods in use in private and public laboratories are similar to those described for measles serology. There is a large amount of serologic testing for immunity to rubella as a result of prenatal immunity testing activities. Most states maintain the ability for serologic confirmatory testing for suspected rubella and CRS cases by IgM detection, either using a variety of commercial kits or through diagnostic testing services.

Samples for domestic rubella testing referred to CDC's rubella laboratory are primarily from state health departments, but occasionally come directly from private physicians or private laboratories. Samples from many suspected cases already have some laboratory data indicating a confirmed case. The majority of samples sent to the CDC laboratory are serum samples. Other common samples include throat swabs, nasals swabs, and urine for molecular diagnostics and viral genotyping. Occasionally, samples such as cerebrospinal fluid and cataracts are received.

Two general types of tests are performed by CDC's rubella laboratory: serological assays and detection of virus and/or virus RNA. Assays for both rubella specific IgG and IgM antibodies are performed on every serum sample received. Commercial ELISA kits are used for both IgG and IgM determinations. An assay to determine the rubella specific IgG avidity of serum samples is performed to aid in case classification for selected sera. CDC's avidity assay is an in-house method based on a commercial IgG ELISA test. An in-house neutralization assay is also available and is occasionally performed with selected sera.

An in-house designed real-time RT-PCR assay based on TAQMAN chemistry is used for the detection of rubella virus RNA in clinical samples including throat and nasal swabs, urine, and serum. Virus isolation in cell culture is performed on any rubella positive samples and on some samples from suspected cases, if requested by the submitter. Additional conventional RT-PCR reactions are performed on positive samples in order to determine the genotype of the virus by sequencing products thus derived from a portion of the viral genome.

The very small number of cases of rubella and CRS in the United States in the last decade has resulted in very little molecular diagnostics and viral genotyping in the states laboratories and other domestic laboratories. At present, no state is known to do viral genotyping for rubella viruses. CDC is in the process of developing surge capacity for molecular diagnostics using standard CDC protocols and viral genotyping in a state laboratory. CDC molecular protocols, which will be implemented for domestic surge capacity, are already in wide use in many countries in the Global Measles and Rubella Laboratory Network.

Standard nomenclature for wild-type rubella viruses was adopted in 2004 and updated in 2007. There are currently two clades designated (Clade 1 and Clade 2), which are subdivided into 10 Clade 1 genotypes (1a, 1B, 1C, 1D, 1E, 1F, 1G, 1h, 1i, and 1j) and 3 Clade 2 genotypes (2A, 2B, and 2C).<sup>9</sup>

### **Evaluating Potential Endemic Genotypes**

Cases in a chain of transmission of measles and rubella share the same viral genotype and nearly identical sequences. If an endemic chain of transmission of measles or rubella occurred, it would be represented by a single genotype, which would be considered an endemic genotype. If endemic transmission were re-established in the United States, it would be as the result of international importation followed by continuous circulation for more than 12 months of at least one viral genotype. CDC analyzed the molecular epidemiology of measles and rubella viruses in the United States to determine if any genotype is occurring in a pattern which might suggest endemic transmission. This analysis was done in the context of what is known about the viruses in current and historical chains of transmission in the United States and other countries.

One of the limitations of molecular epidemiology is that it is difficult to distinguish between endemic transmission and multiple importations of genetically homogeneous viruses from the same external source. Therefore, it is critical to have thorough epidemiologic investigations of each case and outbreak, and to have a complete understanding of the viruses circulating in other countries.

If endemic transmission is suspected, the genotypes and sequences of the viruses are analyzed to assess the likelihood of endemic transmission. If the epidemiology and the molecular analyses are both consistent with endemic transmission, then endemic transmission is indicated regardless of the source of the virus.

### III. Epidemiology of Measles (2001-2011)

#### Basic Epidemiology

Following the measles resurgence of 1989-1991 and full implementation of the two dose MMR vaccine policy and other immunization interventions, reported measles cases decreased significantly in the United States and remained at very low levels from 1993 onward (Figure 1). Measles case counts and incidence have remained extremely low from 2001 to 2011. A review of the epidemiology of measles in the post-elimination era in the United States was published in the *Journal of Infectious Diseases*, covering the years 2001-2008.<sup>10</sup> The data in that article are updated in this report to cover the period from 2008 through 2011.

For the period 2001-2011, the total number of measles cases reported was 904. The median number of measles cases per year was 60 with a range of 37 to 212 cases/year (Table 1). Measles incidence has remained below 1 case per million continuously since 1997 (Figure 2). The highest incidence has been in infants too young to be vaccinated. The majority of measles cases (2001-2011) were unvaccinated (65%) or had unknown vaccination status (20%).

The highest incidences in recent years occurred in 2008 and 2011. The epidemiology of measles in 2008 was characterized by a high proportion (92%) of cases among U.S. residents who were unvaccinated or who had unknown vaccination status, a high proportion cases occurred in U.S. school-aged children whose parents have religious or philosophical objections to vaccination, and more spread from imported cases than other years. The peak in reported cases in 2011 (212 cases) results from a surge in internationally imported cases, primarily among unvaccinated U.S. residents and primarily from Western Europe, where a large measles epidemic is occurring (Figures 3 and 4).

**Figure 1. Measles Cases, United States, 1962-2011\***

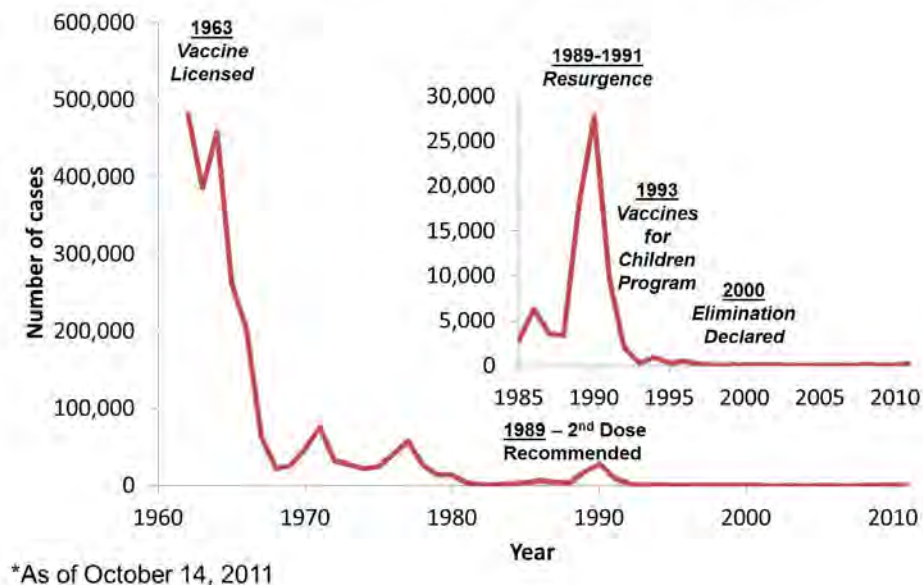


Table 1: Import Status of US Measles Cases by Year, 2001-2011

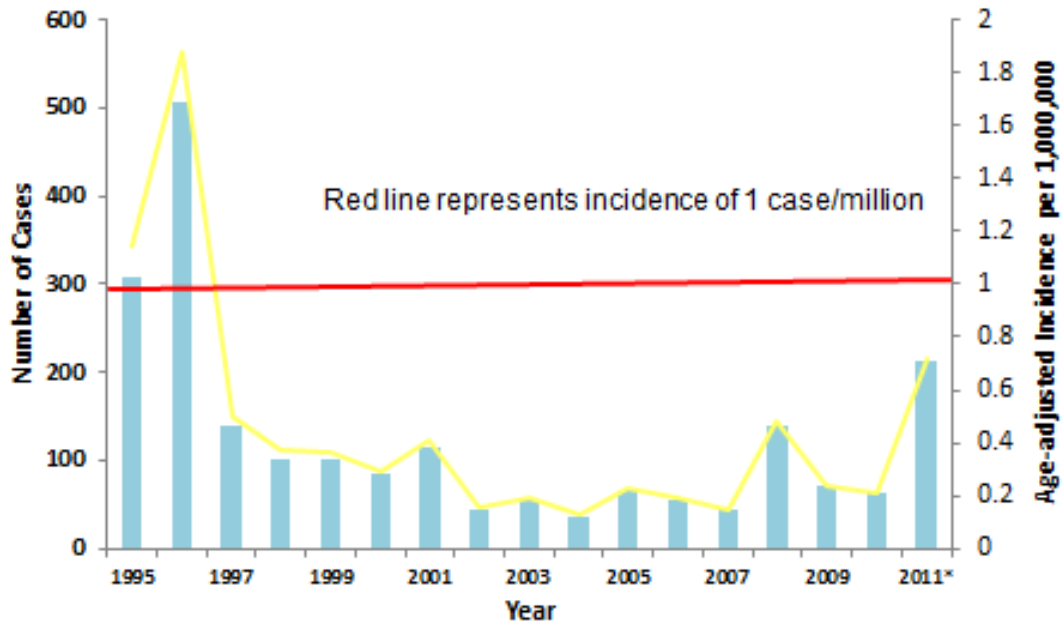
Year	All Cases	Imported			Import-Linked	Imported-Virus	Unknown Source	Import Associated
		Total	Non Res	US Res				
2001	116	54 (47%)	34	20	25(22%)	12 (10%)	25 (22%)	91 (78%)
2002	44	18 (41%)	8	10	15 (34%)	4 (9%)	7 (16%)	37 (84%)
2003	56	24 (43%)	13	11	19 (34%)	2 (4%)	11 (20%)	45 (80%)
2004	37	27 (73%)	13	14	6 (16%)	0 (0%)	4 (11%)	33 (89%)
2005	66	24 (36%)	7	17	38 (56%)	0 (0%)	4 (6%)	62 (94%)
2006	55	31 (56%)	12	19	19 (35%)	2 (4%)	3 (5%)	52 (95%)
2007	43	29 (67%)	12	17	12 (28%)	0 (0%)	2 (5%)	41 (95%)
2008	140	25 (18%)	13	12	31 (22%)	73 (52%)	11 (8%)	129 (92%)
2009	71	21 (30%)	7	14	12 (17%)	26 (37%)	12 (17%)	59 (83%)
2010	64	39 (61%)	15	24	5 (8%)	12 (19%)	8 (13%)	56 (88%)
2011	212	72 (34%)	20	52	67 (32%)	54 (25%)	19 (9%)	193 (91%)
<b>Total</b>	904	364 (40%)	154	210	249 (28%)	185 (20%)	106 (12%)	798 (88%)

**Note:**

\*Total for Imported-virus column includes number of unknown source cases with imported virus and the number of cases with epi-link to imported virus cases. This case breakdown has been available since 2008:

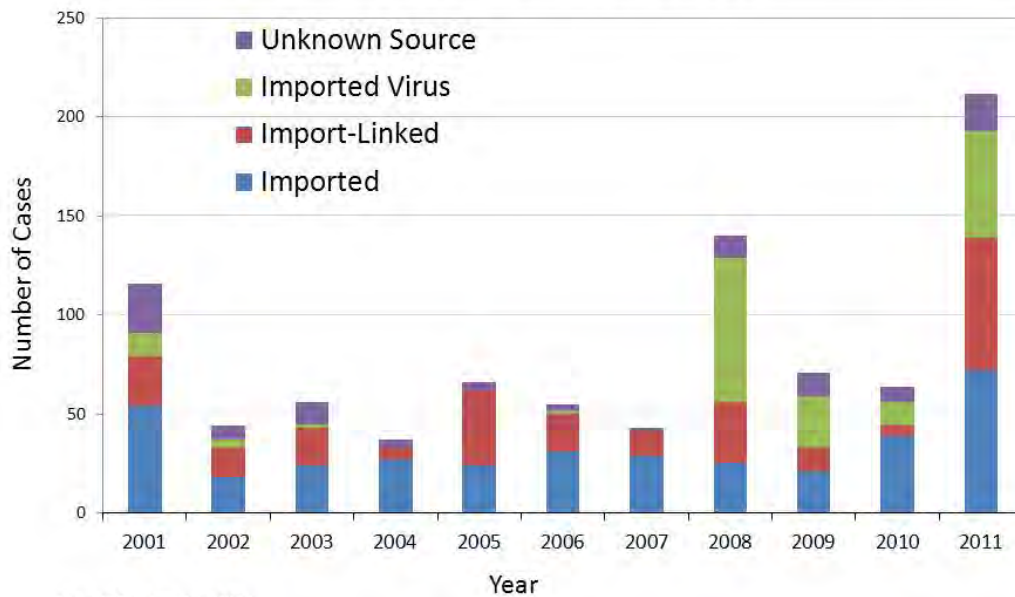
- 2008: 73 total cases; 22 imported virus and 51 epi-linked cases
- 2009: 26 total cases; 12 imported virus and 14 epi-linked cases
- 2010: 12 total cases; 8 imported virus and 4 epi-linked cases
- 2011: 54 total cases; 32 imported virus and 22 epi-linked cases

**Figure 2. Measles, United States, 1995-2011\***  
**Reported Cases and Incidence**



\*As of October 14, 2011

**Figure 3. Measles Cases by Import Status**  
**United States, 2001-2011\***



\*As of October 14, 2011



**Figure 4. Measles, United States, 2011\*  
Source of Importations (N=72)**

WHO Region	Total # of cases	Countries (# of cases)	Genotype identified
African	4	Kenya (2), Ethiopia (1), Nigeria (1)	B3 (3)
Eastern Mediterranean	3	Pakistan (2), Jordan (1)	D4 (1)
European	34	France (13), Italy (4), United Kingdom (5), Romania/Hungary†(2), Poland (1), Romania (1), Spain (1), France/United Kingdom‡(1), France/Italy/Spain/Germany*(1), Bulgaria (1), France/Italy*(1), France/Spain/United Kingdom*(1), France/Germany/Spain†(1)	D4 (16), G3 (1)
Americas	2	Dominican Republic†(1), Canada (1)	D4 (1)
South-East Asia	19	India (16), Indonesia (2), Bangladesh (1)	D8 (5), D4 (1)
Western Pacific	11	China (2), Philippines (6), Malaysia (2), Philippines/Vietnam/Singapore/Malaysia*(1)	H1 (1), D9 (6)

\*As of October 14, 2011

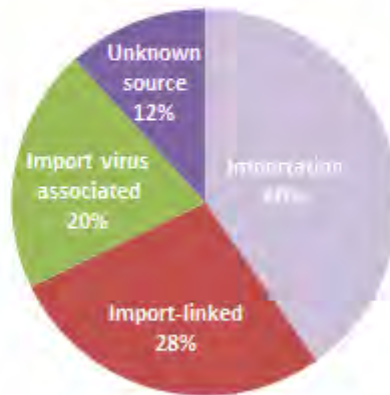
‡ Patient visited more than 1 country during the incubation period

† Likely acquired disease from French tourist

## Importation Classifications

For all years in the post-elimination period, the majority of reported measles cases in the United States have a documented association with international importation. For the period 2001-2011, 364 (40%) reported measles cases were imported cases. The majority (58%) of the imported cases (210) occurred in U.S. residents returning from international travel while 154 imported cases occurred in foreign visitors (Table 1). An additional 28% of cases were import-linked cases and 20% of cases were *imported-virus cases*. For the period 2001-2011, 88% of reported measles cases were importation associated. The remaining 12% of the reported measles cases were unknown source cases (Table 1, Figure 5). The distribution of cases across the importation classifications has varied during this period, with internationally imported cases typically predominant.

**Figure 5. Measles, United States, 2001-2011\*  
Import Classification of Cases (N=904)**



\*As of October 14, 2011

The number of import-linked cases resulting from each identified imported case is a measure of the population susceptibility to measles as well as public health response. From 2001-2011, 84% of imported cases did not result in any additional reported cases, 9% of imported cases resulted in transmission to only one reported import-linked case and only 7% of imported cases resulted in outbreaks (3 or more cases).

Imported-virus cases demonstrate the strength of the surveillance system because viral specimens from these cases or their associated chains of transmission were collected and tested to demonstrate that the detected viruses are not endemic measles viruses. However, imported-virus cases also reveal the incompleteness of measles surveillance because the cases, or chains of transmission that linked them to internationally imported cases, were not detected. For 2001-2011, 185 (20%) of measles cases were imported-virus cases. No imported-virus cases were reported in 2004, 2005 and 2007 (Table 1). The maximum number of imported-virus cases (73) were reported in 2008, when two large imported-virus outbreaks occurred in Washington and Illinois, with 30 and 19 cases, respectively (see Measles Outbreaks below).

In 2011, measles cases of all classifications increased. Most notably, a surge in internationally imported cases was associated with a concomitant surge in both import-linked and imported virus cases. During 2011, as of October 14, 72 importations occurred from over 20 different source countries with 6 different genotypes isolated (Figure 4). The number of unknown source cases also increased in 2011 (Figure 3, Table 1). In 2011, despite an unusually high number of importations, only 7% of imported measles cases resulted in measles outbreaks (i.e., chains with 3 or more cases, including the imported case).

## Unknown Source Cases

Documentation of the sustained elimination of endemic measles requires careful analysis of the reported unknown source cases. These cases have no known epidemiologic link to importation and no genotype information available, therefore they must be evaluated as potential links in an unrecognized endemic chain of transmission. A total of 106 unknown source cases were reported from 2001 through 2011, representing 12% of all cases. The highest annual number of unknown source cases and highest proportion cases with unknown source, 25 cases (22% of total cases) was reported in 2001. In 2011, 19 unknown source cases have been reported thus far, representing 9% of all 2011 cases (Table 1). Notably, the geographic distribution of unknown sources cases was dispersed, without evidence of clustering, while the import-associated cases clustered on the East Coast and in California (Figure 6).

**Figure 6. Measles, United States, 2011  
Geographic Distribution of Cases.**



**Note:**

*Blue dots represent import associated cases. Yellow dots represent unknown cases.*

Only 65 of 3130 counties in the United States (2%) reported any unknown source cases for the period 2001-2011. Of these counties, 48 reported only 1 unknown source case. These isolated unknown source cases have no link to other measles cases and no virologic confirmation of infection. Therefore, it is likely that some of these cases were not measles but were confirmed by false positive IgM tests. Only 17 counties in 10 states reported more than 1 unknown source case, (range 2-9 cases) during this period (Table 2). No county reported more than 1 unknown source case in multiple years. Los Angeles reported the most unknown source cases, and 5 of these cases were reported in 2001, with 1 case reported during each of the following years: 2002, 2008, 2009, and 2010. It should be noted that Los Angeles County has a population of > 9,800,000, and 35.4% of residents are foreign born, an indicator of a high level of international travel (US Census, 2010 <http://quickfacts.census.gov/qfd/states/06/06037.html>).

Although the four isolated unknown source cases from 2002-2010 had no known epi-link to other cases, a total of 10 imported cases were reported in Los Angeles county during this period. Seven other counties had unknown source cases reported in more than 1 year. There were 8 counties that reported unknown source cases in 2001, 4 in 2008, and 3 in 2011. In every other year, there were 2 counties or fewer reporting unknown source cases. From 2001-2011, there were 5 instances in which a county reported more than 2 unknown source cases in a given year (Table 2).

Table 2: Unknown Source Cases by County by Year 2001-2011, Counties with >1 Unknown Source Case

State	County	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011*	County total
AR	Scott								2				2
CA	Los Angeles	5	1						1	1	1		9
CA	San Francisco	2			2								4
CA	Orange		2						1				3
CA	Marin	2											2
HI	Honolulu	1		5									6
MA	Middlesex											5	5
MA	Suffolk											2	2
MA	Worcester											2	2
MI	Wayne			1				1					2
MO	Warren									6			6
MO	Green										3		3
NY	New York	2				1							3
NY	Bronx				1				1				2
OR	Washington	2											2
PA	Allegheny	1					1		1				3
WA	Island	2											2
	<b>Year Total</b>	17	3	6	3	1	1	1	6	7	4	9	58

These small sets of unknown cases represent the only potential signals that undetected endemic measles transmission might be occurring in the United States, so each instance is described in detail below. In Los Angeles, California in 2001, there were 5 unknown source cases, all isolated single cases. The earliest rash onset occurred in week 3 and the latest in week 20 of 2001. Los Angeles County reported a single unknown source case in each year in the year 2002, 2008, 2009 and 2010. In Honolulu, Hawaii, there were 5 unknown source cases in 2003. Three of these cases were linked as a 3 case outbreak, with rash onsets in weeks 17 and 18 of 2003 and no link to any case was detected for the other two cases, which occurred in weeks 19 and 20. There was a large outbreak in the Republic of the Marshall Islands in 2003, and many Marshallese people travel to Hawaii. Honolulu also reported a single unknown source case in 2001. In Warren County (St. Louis Metro Area), Missouri, there was a 6 case unknown source outbreak in 2009, the first reported case

occurring in week 15 and the 5 remaining cases in week 17. An additional case in this outbreak occurred in Montgomery County. Warren County did not report unknown source cases in other years from 2001-2011. In Green County (Springfield), Missouri, a three case unknown source outbreak occurred in 2010, with cases in weeks 16, 17 and 20. Green County did not report unknown source cases in other years from 2001-2011. Warren County and Green County are >200 miles apart and there was a 50 week interval between these two outbreaks with no unknown source cases reported in Missouri. In 2011, Middlesex County, Massachusetts reported 5 unknown source cases. None of the cases were linked to each other or other measles cases. The first case had rash onset in week 19 and the last case had rash onset in week 29. Massachusetts has reported over 20 measles cases in 2011, most of them import-associated, which provide a likely source for these unknown source cases, although the epidemiologic links were not detected. In each of these counties with unknown source cases, the number of cases has been small and the time spans over which they occurred have been limited. These situations are not consistent with endemic transmission of measles.

### **Estimated Effective Reproduction Number for Measles in the United States**

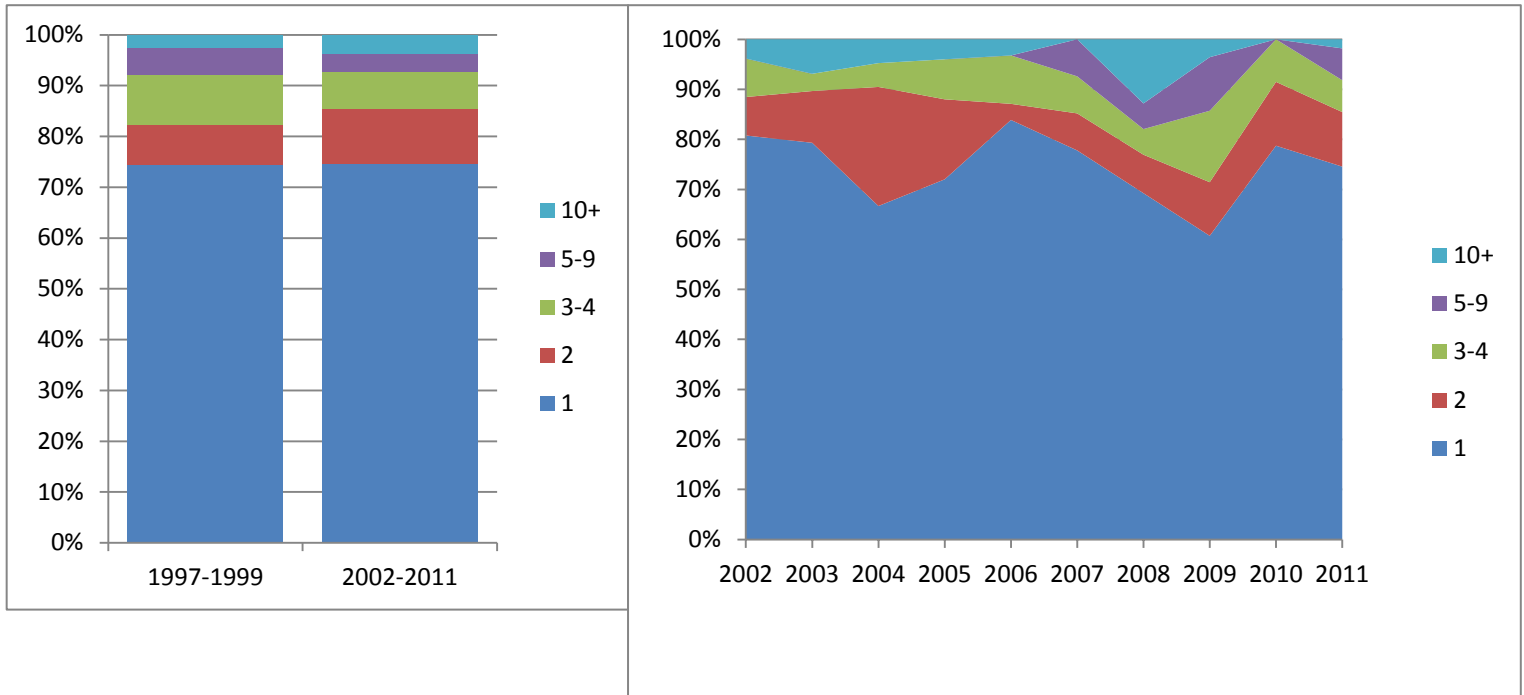
Among the data reviewed by the U.S. measles elimination panel in 2000 was an estimate of the *effective reproduction number* ( $R$ ) in the United States.<sup>11</sup> The *basic reproduction number* ( $R_0$ ) is a measure of the communicability of an infectious agent, specifically representing the number of secondary cases that would occur in a completely naïve (i.e., not immune) population during the first generation after introducing a single infected person. Measles has a very high  $R_0$ , estimated to be on the order of 15–16. As immunity in a population increases, either because of infection or immunization, the effective  $R$  drops. If enough individuals in the population are immune either through immunization or natural immunity such that the  $R$  drops below 1, transmission is no longer sustainable – a condition consistent with elimination of transmission.

$R$  can be inferred from epidemiologic data by looking at the distribution of the length of chains and the distribution of the duration of outbreaks. In the 2000 analysis, based on U.S. data from 1997 to 1999, the estimated  $R$  was 0.63 (95%CI: 0.51–0.76),<sup>11</sup> well below the threshold of elimination (1.00) and consistent with other data reviewed by the panel showing that measles was no longer endemic. This analysis was repeated using the distribution of measles transmission chain lengths from 2002 through 2011 and yielded an  $R$  of 0.70 (95%CI: 0.61–0.79), not statistically different from the 1997 to 1999 estimate and still well below the elimination threshold value.

These estimates of  $R$  can be misleading in that the equations on which they are based assume homogeneous mixing in the population and ignore any public health efforts to contain measles cases. Neither of these assumptions is likely to be met. Aggressive public health response is undertaken for every measles case in the US and vaccine exemptors cluster geographically and homogeneous mixing in the population is unlikely. However, it is reasonable to assume if population immunity in the United States were falling, that we'd see progressively longer chains of measles transmission, and the fact that the estimated  $R$  has changed so little strongly suggests that there has been little or no change in population immunity. A visual examination of trends in chain lengths further confirms that there are no clear trends that would suggest a change in population immunity since 1997 (Figure 7). Since the initial documentation of elimination of measles in the

United States, the lengths of measles transmission chains have not increased, providing further evidence in support of continued measles elimination.

**Figure 7. Measles Chains of Transmission  
Proportion by Chain Length, United States 1997- 2011**



**Note:**

A “chain length” of 1 represents a single case of disease with no spread, a chain length of 2 represents a chain of 2 related cases, etc. The longest chains (outbreaks with  $\geq 20$  cases) included 34 cases (2005), 33 cases (1998), 30 cases (2008) and 21 cases (2011). The graph on the left compares the proportion the proportion of chain lengths during 1997–1999 with those in 2002–2011. The graph on the right shows trends in chain lengths from 2002 through 2011. The 2011 data only include cases reported through October.

**Measles Outbreaks**

To assess whether a measles outbreak of 12 months duration might be occurring in the United States (i.e., endemic transmission), we carefully analyzed the epidemiology of reported measles outbreaks. These have been limited in number, size and duration for the period 2001-2011. A total of 64 outbreaks were reported (median 4 outbreaks/year, range 2-16 outbreaks/year). The median size of outbreaks over this period was 6 cases; the largest reported outbreak included 34 cases (Table 3). Outbreak-related cases comprised between 22%-77% of total measles cases from year to year. There were 16 outbreaks which included 10 or more measles cases (Table 4). The longest reported outbreak lasted 11 weeks and three outbreaks lasted 10 weeks. Twelve of these outbreaks (80%) had a known internationally imported case as the index case. The remaining 3 outbreaks,

highlighted in Table 4, had genotype information from at least one case in the outbreak which indicated an imported measles virus. A variety of measles genotypes were found in the measles outbreaks during the post-elimination era; since 2008 genotype D4 has been the most common genotype detected. Measles outbreaks occurred in multiple settings, predominantly in unvaccinated sub-populations in communities that object to vaccination. Reflecting ages of imported cases and their subsequent exposures, outbreaks affected a wide range of ages (median age of 10 months in an outbreak in a day care center in AL to 36 years in an outbreak in an office building in Boston).

Table 3: Summary of Measles Outbreaks by Year, 2001-2011

<b>Year</b>	<b>Measles cases #</b>	<b>Cases associated with outbreaks</b>	<b>Outbreaks #</b>	<b>Outbreak Size Median (max)</b>
<b>2001</b>	116	57 (49%)	10	4 (14)
<b>2002</b>	44	19 (43%)	3	3 (13)
<b>2003</b>	56	27 (48%)	3	11 (13)
<b>2004</b>	37	13 (35%)	2	6.5 (10)
<b>2005</b>	66	40 (61%)	3	18.5 (34)
<b>2006</b>	55	26 (47%)	4	3 (17)
<b>2007</b>	43	18 (42%)	4	4 (7)
<b>2008</b>	140	108 (77%)	7	14 (30)
<b>2009</b>	71	48 (68%)	8	5 (15)
<b>2010</b>	63	14 (22%)	4	3.5 (4)
<b>2011</b>	212	106 (50%)	16	5.5 (21)

Table 4: Measles Outbreaks with 10 or more Cases, 2001-2011

Year	Outbreak Name	State	Cases #	Import Status	Genotype	Setting	1st & last rash onsets	Duration	Median Age	Age Range
2005	Tippecanoe County	IN	34	Imported (Romania)	D4	Church/household	5/16/2005 - 6/24/2005	6 weeks	12 y	9 mo - 49 y
2008	DuPage/Cook County	IL	30	Imported-virus	D4	Homeschool	5/17/2008 - 7/3/2008	7 weeks	10 y	8 mo - 43 y
2011	Hennepin County	MN	21	Imported (Kenya)	B3	Shelter	2/15/2011 - 4/24/2011	10 weeks	23 m	3 mo - 51 y
2008	Brooklyn/Kings County	NYC	21	Imported (Israel, Belgium)	D4	Community	2/17/2008 - 4/25/2008	10 weeks	15 m	5 mo - 11 y
2008	Grant County	WA	19	Imported-virus	D5	Homeschool	4/12/2008 - 5/30/2008	7 weeks	12 y	9 mo - 23 y
2006	Boston	MA	17	Imported (India)	D8	Office	5/5/2006 - 6/31/2006	8 weeks	36 y	23 y - 46 y
2009	Brooklyn	NYC	15	Imported-virus	D4	Community	5/6/2009 - 7/13/2009	10 weeks	24 m	8 mo - 51 y
2001	Adoptees 2001	Multiple	14	Imported (China)	n/a	Orphanage	2/15/2011 - 3/13/2001	4 weeks	10.5 m	9 mo - 46 y
2011	Noble County	IN	14	Imported (Indonesia)	D4	Household	6/3/2011 - 6/24/2011	3 weeks	21 y	15 mo - 27 y
2008	Pima County	AZ	14	Imported (Switzerland)	D5	Medical	2/13/2008 - 5/2/2008	11 weeks	14 y	7 mo - 50 y
2001	South King County	WA	11	Imported (Korea)	H1	Community	1/10/2001 - 2/13/2001	4 weeks	16 y	14 mo - 40 y
2002	Lee County	AL	13	Imported (Philippines)	D3	Day-care	10/19/2002 - 11/15/2002	4 weeks	10 m	9 mo - 50 y
2003	Delaware County	DE, PA	11	Imported (Lebanon)	D4	Boarding school	3/21/2003 - 4/29/2003	6 weeks	17 y	13 mo - 33 y
2003	Honolulu	HI	13	Imported (Marshall Islands)	H1	Community	7/13/2003 - 9/11/2003	9 weeks	11 m	3 mo - 21 y
2008	San Diego	CA/HI	12	Imported (Switzerland)	D5	Community	1/25/2008 - 2/16/2008	3 weeks	6 y	10 mo - 9 y
2004	Adoptees 2004	WA	10	Imported (China)	H1	Orphanage	3/22/2004 - 4/18/2004	4 weeks	12 m	12 mo - 19 y

**Note:**

*Highlighted rows indicate imported-virus outbreaks. For all other outbreaks listed an imported source case was detected.*

Public health responses to recent measles outbreaks have demonstrated the effectiveness of the rapid and thorough outbreak containment measures implemented by state and local health departments. A measles outbreak in Indiana in 2005 resulted from an unvaccinated traveler importing the virus and spreading it into a population of children and adolescents whose parents objected to vaccination. The health department was notified during the first generation of spread. The second generation of case-patients had already been exposed by the time the health department began investigating contacts and implementing isolation and voluntary quarantine measures. Only two additional cases occurred in the third generation before the outbreak ended despite presence of unvaccinated persons in the affected community.<sup>10</sup> State and local health departments spent \$51,945 (\$1,528 per case reported) containing the outbreak. In a measles outbreak in San Diego in 2008, an unvaccinated traveler imported the virus resulting in >800 exposures and 11 additional



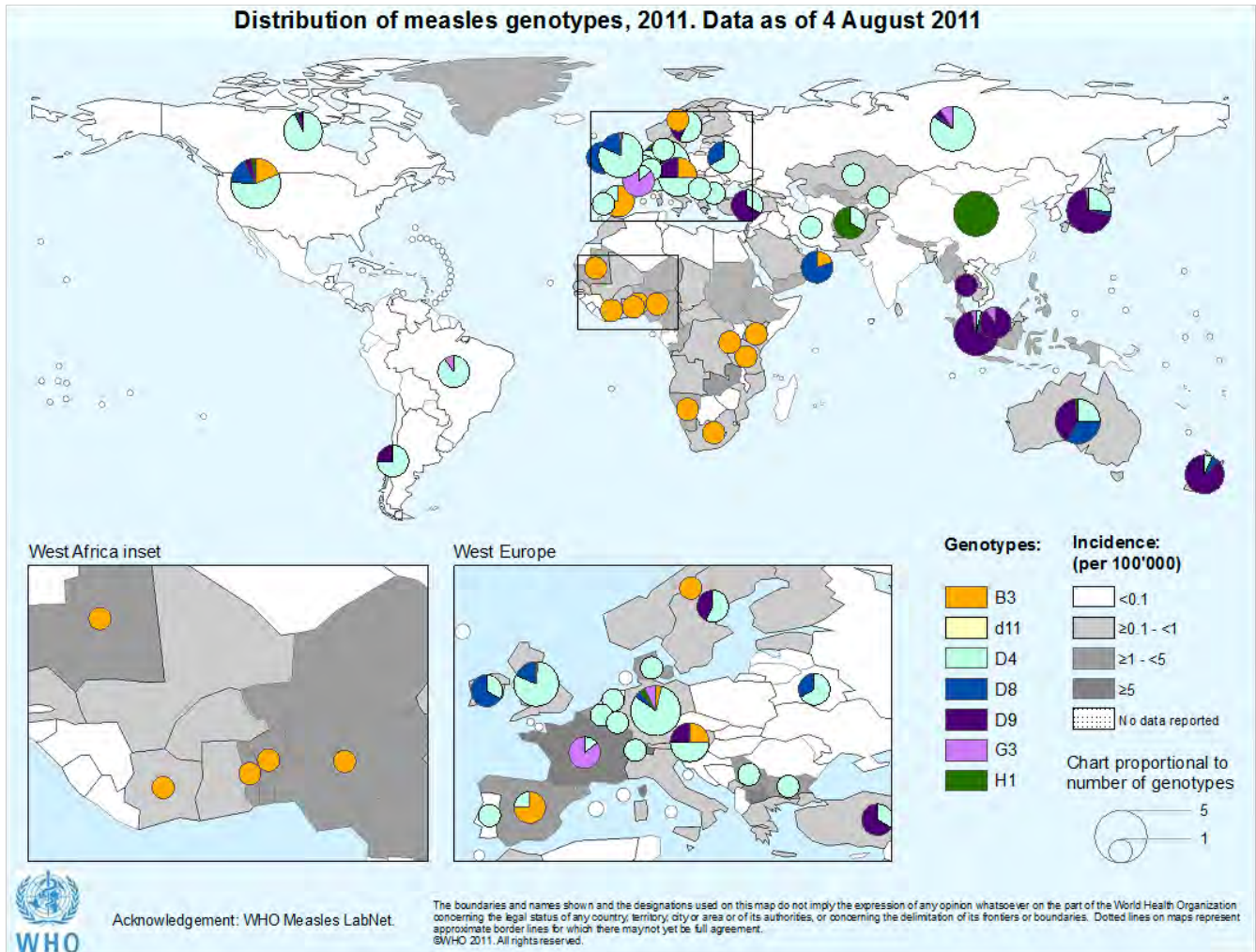
cases. A vigorous public health response that included voluntary quarantine of 73 children whose families declined vaccination during the outbreak, halted transmission beyond the third generation at a public-sector cost of more than \$10,000 per case.<sup>12</sup>

## **Molecular Epidemiology of Measles Viruses in the United States**

Virologic surveillance for measles has improved in the United States, since the last report in 2002 because our understanding of the global circulation patterns of measles genotypes has improved substantially in the last 5 years.<sup>13</sup> Because of the efforts of the WHO Global Measles and Rubella Laboratory Network, measles genotype information has been reported from 131 countries and from every WHO region.<sup>8,14,15</sup> The WHO Measles Genotype Database now has over 10,000 entries and the MeaNS sequence database at the Health Protection Agency in London has nearly 7000 measles virus sequences. This information has been used to define the endemic genotypes in many parts of the world and to track the spread of these endemic genotypes to other parts of the world. Access to sequence and genotype information greatly facilitates our ability to identify the source or suggest a source for imported viruses. This information has helped to generate a detailed picture of the global distribution of measles genotypes measles (Figure 8).

The goal of virologic surveillance is to obtain samples adequate for detecting measles virus from at least 80% of the chains of transmission with  $\geq 2$  confirmed cases.<sup>16</sup> In the United States, genotype information has been obtained from 66% chains of transmission with  $\geq 2$  confirmed cases (Table 5). The proportion of chains with genotype information increased from 50% for 2-case chains and 66% for small outbreaks of 3-5 cases to 93% for larger outbreak of more than 5 cases. For isolated cases, 32% had genotype information (see Table 5 and Measles Surveillance Indicators below).

Figure 8: Global Distribution of Measles Genotypes and Measles Incidence in 2011



**Note:**

Figure 8. Global distribution of measles genotypes and measles incidence in 2011. Colored circles indicate measles genotypes reported to the WHO Database for the year 2011, and the size of the circles is proportional to the number of genotypes reported for the indicated areas (see insert of figure). Countries are shaded in gray to indicate measles incidence rates (see insert in figure). Two areas, Western Africa and Eastern Europe, are also shown as inserts to provide more resolution. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Table 5: Distribution of Sizes of Measles Chains of Transmission\* and Detection of Measles Genotypes, 2001-2011

Year	Total Cases	Isolated Cases		2 Case Chains		Outbreaks with 3-5 Cases		Outbreaks with >5 Cases		All Chains of Transmission*		Genotypes Detected (#)
		Total #	Genotype d # (%)	Total #	Genotype d # (%)	Total	Genotype d # (%)	Total #	Genotype d # (%)	Total #	Genotyped # (%)	
2001	116					7	4 (57)	3	2 (66)	61	15 (24)	D3, D4 (2), D5 (4), D7 (3), H1 (3), H2
2002	44	21	6 (29%)	2	1 (50%)	2	0 (0%)	1	1 (100%)	26	8 (31)	B3, D3 (2), D4, D7 (2), D8 (2)
2003	56	23	5 (22%)	3	0 (0%)	1	0 (0%)	2	2 (100%)	29	7 (24)	D4, D6, D7 (2), H1 (3)
2004	37	14	2 (14%)	5	2 (40%)	1	1 (100%)	1	1 (100%)	21	6 (28)	D3, D8 (3), H1 (2)
2005	66	18	8 (44%)	4	2 (50%)	2	1 (50%)	1	1 (100%)	25	12 (48)	B3 (2), D4 (5), D6, D8 (3), D9
2006	55	26	11 (42%)	1	1 (100%)	3	1 (33%)	1	1 (100%)	31	14 (45)	B3 (2), D4 (2), D5, D6 (2), D8 (2), H1 (3)
2007	43	21	3 (14%)	2	1 (50%)	3	2 (67%)	1	1 (100%)	27	7 (26)	D4 (2), D5 (4), D9
2008	140	27	5 (19%)	3	1 (33%)	3	3 (100%)	6	6 (100%)	39	15 (39)	D4 (9), D5 (4), H1 (2)
2009	71	17	7 (41%)	3	1 (33%)	4	3 (75%)	4	3 (75%)	28	14 (50)	D4 (6), D8 (4), H1 (4)
2010	64	37	16 (43%)	6	3 (50%)	4	3 (75%)	0	0	47	22 (47)	B3 (4), D4 (5), D8 (5), D9 (6), H1 (2)
2011	212	82	36 (44%)	12	8 (67%)	8	7 (88%)	8	8 (100%)	110	59 (54)	B3 (1), D4 (35), D9(7), D8 (6), G3(6), H1(3)
<b>Total</b>	904					31	21 (68%)	25	24 (96%)	383	165 (46)	

**Note:**

\*For the purposes of this table isolated cases are considered as chains of transmission.

During 2001 to 2011, a total of 12 different measles virus genotypes (of 24 recognized genotypes) were identified in the United States with 3-6 different genotypes identified each year. The most frequently identified genotypes have changed over the decade: D5 in 2001 and 2007, D3, D7 and D8 in 2002 and 2005, H1 in 2003 and 2006, D8 in 2004, D9 in 2010 and D4 in 2005, 2008, 2009 and 2011 (Table 5). The evidence indicates that there is no endemic genotype of measles virus in the United States. The proportion of the different measles genotypes detected in imported measles cases in the United States varies from year to year (Table 5). This variation is due to changes in the pattern of endemic genotypes in the countries that are frequently the sources of imported measles cases, notably countries in Western Europe. For example, genotype D7 was the most frequently detected genotype in Europe in 2000-2003. Later in the decade, genotype D5 was associated with large outbreaks in Europe as well as in Japan. Since 2008, genotype D4 has been the most

frequently detected European genotype. In other source countries such as China, India and Sub-Saharan African countries, the pattern of endemic genotypes has remained the same over the last 10 years.<sup>14</sup> However, all of the genotypes detected in the United States are associated with endemic circulation in other regions of the world.

As previously mentioned, the increase in importations of D4 genotype in recent years has been linked to large measles outbreaks occurring in many countries in Europe. The measles genotypes detected in the U.S. did not occur in a pattern which indicates the presence of an endemic genotype. There is a wide variety of measles genotypes detected which reflect multiple imported sources of virus. Most are from known imported cases or chains of transmission with imported sources, and the genotype is typically consistent with the known country of origin. Even among the imported-virus cases, which do not have a detected epidemiologic link to importation, there is a wide variety of genotypes which suggests multiple undetected imported cases as the source of these cases, rather than an endemic chain of transmission, which would be represented as a single genotype.

Between 2008 and 2011, there have been multiple imported-virus cases in which genotype D4 was detected. By definition, an epidemiologic link to importation was not detected for these cases. Therefore, the distribution of these cases must be carefully analyzed to determine if endemic transmission occurred. In Table 6, we plotted the occurrence of imported-virus cases with genotype D4 by county and month for 2008-2011, listing the number of cases in each box and highlighting the cells in yellow. We added the unknown source cases (highlighted in red) from this period because some of these might have genotype D4. Finally, we also included the imported and import-linked cases from chains with genotype D4 (highlighted in green) to demonstrate the genotype D4 virus importation pattern. It should be noted that this two page table includes only those counties which had cases with D4 genotype or unknown source cases during this 4-year period. More than 3000 counties did not have such cases and these are not shown in the table.

Inspection of Table 6 shows that the occurrence of genotype D4 cases across space and time is scattered, with a few exceptions circled in red. Several of these clusters of cases occurred in counties in New York City (Table 4 and Table 6). New York City includes 5 counties (called boroughs) and has a population of > 8,175,000 and 36.8% of residents are foreign born, an indication of a high level of international travel (US Census, 2010 <http://quickfacts.census.gov/qfd/states/36/3651000.html>). Kings County, in New York City, reported cases of measles associated with genotype D4 in 2008, (24 cases) 2009 (20 cases) and 2011 (6 cases). There were internationally imported cases with genotype D4 interspersed among the imported virus cases in 2008. Long intervals of 12 and 26 months with no reported genotype D4 or unknown source cases occurred between the outbreak periods. There was also a mix of imported genotype D4 cases (6 cases) and imported-virus genotype D4 cases (3 cases) and 1 unknown source case in New York County (New York City) in 2011. The frequent importation of genotype D4 measles cases into New York City provides a reasonable explanation of the repeated detection of genotype D4 clusters, although epidemiologic links between the imported cases and imported virus cases were not detected. The long intervals with no clusters of unknown source cases or genotype D4 imported-virus cases in New York City indicates it is unlikely an endemic chain of transmission of genotype D4 has occurred. In addition to the New York City cases, a large genotype D4 outbreak was reported in Illinois in 2008 (Table 4 and Table 6). Though a source case was not identified, the outbreak followed a visit to Italy by a girls' choir and parents of some of the

cases reported a likely source case whose family declined to be interviewed. There were no genotype D4 or unknown sources cases reported in Illinois following this outbreak. Also in 2011, there was a small cluster of unknown source cases in Massachusetts (as described above) and a small cluster of imported virus cases in Pennsylvania.

The number of imported or import-linked cases with genotype D4 increased from 4 in 2010 to 47 in 2011. The predominance of the D4 genotype identified from cases in the United States reflected the widespread transmission of a single lineage of genotype D4 measles virus in the UK and Europe with a surge in cases during 2011.<sup>17</sup> The parallel increase in imported-virus genotype D4 cases from 3 in 2010 to 43 in 2011 suggests these cases result from transmission from imported cases, either via undetected imported cases or from an undetected link to reported imported cases. The imported-virus genotype D4 cases did not occur in a continuous or focused pattern suggestive of an endemic chain of transmission, even when the unknown source cases are included.





## IV. Epidemiology of Rubella (2004-2011)

### Basic Epidemiology

Since the initial verification and documentation of the elimination of endemic rubella and CRS from the United States in 2004, the incidences of rubella and CRS have remained extremely low. Data from a variety of sources including rubella epidemiology, surveillance, molecular epidemiology, population immunity and rubella epidemiology in Latin American countries provided continued evidence that endemic rubella elimination, was maintained through 2007.<sup>18,19,20,21</sup> From 2008 through 2011, the epidemiology of rubella has not changed. Since 2004, the annual reported rubella incidence has consistently remained below 1 case per 10 million population and the average annual reported CRS incidence for this period is less than 1 case per 5 million births. Annually, from 2004 to 2011, the median number of reported rubella cases was 10 (range 3–18). In the past three years, the reported numbers of rubella cases were the lowest on record, with only 4 cases in 2009, 7 in 2010, and 3 thus far in 2011 (Table 7). Among the cases where country of birth is known, the majority (33; 55%) were born overseas. Eighty-seven percent of rubella cases were unvaccinated or had unknown vaccination status; 10% had 2 doses and 3% had 1 dose. The median age was 29 years (range 2-61 years); 84% of rubella cases occurred among adults with the majority occurring among adults 20-49 years.



Table 7: Importation Sources of Rubella Cases, United States, 2004-2011

Year	Cases #	Imported # (%)	Import Sources	Genotyped # (%)	Genotypes
2004	10	3 (30%)	Bangladesh, India, Senegal	0 (0%)	
2005	11	2 (18%)	Malaysia, France	1 (9%)	1E
2006	11	5 (42%)	Bangladesh(2), France, Philippines (2)	0 (0%)	
2007	12	3 (25%)	Uganda, Brazil, Russia.	4 (33%)	1G (1), 2B (3)
2008	18	9 (50%)	Italy, Cape Verde, India (3), China, Mexico, Argentina, Africa/United Kingdom	4 (22%)	1E (2), 2B (2)
2009	4	1 (25%)	Italy	1 (25%)	2B
2010	7	4 (57%)	Kenya, Philippines, India, Vietnam	4 (57%)	1G, 1j, 2B (2)
2011	3	2 (67%)	Indonesia, India	2 (67%)	1E, 2 B

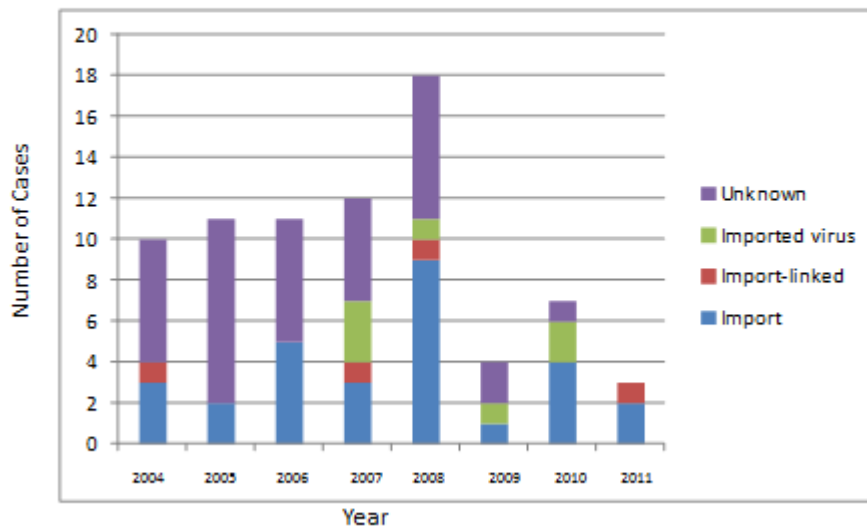
During 2004-2011, geographic distribution of reported rubella cases was not clustered. In total, 76 cases were reported from 58 counties, with no county reporting more than 4 cases for the entire period. Cases were reported in 65 weeks (14% of weeks during this period).

Of the 76 rubella cases reported, 10 were confirmed based on IgM positive serology in previously vaccinated persons. Due to the extremely low prevalence of rubella in the United States, and high rubella vaccine effectiveness, IgM positive results in vaccinated individuals are expected to be almost all false positives. Differentiating between a false positive IgM and a rubella case was not possible in 8 of these previously vaccinated cases because additional laboratory tests (avidity, repeat IgM, IgG testing) were not conducted. The remaining two cases were tested by the CDC laboratory using additional tests and both were considered IgM false positives. However, these two cases were still reported by state health departments through NNDSS as confirmed rubella cases to the CDC.

## Importation Classifications

During 2004–2011, there were a total of 29 (38%) imported cases, 4 (5%) import-linked cases, 7 (9%) imported-virus cases, and 36 (47%) unknown source rubella cases. Overall, 40 (53%) rubella cases were importation-associated. The distribution of importation classifications by year is shown in Figure 9. Importations occurred from a variety of countries; the most common being from India (6 importations) with four importations from Europe (Table 7).

**Figure 9. Rubella Cases by Import Status  
United States, 2004-2011**



## Unknown Source Cases

From 2004-2011, the total number of unknown source rubella cases was 36, the median was 6 cases per year, and the range was 0-9 cases per year (Figure 9). California reported a total of 6 unknown source cases during the period, which was the most reported by any state. Three counties (San Francisco, CA; Los Angeles, CA; and Hillsborough, NH) each reported 2 unknown source cases and 30 counties each reported one unknown source case. The remaining 99% of U.S. counties reported no unknown source cases during 2004-2011.

## Outbreaks

During 2004–2011, 2 rubella outbreaks were reported, each consisting of 3 cases. In 2005, 2 cases occurred in attendees of an international conference in Massachusetts with spread to one of their spouses. The genotype of the rubella virus could not be determined. In 2007, an outbreak occurred among 3 foreign-born college students with history of recent international travel. Viral specimens identified a genotype 2B virus. No source of exposure was identified for either outbreak. A total of 8 cases occurred in 4 chains of transmission of 2 cases each. The remaining 62 (82%) cases were

isolated cases. Despite intensive case investigation, no epidemiologically linked cases were detected in association with these isolated cases.

**Congenital Rubella Syndrome**

From 2004–2011, 4 cases of infants with CRS were reported (Table 8). The first infant was born in 2003, and classified as an imported case from Nigeria. The second infant was born in 2004, and classified as an imported case from Cote d’Ivoire. Both mothers of infants with CRS had unknown vaccination status and were born outside the United States, in Nigeria and Liberia, respectively. The third infant with CRS was born in 2008, with maternal exposure to rubella occurring outside of the United States, most likely in India. The mother’s vaccination status was unknown. The fourth infant was also born in 2008. The mother of this case had documented receipt of one dose of MMR vaccine, she did not travel outside of the United States during pregnancy and the source of the rubella infection is unknown. This is an unusual case, as reports of CRS in children of vaccinated mothers are extremely rare.

Table 8: Line Listing of CRS Cases 2004-2011

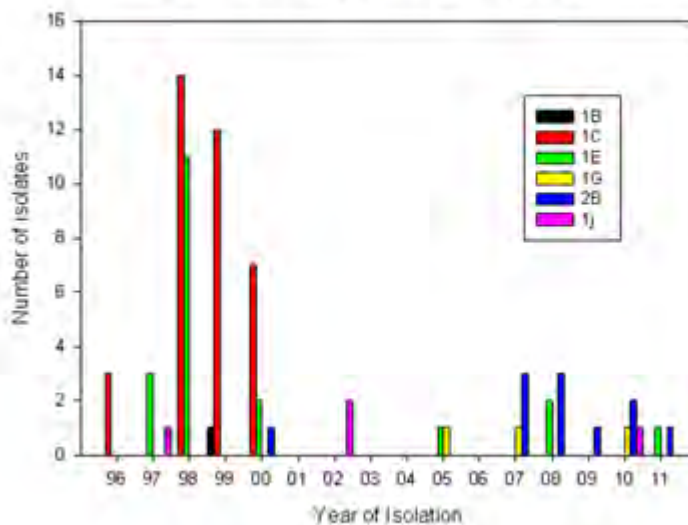
Birth Year	State	Year Reported	Age at Diagnosis	Exposure Setting Details	Mother's Country of Birth	Import Source	Genotype
2003	CA	2006	21 mo	Nigeria, child born in US	Nigeria	Nigeria	unsuccessful
2004	NH	2005	10 wks	Mother in Ivory Coast in early pregnancy, child born in US	Liberia	Ivory Coast	1G
2008	CA	2009	6 mo	Mother in India February 2008 and Singapore and China in June 2008; conceived out of the US	Unknown but US resident	Most likely India	2B
2008	NJ	2009	7 mo	Child born in US, mother not outside of US during pregnancy, no known rubella exposure?	US	Unknown	unsuccessful

**Molecular Epidemiology of Rubella Viruses in the United States**

Genetic analysis of wild-type rubella viruses was important for reaching the conclusion in 2004 that rubella and CRS had been eliminated in the United States.<sup>20</sup> One critical observation and

conclusion in 2004 was that genotype 1C viruses, which were endemic in and exclusive to Central and South American countries, were commonly found in the United States from 1996-2000,<sup>20</sup> but after 2000, when rubella control in Central and South American countries improved,<sup>22</sup> importations of viruses of genotype 1C into the United States ceased (Figure 10). Thus, even though viruses of genotype 1C were common during this period, they were not considered endemic. In addition, viruses of genotype 1E found until 2000 were from only 7 independent events (including 3 known importations) and thus were not considered endemic viruses.<sup>19, 20</sup>

**Figure 10. Number and Genotypes of US Rubella Viruses, 1996-2011**



A summary of the global distribution of rubella viruses of different genotypes has recently been published.<sup>23</sup> Summaries of the genetic analysis of wild-type rubella viruses found in the United States until 2007 and until the end 2010 showed no evidence of endemic circulation of rubella virus in the United States.<sup>21,23</sup> Indeed, analysis of viruses from 2005 through 2010 showed the United States was one of the top countries identifying imported viruses.<sup>23</sup>

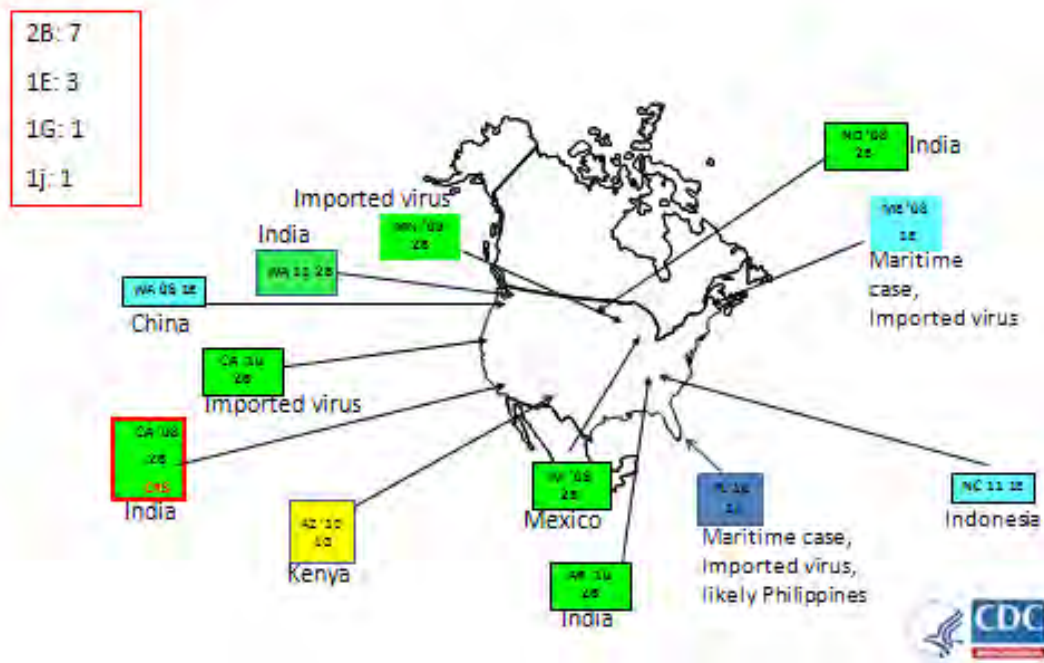
Since the elimination of rubella and CRS from the United States, the cases occurring in the United States have received intense investigation, including, when possible, determinations of the genotypes of the viruses. Even though most cases are isolated, single cases, from a total of only 34 confirmed cases of rubella and CRS, including 16 imported rubella cases from 2008 until through September 30, 2011, 12 viruses representing 4 different rubella genotypes (1E, 1G, 1J and 2B) have been identified. Viruses of genotype 2B are now found in the United States; viruses of this genotype are now widely distributed in the world.<sup>23</sup>

Descriptions of viruses found in the United States from 2004 through 2007 have already been published.<sup>19,21</sup> These descriptions led to the conclusion that there was no evidence of endemic circulation of any rubella virus in the United States during this period, and specifically no evidence

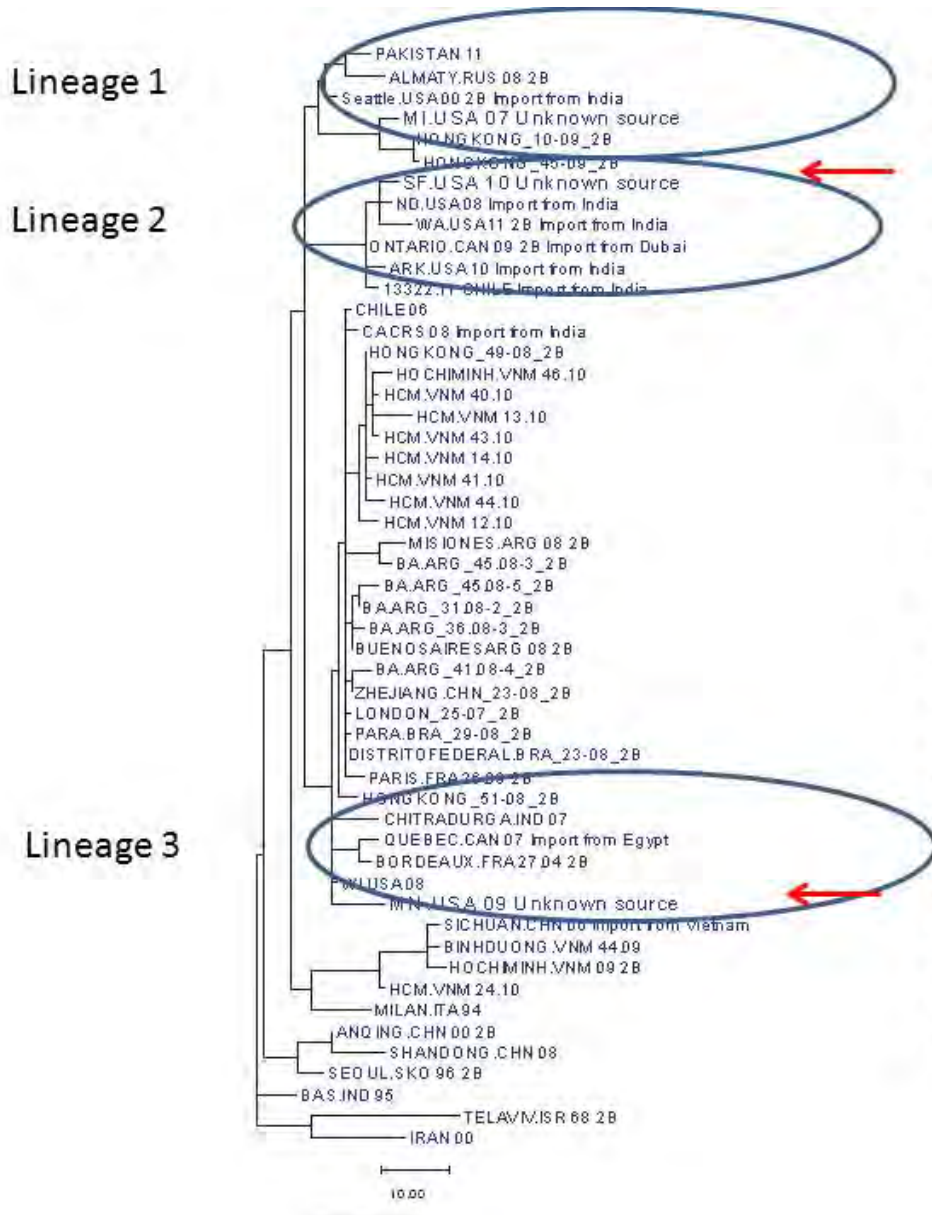
of circulation of genotype 1C viruses. The accumulation of sequences as a result of the laboratory's role as a Global Specialized laboratory has allowed further characterization of the genotype 2B virus from 2007, which was not confidently classified<sup>7</sup>; there is now phylogenetic evidence further confirming that this virus (MI USA 07) was not endemic and likely originated in India/Pakistan (see below). Cases from this outbreak are now confidently classified as imported-virus cases.

A summary of viruses found in the United States from 2008 through 2011 showed that 7 viruses had genotypes consistent with the known source of the imported case (Figure 11). The exposure for the case occurring in Wisconsin in 2008 occurred in Mexico, but viruses of genotype 2B were not known to be circulating in Mexico. In 2006, a virus or viruses of genotype 2B caused a large epidemic, predominantly in Brazil, Chile, and Argentina, which lasted for more than 1 year. Although there is no direct epidemiologic link, the virus imported into Wisconsin from Mexico is genetically similar to viruses causing this large epidemic in South America, suggesting an undetected link between this large epidemic and the imported case exposure which occurred in Mexico. Two viruses were from cases infected on board ships with diverse populations, and correlation of genotypes with source country for these infections was not possible; nevertheless, these were classified as imported-virus cases (Figure 11).

Figure 11: Imported Rubella Viruses for which Genotypes were Determined, 2008-2011



Two cases which were not epidemiologically linked to importation both had rubella genotype 2B. Although rubella viruses of genotype 2B are not known to have ever been endemic in the United States, these cases, which occurred in Minnesota in 2009 and in California in 2010, merit additional discussion. These viruses from Minnesota and California were compared with a recently accumulated collection of sequences of other viruses of genotype 2B from various countries. These two viruses of genotype 2B are from two different lineages (Figure 12). Thus, the molecular evidence combined with the temporal and geographic separation indicates these two genotype 2B rubella cases are not the result of endemic circulation. These two cases are classified as imported-virus cases. Note that the virus identified as MI USA 07 is a genotype 2B lineage 1 virus.



**Figure 12. Phylogenetic analysis of viruses from Minnesota (2009) and California (San Francisco) (2010) (arrows).**

Sequences of these viruses were compared with sequences of other representative viruses of genotype 2B in CDC's collection using the 739 nucleotide window accepted for classifying wild-type rubella viruses and the PAUP Maximum Parsimony program. Groups of viruses considered to be from different lineages are circled.

In summary, virologic surveillance and molecular analysis has helped reclassify some rubella cases from unknown source cases to imported virus cases. There has been considerable virologic surveillance for rubella viruses recently. Molecular epidemiologic evidence in combination with epidemiologic evidence does not support endemic transmission of rubella during any period between 2005 and September 30, 2011.

## V. Quality of U.S. Measles, Rubella and CRS Surveillance and Outbreak Response

As described in surveillance methods, the U.S. surveillance system for measles, rubella and CRS is a passive reporting system to CDC but reports are expected within 24 hours of disease confirmation. Once a case is reported, the system changes immediately to active investigation mode to fully investigate the case and to identify and respond to contacts of cases to prevent further transmission and identify additional cases.

In the original documentation of elimination in 2004, the concern of potential significant underreporting of rubella was addressed by going to specific areas to actively look for cases. Retrospective studies of state labs, HMOs, and intensive reviews in places expected to see importations (New York, California, North Carolina, along the Mexican border) were completed. No additional clinical or laboratory confirmed cases were found, indicating that significant outbreaks were not being missed.<sup>24</sup> Because the surveillance system and epidemiology for measles and rubella have not changed significantly since the original documentation of elimination, such studies were not repeated for this report.

All surveillance systems are imperfect, and it is expected and understood that some cases of measles, rubella and CRS go undetected or unreported in the United States. To verify and document the sustained elimination of endemic measles, rubella and CRS we must determine if the surveillance and public health response system is adequate to detect endemic measles or rubella transmission, including responding to outbreaks, if they were occurring. To assess this, we examined the following topic areas:

### **Detection of Imported Cases of Measles and Rubella**

The U.S. surveillance system consistently detects imported cases of measles and rubella (Figures 3, 4, 5, 9 and 11) despite potential challenges that imported cases of measles or rubella may present with respect to surveillance. Many imported cases occur in foreign visitors who may not have access to care or be unfamiliar with the U.S. health care system and may be less likely to seek health care. Patients may return to their home country early in the course of their disease, before a diagnosis is made.

For both measles and rubella, a significant proportion of the cases detected in recent years are international importations. Although imported cases are occasionally detected retrospectively by contact tracing from another case, most often they are detected in the absence of transmission or before transmission has occurred. Some imported cases go undetected. However, a surveillance system which consistently detects imported cases would be unlikely to miss the large chains of transmission, which would be necessary to constitute endemic transmission of measles or rubella. For measles, where ~ 30 importations are detected every year, it is important to reiterate that the vast majority of imported measles cases (84%) do not result in any spread cases and only 7.5% over the last decade resulted in outbreaks.

Also, CRS surveillance detects imported CRS cases (Table 8). Of the four CRS cases reported from 2005-2011, three were imported and only one unknown source CRS case was identified.



## **Detection of Isolated Cases and Short Chains of Transmission**

The U.S. surveillance system consistently detects isolated cases of measles and rubella and small chains of transmission and therefore would be unlikely to miss large chains of transmission if they were occurring. For example, of the 444 chains of measles transmission shown in Table 5, 378 (85%) were isolated cases or two case chains. All reported rubella cases were either isolated cases or occurred in 2 case chains with only 2 outbreaks (3 cases each).

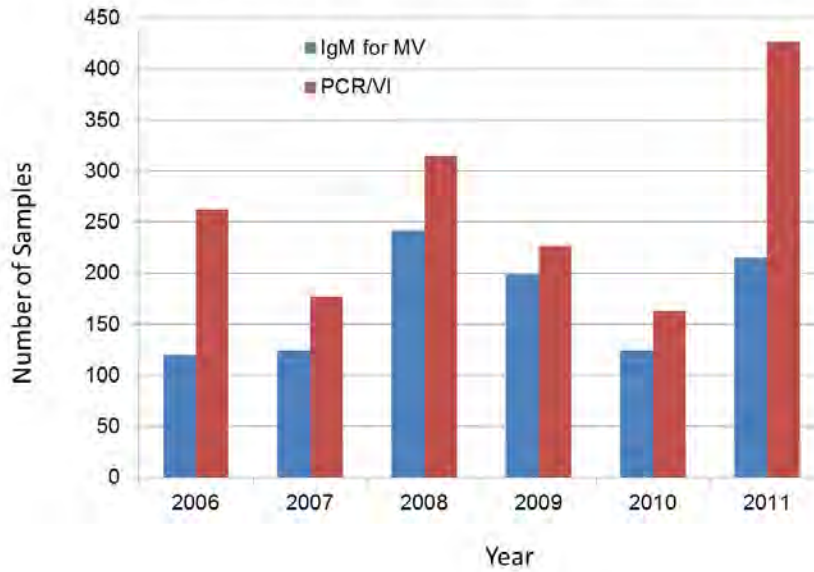
## **Rapid Public Health Response to Measles and Rubella Cases and Outbreaks**

Upon receiving a report of a suspect measles or rubella case, state and local health departments implement active investigation and response. This means that they attempt to identify the source of infection, assess potential transmission, identify contacts of the case-patient (e.g., household, child care, and other close contacts), obtain immunization histories, vaccinate persons without presumptive evidence of immunity, isolate case-patients, quarantine contacts of case-patients without presumptive evidence of immunity who refuse vaccination, and collect specimens for virus detection. State and local health departments promote awareness about the outbreak via Epi-X, Health Alert Network messages, and media interviews. They also follow up with persons without presumptive evidence of immunity in efforts to reveal previously undiagnosed and unreported cases. This rapid and thorough response has been an important strategy for limiting the spread from measles and rubella cases in the U.S.

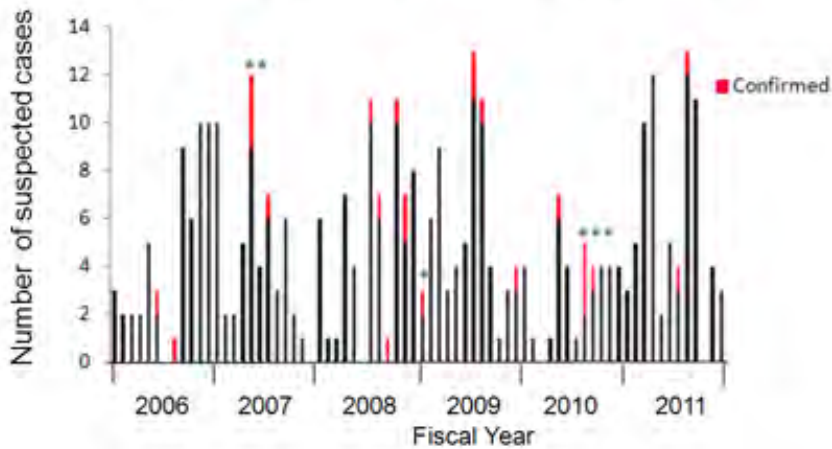
## **Laboratory Testing Volume at CDC**

The amount of laboratory testing for measles, rubella and CRS is not routinely reported in the United States. In the last 6 years, CDC's measles laboratory has performed confirmatory measles IgM testing on over 1000 serum samples and attempted to detect measles virus in over 1500 specimens (Figure 13). In order to assess the continuation of adequate laboratory activities in the United States since 2007, the temporal and spatial separation of samples referred to CDC's Rubella reference laboratory was summarized. No temporal dependence of the samples from suspected rubella and CRS cases received by CDC for fiscal years 2006 through 2011 was observed (Figure 14). The maximum number of confirmed cases in any month during the years 2008 through 2011 (fiscal year ending September 30, 2011) was 3 in May 2010, but these cases were from 3 geographically distant states. From 2006 through 2011 (fiscal years), the minimum number of states referring specimens was 12, and the maximum was 24; no spatial distribution of the states referring specimens was observed (Figure 15). Furthermore, the states referring specimens varied over the years. CDC's laboratory was engaged by most states when highly suspect cases occurred, even though the incidence of rubella and CRS is very low. Collectively, these data show that there is no significant change in laboratory activities in support of rubella and CRS surveillance in the United States from 2006 through 2011.

**Figure 13. Measles Samples Referred to CDC for Confirmatory and/or Reference Testing: 2006-2011**



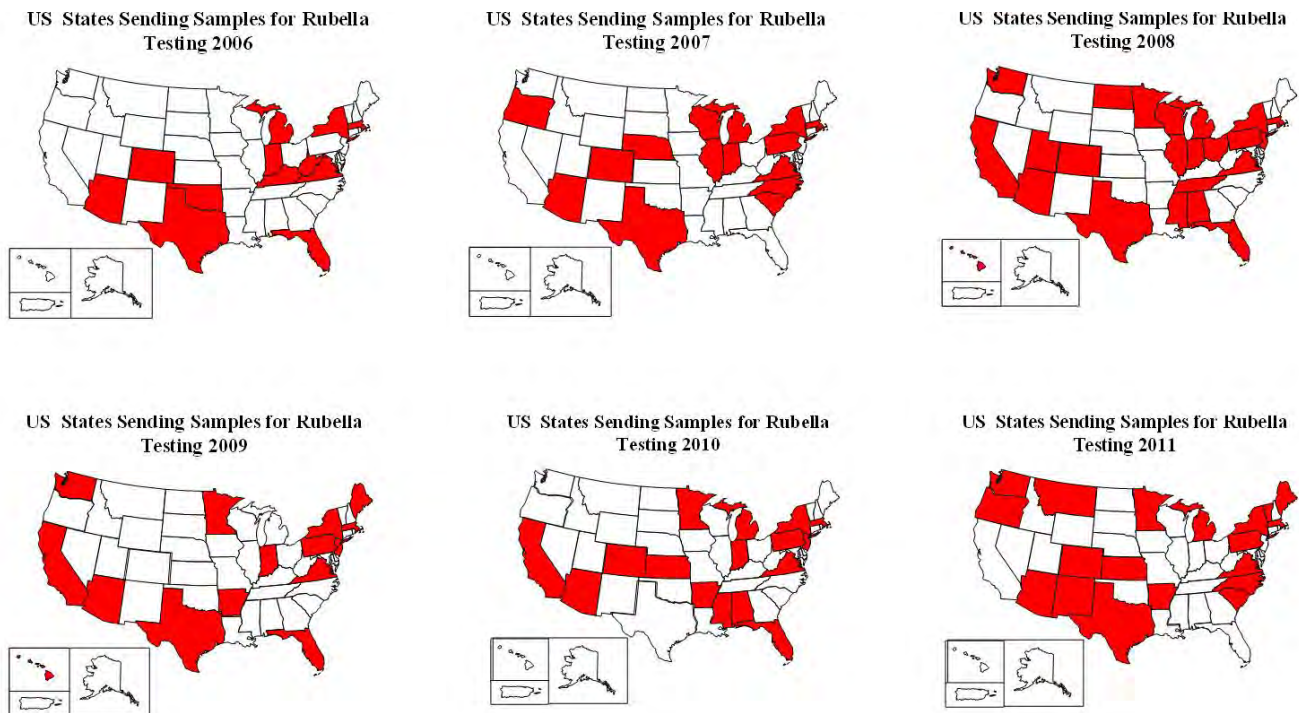
**Figure 14. Specimens Received Monthly from Suspected Rubella and CRS Cases for Testing at CDC Laboratory**



- \* Confirmed case counted in calendar year 2008.
- \*\* Confirmed cases are from an outbreak in MI.
- \*\*\* Confirmed cases were from VA, CA, and FL.



**Figure 15. States Submitting  $\geq 1$  Specimen to the CDC Rubella Laboratory for Case Confirmation, 2006-2011**



For fiscal years 2006 through 2011, the testing volume in the CDC rubella laboratory has remained relatively constant (Table 9). In 2006 a diagnostic RT-PCR was used to help classify cases; in 2007, the real-time assay for rubella RNA was implemented. An update of the maintenance of rubella and CRS elimination through 2007 was recently published.<sup>19</sup> Since that time CDC has been involved in laboratory testing used for the classification of approximately 50% of the confirmed cases of rubella and CRS occurring in the United States. CDC rubella laboratory does not routinely test all sera that test negative for measles IgM but conducts such testing when the submitter requests testing for both measles and rubella. From 2004 – 2011, 131 such tests were requested. Fourteen of these were IgM positive or equivocal of which 5 were sera from recently vaccinated persons. On further investigation (avidity, repeat IgM, IgG testing), 5 were classified as rubella cases and 4 were determined to not be rubella cases. Thus, from rash illness surveillance for suspect cases that were suspected as either measles or rubella, less than 4% (5/131) were rubella cases. The identification of vaccine associated rash illness in these suspect cases is also an indicator of good surveillance.

Table 9: Number of Rubella Tests Performed at CDC, 2006-2011

<b>Fiscal Year+</b>	<b>Rubella ELISAs</b>	<b>Rubella IgG Avidity</b>	<b>Diagnostic RT-PCR</b>	<b>Virus Isolations</b>	<b>Total</b>
<b>2006</b>	63*	10	6	20	<b>99</b>
<b>2007</b>	53	15	17	25	<b>110</b>
<b>2008</b>	92	26	51	14	<b>183</b>
<b>2009</b>	82	20	48	30	<b>180</b>
<b>2010</b>	48	19	28	17	<b>112</b>
<b>2011</b>	77	29	27	7	<b>140</b>

**Note:**

\*All specimens routinely tested for IgM and IgG.

†Fiscal Year from October 1 to September 30.

**Monitoring Indicators for Measles and Rubella Surveillance**

**Data reported via National Notifiable Diseases Surveillance System (NNDSS)**

Surveillance indicators for measles and rubella cases reported through NNDSS and transmitted to CDC through electronic reporting systems for the time period 2001-2010 are shown in Table 10. For both measles and rubella, the proportion of case investigations with complete data received through the NNDSS (medians 73% and 60% respectively) warrants further efforts by state and local health departments to transmit, and for CDC informatics to receive, sufficient information to ensure high quality monitoring of these diseases in the post elimination era. For measles, this indicator has declined from 96% in 1996-1998. However all other measles surveillance indicators have improved including median number of days from symptom onset to public health report (median from 4 days in 1996-1998 to 3 days for 2001-2010), percent of confirmed cases with laboratory confirmation has improved from 79% to 83%, percent of cases with imported source increased from 30% to 45% and percent of cases with viral specimens sent to CDC increased from 14% in 1998 to 36% from 2001-2010. These comparisons provide reassurance that surveillance quality for measles has not changed substantially over the last decade and has potentially improved. The indicator of proportion of cases with imported source is a less useful indicator, perhaps, than the proportion of cases that are import associated, reported earlier in this document as 88%. For rubella, reported cases are sufficiently low in the United States that some surveillance indicators may be less useful than others. It is reassuring that 88.5% of confirmed cases are laboratory confirmed and given that approximately 50% of rubella infections may be sub-clinical, detecting the source of the case is frequently not possible. In summary, especially for measles where the same indicators were analyzed and reported for the period 1996-1998 for documentation of measles elimination as for this report, surveillance indicators have generally improved and suggest that surveillance is

adequate to detect measles cases and outbreaks. Nevertheless, there is clearly room for improvement including completeness of case investigations, collection of measles virus specimens from cases for genetic analysis. The CDC and health departments need to continue efforts directed at health care professionals to ensure the recognition, proper diagnostic workup, and reporting of measles.

***Data reported to CDC/NCIRD: completeness of surveillance data for measles and rubella***

Data received via NNDSS may be artificially incomplete due to technical issues with the informatics system. To compensate for these shortcomings, and to ensure timely reporting to and assistance from CDC, CDC NCIRD collects detailed information directly from the state on every measles and rubella case. PAHO has identified 10 surveillance variables that are critical to quality surveillance data. The percent completeness of these data elements for measles and rubella cases reported to CDC for 2008-2011 is shown in Table 11. Note that CDC does not routinely collect all of these variables from state health departments, but states are able to provide these numbers if requested.

Table 10: Surveillance Indicators for Measles and Rubella  
United States 2001-2010

	Number of Cases*		Percent Completeness of Information for 10 Key Variables**		Median Number of Days from Symptom Onset to Public Health Report		Percent of Confirmed Cases that are Lab Confirmed		Percent of Cases with Imported Source		Percent of Measles Cases with Viral Specimen Sent to CDC	Percent of Rubella Cases in Females with Known Pregnancy Status
	Measles	Rubella	Measles	Rubella	Measles	Rubella	Measles	Rubella	Measles	Rubella	Measles	Rubella
2001	116	23	87	69	3	11	84	84	47	17	21	73
2002	44	18	80	54	3	16	83	91	41	44	45	75
2003	56	7	68	39	6	8	93	100	42	0	46	40
2004	37	10	56	47	3	3	76	86	73	30	24	67
2005 <sup>†</sup>	66	11	79	66	3	15	59	78	36	18	70	67
2006 <sup>†</sup>	55	11	75	80	1	9	58	73	56	27	45	67
2007 <sup>†</sup>	43	12	78	49	2	4	83	100	68	17	35	33
2008 <sup>†</sup>	140	16	59	76	4	10	82	75	18	38	28	38
2009 <sup>†</sup>	71	3	70	77	2	1	71	100	28	33	30	33
2010 <sup>†</sup>	63	5	48	50	2	23	84	100	63	60	38	50

**Note:**

\*Confirmed and unknown case status

\*\* Clinical case definition, hospitalization, lab testing, vaccine information, date reported to health department, transmission setting, outbreak related, epidemiologic linkage, date of birth, and onset date.

<sup>†</sup>Data from states (AL, AR, ID, MD, ME, MT, NE, NM, NV, RI, SC, TN, TX, VA, VT, WY) with NEDSS Based Systems may not accurately reflect state-based data or surveillance effort.

Table 11: Percent Completeness of 10 Key Surveillance Variables for Measles and Rubella, United States, 2008-2011

Variable	Measles (n=497)	Rubella (n=29)
Place of Residence	100%	100%
Sex	99%	100%
Age/Date of Birth	100%	100%
Date of Reporting	99%	100%
Date of Investigation	NRC*	NRC*
Date of Rash Onset	100%	100%
Date of Blood Draw	NRC*	NRC*
Fever (Y/N)	NRC*	NRC*
Vaccination Status	100%	100%
Travel History	100%	100%

**Note:**

*\*NRC = Not routinely collected from states at CDC, but states can furnish these numbers upon request.*

## VI. Assessment of Measles and Rubella Population Immunity

Population immunity to measles and rubella has been measured by National Health and Nutrition Examination Survey (NHANES) serology. The NHANES is conducted by the National Center for Health Statistics, CDC, to provide nationally representative statistics on the health and nutritional status of the non-institutionalized U.S. civilian population through household interviews, standardized physical examinations, and the collection of biologic samples in special mobile examination centers.<sup>25</sup> Serology tests used for immunity assessments may differ between studies and this must be considered when interpreting reported seroprevalence levels. Presence of antibody may not be a correlate of protection but does indicate prior exposure to the virus.

### Measles Population Immunity

National-level NHANES data from 1999-2004 found a seroprevalence of measles antibodies of 95.9% among persons in the U.S. population aged 6–49 years (Table 12).<sup>26</sup> Measles seropositivity was at or above the estimated threshold of 93%– 95% that is needed for elimination of measles in all birth cohorts except the 1967–1976 cohorts which had a seropositivity of 92.4%.<sup>26</sup>

Table 12: Seroprevalence of Measles Antibody in 4 U.S. Birth Cohorts, NHANES, 1999-2004

Birth Year Cohorts	Participants (N)	Seropositive Proportion, % (95% CI)
1949-1966	3360	96.6 (95.5-97.5)
1967-1976	2321	92.4 (90.8-93.9)
1977-1986	5288	96.4 (95.5-97.2)
1987-1998	5080	97.7 (96.4- 98.6)
All Cohorts	16,049	95.9 (95.1-96.5)

Sub-national level studies also demonstrate high levels of measles seroprevalence or immunity. Using an enzyme immunoassay (EIA), a 1999 study of U.S. residents aged  $\geq 20$  years determined that 93% had antibodies to measles virus.<sup>27</sup> In a longitudinal study of rural Wisconsin kindergarten and middle school students from 1994/95-2006/07, measles antibody, measured by neutralizing antibodies with a cut off level that is accepted as a correlate of protection, persisted in all vaccine recipients available for follow-up 10 years after a second dose of MMR vaccine was administered. No seronegative results were detected and 4.9% (18/364) had low titers.<sup>28</sup>



## Rubella Population Immunity

Although national-level data for the seroprevalence of rubella antibodies is not available for the post-rubella elimination era, NHANES data from 1999-2004 indicated national seroprevalence for rubella antibodies, measured using an EIA test with a cut off level that is accepted as a correlate of protection among persons aged 6-49 years was 91.3% (Table 13).<sup>29</sup> Thus, population rubella immunity levels were at or above the modeled threshold for elimination of rubella virus of 85%–90%,<sup>30</sup> Increases in rubella seropositivity from the 1988–1994 to the 1999-2004 study periods were most evident in groups targeted by immunization programs: school-age children of both sexes and women of childbearing age. In contrast, no significant change in immunity was seen among persons who were not the target of immunization efforts: adult males and persons born in the pre-vaccine era (born before 1957).<sup>29</sup>

On a smaller scale, a study on rubella seroprevalence was done during 2006-2008 among 477 newly hired healthcare personnel at a hospital in North Carolina who were born before 1957, and thus considered immune by age, who could not provide written evidence of immunity to rubella. Serologic testing revealed that 14 (3.1%) lacked detectable levels of antibody to rubella.<sup>31</sup>

In a longitudinal study in rural Wisconsin of 307 kindergarten and 306 middle school children from 1994/95-2006/07, 10% of the kindergarteners were seronegative, and 43% of the middle school children had the lowest detectable titer 12 years after administration of the second MMR dose. The middle-school group showed similar patterns.<sup>32</sup> Although this was a high percentage of children whose serology results were at the lowest detectable titer, there is no criterion for immunity to rubella determined by neutralization. In addition, with the exception of two children, all had high avidity antibodies one month after receiving their second MMR dose, which is reflective of an anamnestic response. Furthermore, rubella surveillance data do not indicate that rubella and congenital rubella syndrome (CRS) are increasing among vaccinated persons. If protection in the two-dose vaccinated young adult population were dropping close to or below the commonly accepted rubella herd immunity threshold of 85%–90%,<sup>30</sup> one might expect to see large numbers of cases reported in these age groups.

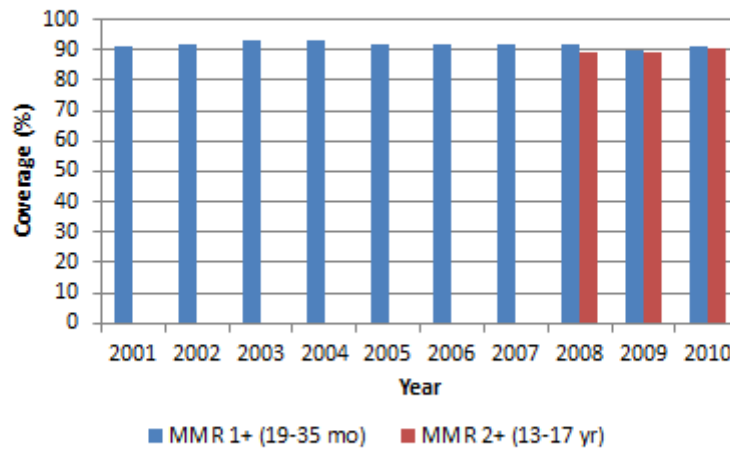
## Vaccine Coverage Data

Vaccine coverage data were obtained by the National Immunization Survey (NIS), National Immunization Survey-Teen (NIS-Teen), and the kindergarten survey. The NIS and NIS-Teen surveys are nationally representative landline telephone surveys that use random-digit dialing to identify households with children aged 19–35 months or adolescents aged 13-17 years, respectively. Among households with children in the above-mentioned age groups that complete the NIS and NIS-Teen telephone interviews, consent is obtained to contact the age-eligible children's vaccination providers to obtain provider-reported vaccination histories.<sup>33</sup> The NIS provides national and state level coverage estimates and are measured and published annually.

NIS data show that national-level MMR vaccine coverage in the United States has remained high over the last decade at  $\geq 90\%$ . A total of 91.5% of children aged 19–35 months had received 1 dose

of MMR vaccine during 2009-2010 (Figure 16).<sup>34</sup> However, coverage varies by state; 1 dose MMR coverage among children aged 19-35 months ranged from 85.1% in Montana to 97.8% in Connecticut in 2010 (Table 14). Kindergarten coverage data showed that a total of 94.8% of kindergartners had evidence of 2 MMR doses in 2010.<sup>35,36</sup> Of the 50 states and 11 municipalities that receive Section 317 immunization grant funding from the federal government, 87% reported  $\geq 90\%$  coverage and 50% reported  $\geq 95\%$  coverage among kindergartners.

**Figure 16. Estimated MMR Vaccination Coverage Children 19-35 months 2001-2010 and 13-17 Years, 1998-2010, United States**



2010 National Immunization Survey for children and teens, available at <http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm>

NIS-Teen vaccine coverage data for adolescents have only been available since 2008. In 2010, a total of 90.5% of adolescents had evidence of 2 MMR vaccine doses.<sup>37</sup> Coverage was at its lowest in 2006 at 86.9%. Two-dose MMR coverage varies among the states; in 2010, West Virginia had 79.7% two dose coverage, whereas the District of Columbia had 98.4% two dose coverage.<sup>37</sup>

There are limitations to the NIS and NIS-Teen data. NIS is a landline telephone survey and does not contain data from children who live in households with no telephone service or only cellular phone service. However, recent studies suggest that bias in surveys that only sample households with landline telephones may be small.<sup>38,39</sup> Coverage estimates are verified from provider records that provide dates of vaccination. This may result in underestimation of vaccine coverage because of the exclusive use of provider-reported vaccination histories; completeness of these records is unknown.<sup>40</sup>

There are also limitations to the kindergarten survey. The methodology differs among the states. Some states survey all schools, whereas other states take a small sample. In addition, states and local jurisdictions handle exemptions differently. In some states, if a child is missing one vaccine, that child is considered an “exemptor” for all vaccines. Data are a cross-sectional representation of

vaccination coverage at one point in time; therefore, students who were in the process of obtaining required vaccines might not be accounted for in the reported estimates. Consequently, kindergarten vaccination coverage rates might be underestimated in some states (the level of “unaccounted for” students ranges from 0% to 17.5%). Despite the limitations of the kindergarten survey, a number of states have documented similar MMR coverage levels in their state level populations.<sup>41,42</sup>

## Vaccine Exemptors

Vaccine exemptors, who refuse vaccination for themselves or their children, contribute to lowering population immunity to the respective vaccine preventable diseases. With respect to requirements for vaccination for school students, vaccine exemption is measured during school surveys of coverage among children entering kindergarten and is subject to the same limitations regarding study methods. Vaccine exemptors represent a small percentage of the school student population ranging from <0.1% in Mississippi to 6.2% in Washington; 15 states and local jurisdictions had a total exemption rate  $\geq 3.0\%$ . Medical exemptions were the least frequent, ranging from <0.1% (Mississippi) to 1.7% (Alaska). Nonmedical exemptions ranged from 0.2% (Rhode Island) to 5.8% (Washington) among the 45 states and local jurisdictions that allow nonmedical exemptions.<sup>36</sup> There is evidence of an increase in vaccine refusal in the United States.<sup>43</sup> However, reported exemptions do not distinguish between exemption for one vaccine versus all vaccines; thus a student with a claimed exemption could have received one or more vaccines. A recent study of 277 children with nonmedical vaccine exemptions residing in four states found that 209 (75%) had received at least one vaccine.<sup>44</sup> Additionally, vaccination coverage estimates from the 2009 National Immunization Survey showed that <1% of infants aged 19--35 months had not received any vaccines.<sup>33</sup>

Researchers have used data from school surveys to report on trends in vaccine exemption. These studies have highlighted that vaccine exemptors tend to cluster geographically and within schools.<sup>12,45</sup> Thus, even if a state has high vaccination coverage, there may be areas within the state with clusters of under-vaccinated children. A state may have a relatively low percentage of exemptors overall, but a community or county within that state may have a substantially higher percentage of exemptors.<sup>46</sup> There is extensive variation in nonmedical-exemption rates between and within states.<sup>43,47,48</sup> From 2010 through 2011 in Washington, for instance, the state-level nonmedical-exemption rate was 6.3%; however, the county-level rate ranged from 1.3 to 27.5%.<sup>43,48</sup> During 1995--2008, 233 counties (among the 3,141 counties in the United States) met the sample size requirement to ensure confidentiality of the data for inclusion in the analysis of county-level MMR vaccine coverage data of children aged 19—35 months sampled by NIS who had adequate provider data.<sup>49</sup> County level vaccine coverage with  $\geq 1$  dose of MMR ranged from 86.4% in Clark County, Nevada, to 96.6% in Suffolk County, Massachusetts during 2007—2008.<sup>49</sup>

## VII. Sustainability of Measles, Rubella and CRS Elimination

The United States is committed to sustaining elimination of endemic measles, rubella and congenital rubella syndrome (CRS) and has a long history of high-level political commitment to establishing national health goals for disease reduction, elimination and national childhood immunization coverage levels. For example, in response to the measles resurgence from 1989-1991 that highlighted low vaccine coverage among preschool children in many inner city populations, the Childhood Immunization Initiative was launched in 1993 by President Clinton to increase vaccination coverage among preschool-aged children for all recommended vaccines to >90%.<sup>50</sup> During the early 1990s, the U.S. Federal Government spent an average of \$233 million annually on immunizations.<sup>51</sup> Today, \$4 billion annually is spent on the two components of the national immunization program: the Vaccines for Children (VFC) Program, an entitlement program that was established in 1994 to remove cost as a barrier to receiving vaccines for poor and uninsured children in the United States, and the discretionary Section 317 program which provides funds to support some vaccine purchase at the state level as well as critical state immunization infrastructure and operational costs.<sup>52</sup> Achieving and now maintaining measles, rubella and CRS elimination has consistently been included in the national health goals, as documented by the Healthy People 2000, 2010 and 2020 objectives.<sup>53</sup>

The United States also provides substantial financial and technical support to global measles elimination efforts in order to reduce global morbidity and mortality and minimize the risk of importations of measles and rubella viruses into the United States. From fiscal year 2001 through fiscal year 2011, CDC spent approximately \$438.9 million on global measles control activities in 42 sub-Saharan African and 6 Asian countries.<sup>54,55</sup> With the funds, CDC has purchased over 200 million measles vaccine doses and provided technical support to ministries of health in those countries.<sup>54</sup> The CDC is a founding member of the Measles Initiative ([www.measlesinitiative.org](http://www.measlesinitiative.org)) a partnership with the American Red Cross, United Nations Foundation, UNICEF and World Health Organization that is committed to reducing measles deaths worldwide. In addition, over the past two decades, a broad coalition of partners has been formed to promote childhood immunization, including professional organizations, such as the American Academy of Pediatrics and the American Academy of Family Physicians, nongovernmental organizations, such as Healthy Mothers, Healthy Babies and Every Child by Two, as well as state and local governments.<sup>51</sup> These groups and agencies have provided influential community leaders as spokespersons on immunization issues, disseminated information about vaccines to high risk groups, and have helped ensure that immunization messages are consistent, as well as targeted to the appropriate populations.<sup>56</sup>

### **Correlation and Integration of the Evidence for Maintenance of Elimination of Measles, Rubella and CRS**

The data presented in this report provide strong evidence that elimination of endemic measles, rubella and CRS has been maintained in the United States since the documentation and declaration of elimination of these diseases in 2000 and 2004 respectively. In the post-elimination eras for measles and rubella, reported disease incidences have remained extremely low, with annual reported measles incidence below 1 case per million people, annual reported rubella incidence at

record low levels of less than 1 case per 10 million people and average annual reported CRS incidence of less than 1 case per 5 million births.

Measles elimination in the United States is tested continually by measles importations. Due primarily to high population immunity, 84% of measles importations do not result in any spread cases. Almost all measles cases are importation-associated and those that have unknown source are likely have an undetected epidemiological link to an imported case or be the result of false positive laboratory tests. During 2001 to 2011, only a very small proportion (7.5%) of measles importations resulted in outbreaks.

Measles outbreaks have been limited in size and duration since 2000, with only 15 outbreaks including 10 or more cases. The largest outbreak included 34 cases, and the longest lasted 11 weeks. The vast majority of these larger outbreaks have known imported cases as their origin. Outbreak size is limited by high vaccine coverage which limits spread to the surrounding community but also, especially in high risk unvaccinated populations, by rapid and aggressive public health response. Outbreak responses by local and state health departments include measures taken to prevent further transmission such as: providing MMR vaccine or immune globulin for exposed people who do not have presumptive evidence of immunity, and implementing voluntary and sometimes mandatory quarantine of contacts who decline vaccination and remain at risk for acquiring measles.

Reported rubella cases are rare and outbreaks are few and very small. Public health response to reported rubella cases is aggressive. Though rubella cases are undoubtedly being missed by the surveillance system, it is unlikely that large outbreaks, as occurred during the 1990's among at risk Hispanic populations, would be missed.

The molecular epidemiology for both measles and rubella shows a pattern of varied genotypes consistent with multiple imported sources, even among cases with no detected link to importation. For rubella there is no suggestion of a possible endemic genotype, as there are not two cases without epidemiologic link to importation which share the exact same sequence. For measles, the case is not quite as clear, as genotype D4 has been repeatedly detected in the United States since 2008. However, careful analysis showed the majority of these cases are epidemiologically linked to importations with links to large measles outbreaks that have been occurring in Europe over the last 3-4 years. The remaining D4 cases, without epi-link to importation, are so sparsely distributed in place and time that they do not suggest an endemic chain of transmission.

Serologic surveys and detailed vaccine coverage surveys indicate a high-level of population immunity to measles and rubella and do not suggest any decrease (and for measles, in fact, an increase) in coverage or immunity since the initial documentations of elimination of these diseases. Population immunity remains above the levels needed to achieve and maintain elimination. However, trends in vaccine exemption are a cause for concern and their impact on population immunity will need careful monitoring.

These converging lines of evidence indicate the sustained elimination of measles and rubella as endemic diseases in the United States. Because these lines of evidence are based on the surveillance

systems for these two diseases, it is essential to assess the quality of surveillance to assure it is adequate to detect endemic measles or rubella should they be reestablished in the United States.

There are several important limitations to the surveillance systems for measles and rubella. First, it is not possible to monitor the completeness of reporting of measles and rubella in an ongoing manner. Secondly, there is no system in place for monitoring the level of surveillance effort, such as reporting numbers and rates of suspected cases investigated and discarded, or the related number of IgM tests for measles and rubella performed. The third limitation is that health care providers in the United States are not familiar with these diseases and may miss the diagnosis for sporadic cases, especially if providers do not seek patient history of international travel or possible exposure to measles or rubella.

Despite these limitations, multiple studies conducted in the initial documentation of elimination efforts concluded that although some cases are not detected and reported, the surveillance system was adequate to detect endemic measles or rubella if it were occurring. The lines of evidence which indicate the sustained adequacy of the surveillance system to detect endemic measles or rubella if it were occurring include:

- Consistent detection of imported cases, which can be the most difficult cases to detect.
- Detection of isolated cases and small chains of transmission, which makes it unlikely the system would fail to detect the large chain of transmission which endemic disease would require.
- Active investigation only detects a few unreported cases found retrospectively.
- Rapid public health response with active investigation and response through contact tracing following case report.
- Substantial IgM testing volume as evidenced by CDC confirmatory testing volume. Few cases of measles or rubella are confirmed even in the presence of substantial testing.

The surveillance system judged adequate to document the initial elimination of measles, rubella and CRS has not changed markedly in the intervening years. Although some individual cases may not be detected and reported, the surveillance system would detect any endemic chain of transmission, which by definition would have to be large enough to last an entire year.

Finally, the United States has consistently demonstrated a high level of political and financial commitment from the public and private sectors to immunization in general and measles and rubella elimination specifically, both domestically and internationally.

## VIII. Challenges

The year 2011 represented an extreme test for the United States regarding maintenance of measles elimination. Through September 30, 2011, the cut-off date for data presented in this report, 212 measles cases had been reported and by December 31<sup>st</sup>, 222 measles cases had been provisionally reported. Associated with large outbreaks of measles in Europe and elsewhere, during 2011, the US detected more than 70 measles importations from more than 20 countries and 6 different genotypes reflecting their country of origin. In the face of these continued tests of population immunity and capacity for public health response, only 7% of the importations resulted in outbreaks. Rapid and efficient public health response limited outbreak size, especially in communities with sub populations who chose not to vaccinate their children. The largest outbreak of 21 cases lasted 10 weeks. Experience with maintenance of elimination has highlighted continued challenges and current and future actions to respond to these challenges:

- Challenge: Despite progress in global measles elimination and measles mortality reduction, the continued high-level of global incidence of these diseases and the resulting ongoing international importation of cases poses an ongoing threat of importations. The European region has had large, sustained measles outbreaks in recent years and rates of international travel between the United States and countries in Europe are high.
  - Action: Continue efforts to support goals for global measles, rubella, and CRS elimination and control.
  - Action: Support state health department efforts to respond rapidly to outbreaks including implementing strategies to reduce risk of transmission including quarantine of exposed people who lack evidence of immunity.
  
- Challenge: Increasing rates of vaccine exemption among school aged children in a number of states and demographic pockets of susceptibility to measles and rubella which collectively might sustain endemic transmission following international importation. MMR vaccine has been a target of concern due to a suggested association with autism.
  - Action: Continue education efforts regarding vaccine safety science (no demonstrated association with MMR vaccine and autism) and risks of measles disease with respect to mortality and short and long term morbidity.
  - Action: Provide technical assistance to state health departments regarding school requirements and educate them on the effect of philosophical requirements and link with increasing trends in vaccine exemption and on successful models for implementing requirements linked with parental education.
  - Action: Support state health department efforts to respond rapidly to outbreaks including implementing strategies to reduce risk of transmission including quarantine of exposed contacts who lack evidence of immunity.
  
- Challenge: Health care providers are not familiar with measles or rubella or CRS and are likely to misdiagnose rare cases they may see.
  - Action: Publish scientific and clinical news articles (e.g AAP news), using a variety of communication media including MMWRs and peer review publications about measles and MMR vaccine policy. Increase communications when cases are being

reported and communicate messages through private and public partnerships. Highlight clinical features, disease burden and the need for physicians and other primary health care providers to maintain a high index of suspicion among persons who travel abroad including infants and young children.

- Action: Publish information about measles, and rubella for the general public and travelers and through podcasts, social media, radio and print media.
- Challenge: Active measles case investigation and public health response is resource intensive and costly especially in a time of declining budgets for state health departments.
  - Action: Educate key decision makers and politicians that maintaining measles surveillance and response capacity is excellent preparedness for any acute infectious public health threat.
  - Action: Continue provision of timely technical assistance from CDC epidemiology, laboratory and surveillance/public health and health economic experts to support state health department surveillance and public health response efforts and to document economic costs of maintaining elimination.



## IX. Summary

Although no single source of information alone provides conclusive evidence of the sustained elimination of endemic measles, rubella, and CRS in the United States; the critical lines of evidence of converge to demonstrate convincingly that these diseases are no longer endemic in country. The specific lines of evidence are:

- Extremely low disease incidence: Annual measles incidence <1 reported case per 1 million population, annual rubella incidence < 1 reported cases per 10 million population, and only 4 cases of CRS were reported between 2005 and 2011..
- A large proportion of cases are international imported or associated with importation. For measles 40% of cases were imported and 88% were importation-associated. For rubella, 38% of cases were imported and 53% were importation-associated.
- Unknown source cases are insufficient to represent an endemic chain. For measles, only 12% of cases are not linked to importation by demonstrated epidemiologic or virologic evidence. These cases are not clustered in patterns suggesting endemic transmission. Rubella unknown source cases averaged only 6 per year.
- Most imported cases do not lead to spread in the United States. For measles, 84% of imported cases resulted in no spread cases and only 7.5% resulted in outbreaks. During 2004-2011, only 2 rubella outbreaks, with 3 cases each, occurred in the United States.
- The size of the outbreaks was small. For measles only 16 outbreaks had > 10 cases (maximum 34 cases). For rubella, there were no outbreaks with > 3 cases.
- MMR vaccination coverage has been sustained at high levels for many years, including high two-dose coverage. Currently there are no racial or ethnic differences in MMR vaccine coverage.
- National serosurvey data show high population seropositivity for measles and rubella; at or above the herd immunity threshold.
- Detailed molecular analysis does not suggest an endemic strain of measles or rubella virus.
- Surveillance is adequate to detect endemic transmission of measles or rubella if it were occurring.

This evidence indicates the surveillance system remains adequate to detect endemic measles or rubella if it were occurring and confirms the conclusion that elimination of endemic measles and rubella has been sustained in the United States. The commitment of the public and private sectors in the United States to the elimination of endemic measles, rubella, and CRS, combined with the numbers of years which endemic transmission of measles and rubella have remained eliminated, provide assurance that elimination can be maintained. The United States has demonstrated aggressive action in addressing perceived threats to sustaining elimination of endemic measles and rubella. The keys to ongoing success will be sustaining high level of immunity throughout the U.S. population through vaccination, supporting maintenance of strong US surveillance and public health response capacity for these diseases, and supporting other countries in their efforts to control, eliminate and hopefully, in the future, to eradicate measles and rubella from the world.

## **X. External Panel**

### **External Panel for the Verification and Documentation of Elimination of Measles, Rubella, and CRS as Endemic Diseases from the United States**

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