The Changing Epidemiology of Rubella in the 1990s

On the Verge of Elimination and New Challenges for Control and Prevention

Susan E. Reef, MD
Teryl K. Frey, PhD
Katherine Theall, MPH
Emily Abernathy, MS
Cindy L. Burnett
Joseph Icenogle, PhD
Mary Mason McCauley, MTSC
Melinda Wharton, MD, MPH

Context In 1989, the United States established a goal to eliminate indigenous rubella and congenital rubella syndrome (CRS) by 2000. Reported rubella cases are at record low levels; however, cases and outbreaks have occurred, primarily among unvaccinated foreign-born adults.

Objective To evaluate the current epidemiology of rubella and CRS and assess progress toward elimination.

Design, Setting, and Subjects Analysis of rubella cases reported to the National Notifiable Diseases Surveillance System from 1990 through 1999 and CRS cases reported to the National Congenital Rubella Syndrome Registry from 1990 through 1999. Since 1996, US and international viral isolates have been sequenced.

Main Outcome Measures Incidence and characteristics of rubella and CRS cases; molecular typing of virus isolates.

Results Annually from 1990 through 1999, the median number of reported rubella cases was 232 (range, 128-1412), and between 1992 and 1999, fewer than 300 rubella cases were reported annually, except in 1998. During the 1990s, the incidence of rubella in children younger than 15 years decreased (0.63 vs 0.06 per 100000 in 1990 vs 1999), whereas the incidence in adults aged 15 to 44 years increased (0.13 vs 0.24 per 100000). In 1992, incidence among Hispanics was 0.06 per 100000 and increased to a high in 1998 of 0.97 per 100000. From 1997 through 1999, 20 (83%) of 24 CRS infants were born to Hispanic mothers, and 21 (91%) of 23 CRS infants were born to foreign-born mothers. Molecular typing identified 3 statistically distinct genotypic groups. In group 1, the close relatedness of viruses suggests that a single imported source seeded an outbreak that did not spread beyond the Northeast. Similarly, within groups 2 and 3, relatedness of viruses obtained from clusters of cases suggests that single imported sources seeded each one. Diversity of viruses found in 1 state is consistent with the conclusion that several viruses were imported. Moreover, the similarity of viruses found across the country, combined with a lack of epidemiologic evidence of endemic transmission, support the conclusion that some viruses that are common abroad, particularly in Latin America and the Carribean, were introduced into the United States on several separate occasions.

Conclusions The epidemiology of rubella and CRS has changed significantly in the last decade. These changes and molecular typing suggest that the United States is on the verge of elimination of the disease. To prevent future rubella outbreaks and CRS, current strategies must be enhanced and new strategies developed.

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The current epidemiology of rubella and congenital rubella syndrome (CRS) in the United States reflects the overwhelming success of rubella and CRS control strategies that were initiated 31 years ago, when rubella vaccine became available. While the US vaccination program has mainly focused on attaining high rates of childhood immunization, the goal of the program is to prevent fetal infection. When intrauterine rubella occurs in the first trimester of pregnancy, the results can include miscarriage, stillbirth, and CRS—a pattern of fetal anomalies that includes cataracts, hearing impairment, cardiac disease, and developmental delay.[1]

After the vaccination program began in 1969, the number of rubella and CRS cases declined steadily. That year, 57600 rubella cases and 62 CRS cases were reported. By 1988, an all-time low of 223 rubella cases and 4 CRS cases were reported.[2] However, in 1989, the number of reported rubella cases increased

See also p 505 and Patient Page.

Author Affiliations: National Immunization Program (Drs Reef and Wharton and Ms McCauley) and National Center for Infectious Diseases (Dr Icenogle), Centers for Disease Control and Prevention; Georgia State University (Dr Frey and Ms Abernathy), and Emory University School of Public Health (Ms Theall), Atlanta; and Utah Department of Health, Salt Lake City (Ms Burnett).

Corresponding Author and Reprints: Susan E. Reef, MD, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS E-61, Atlanta, GA 30333 (e-mail: sreef@cdc.gov).

nearly 2-fold to 396.[3] This increase occurred concurrently with the measles resurgence, which was attributed in part to failure to ensure timely vaccination of preschool-aged children.

In 1989, a goal was established to eliminate indigenous rubella transmission and CRS in the United States by 2000.[4] Four years later, with the establishment of the 1993 Childhood Immunization Initiative, efforts to attain high vaccination coverage were intensified.[5] To measure the success of rubella control and prevention strategies and to ensure that progress toward rubella elimination could be accurately documented, surveillance was evaluated and enhanced to meet identified needs. For example, during the 1990s, additional data were collected in case reports, and US health officials increased collaborative efforts with nongovernmental organizations representing high-risk populations in the United States and other countries and with international organizations, including the Pan American Health Organization. Also during the 1990s, new tools for rubella surveillance were developed; in particular, molecular typing of rubella virus isolates proved to be a valuable aid in understanding transmission of rubella in the United States.[6]

This article reviews the epidemiology of rubella and CRS in the United States from 1990 through 1999. Significant changes have occurred. These changes demand improved strategies for rubella control among foreign-born populations and enhanced surveillance to document interruption of transmission of indigenous rubella and CRS in the United States.

METHODS

Rubella Cases

We analyzed data from rubella cases reported from 1990 through 1999 to the National Notifiable Diseases Surveillance System (NNDSS). For each case, demographic information regarding age, sex, race/ethnicity, case classification, and relationship to an outbreak was collected. In 1993, the NNDSS was extended to include clinical information, vaccination history, and pregnancy information, as well as source of exposure (imported or indigenous) and site of transmission. Beginning in 1997, the National Immunization Program of the Centers for Disease Control and Prevention collected country of origin and length of US residence for cases and country of exposure for imported cases.

Rubella cases included in this report were classified as confirmed, probable, suspected, or unknown according to the Council of State and Territorial Epidemiologists' case definition.[7] The classification scheme is based on the clinical description and criteria for laboratory confirmation. A clinical case of rubella is defined as a person who has an acute onset of generalized maculopapular rash and a temperature of more than 99°F (37.2°C), if measured, as well as 1 of 3 characteristics: arthritis/arthralgia, lymphadenopathy, or conjunctivitis. Criteria for laboratory confirmation of rubella infection include rubella virus isolation, detection of serum rubella IgM, or a significant rise in serum IgG levels between acute- and convalescent-phase titers. A confirmed case of rubella is defined as a person who has laboratory-confirmed rubella or a person who meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case. A probable rubella case meets the clinical case definition but has no or noncontributory serologic or virologic testing and is not epidemiologically linked to a laboratory-confirmed case. A suspected case of rubella has some compatible clinical findings but does not meet the criteria for a probable case. Cases of rubella were classified by year of report.

To be classified as an imported rubella case, the source of exposure must have occurred outside the United States or the onset of rash must have occurred within 14 to 23 days after entering the United States. All rubella cases that do not satisfy either of these criteria are classified as indigenous.[8]

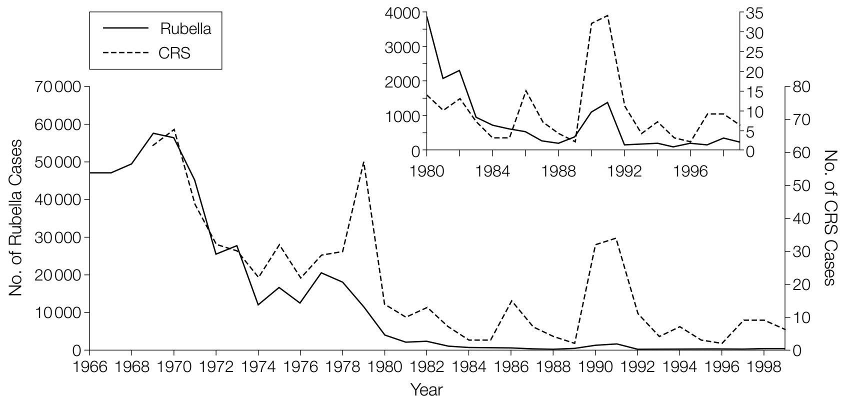
CRS Cases

We analyzed data from CRS cases reported from 1990 through 1999 to the National Congenital Rubella Syndrome Registry (NCRSR), a passive surveillance system. Initiated in 1969, the NCRSR is maintained by the National Immunization Program and receives reports from state and local health departments of US-born infants with CRS, including clinical and demographic data about infants with CRS and their mothers. Since 1996, mothers' country of birth and country of exposure have been collected along with the other demographic data. Cases of CRS are classified by year of birth.

Cases of CRS that were classified as confirmed or probable were included in this analysis. A confirmed case of CRS is defined as a child with congenital anomalies compatible with CRS and laboratory evidence of rubella virus infection documented in the first year of life. Laboratory confirmation of CRS in infants includes rubella virus isolation, detection of serum rubella IgM, or serum IgG levels that persist longer than expected from passive transfer of maternal IgG (ie, decreases at <2-fold dilution per month). A probable CRS case lacks laboratory confirmation of rubella infection but has a clinical presentation consistent with CRS. A clinical case of CRS includes at least 1 of the following: cataracts or congenital glaucoma, heart defect, loss of hearing, or pigmentary retinopathy, along with another of the preceding signs or 1 of the following: purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, or radiolucent bone disease.

Since 1984, CRS cases have been classified as imported or indigenous.[2] An imported case of CRS is defined as CRS in a US citizen or non–US citizen whose mother was outside of the United States during her presumed exposure to rubella. If the timing of exposure to rubella cannot be determined, classification as imported requires that the mother be outside the United States throughout the 21 days before conception and the first 20 weeks of pregnancy. All CRS cases that do not satisfy these criteria are classified as indigenous.

Figure 1. Rubella and CRS Cases Reported to the CDC, United States, 1966-1999



Congenital rubella syndrome (CRS) reports were available beginning in 1969. CDC indicates Centers for Disease Control and Prevention.

Outbreaks

To supplement case reports, we obtained additional information from state and local health departments on outbreak investigations and control measures. An outbreak was defined as 5 or more epidemiologically related cases. For outbreaks with cases in more than 1 setting (ie, school, worksite) the outbreak setting was classified as communitywide. Outbreaks were classified by the year in which the first case was identified.

Virus Isolation, Sequence Determination, and Analysis

Since 1996, virus isolation was attempted on 236 clinical specimens, usually obtained from throat swabs, of suspected rubella case-patients from the 1990-1991 rubella outbreaks in California and from suspected rubella and CRS case-patients, particularly in the United States but also from Latin America and the Caribbean, during 1997 through 2000. The nucleotide sequence of a portion of the virus genome was determined from successful virus isolations. Isolation of rubella virus from clinical specimens by culturing in Vero cells, extraction of the single-strand rubella virus RNA from the cultures, and amplification of the *E1* gene (by reverse transcriptase polymerase chain reaction) were performed as previously described.[6] From the *E1* gene amplification product, the sequence of nucleotides 8869 to 9469 was determined bidirectionally using BigDye Terminator Cycle Sequencing Ready Reaction DNA Sequencing kits (PE Applied Biosystems, Foster City, Calif) and an ABI Prism 377 DNA Sequencer apparatus (PE Applied Biosystems). To cover sequencing of this region, 2 forward primers (351 ACGTCACCACTGAACACCCG [nucleotides 8787-8806] and 615 CTCCACATACGCGCTGGAC [nucleotides 9122-9140]) and 1 reverse primer (86 TGGTGTGTGTGCCATAC [complementary to nucleotides 9529-9545]) were used.

Phylogenetic analysis of 59 viruses, including 49 US isolates, 2 laboratory reference strains (Therien wild type and RA/27/3 vaccine), and 8 recent isolates from other countries in the Western Hemisphere, was conducted. We used the heuristic tree search algorithm with parsimony criterion of the PAUPSearch program of Wisconsin Package Version 10 software (Genetics Computer Group, Madison, Wis). Bootstrap resampling with 100 replicates was done with the "bootstrap analysis using heuristic search" algorithm of this software to place confidence values on nodes within the tree.

Statistical Analysis

Data from CRS case reports were entered and analyzed using Epi Info Version 6.1 (Centers for Disease Control and Prevention, Atlanta, Ga). Data from rubella case reports were analyzed in SAS 6.12 (SAS Institute Inc, Cary, NC). For trend analysis, the χ^2 test was used, and for stratified analysis, the Cochran-Mantel-Haenszel χ^2 test was used.

RESULTS

Epidemiology of Rubella in the United States, 1990-1999

The incidence of rubella decreased dramatically, from 0.45 per 100000 in 1990 to 0.1 per 100000 in 1999. Annually from 1990 through 1999, the median number of reported rubella cases was 232 (range, 128-1412) (FIGURE 1). From 1992 through 1997, fewer than 300 rubella cases were reported annually, with an all-time low in 1995 of 128 cases. From 1997 to 1998, cases increased 100%, from 181 to 364. In 1999, the total was 272.

During the 1990s, cases of rubella were reported from all but 3 states. In 1990 and 1991, approximately three quarters of the states reported rubella cases; however, since 1992, fewer than half of the states reported cases of rubella, with 4 or fewer states annually reporting a majority of the cases.

Characteristics of Case-Patients

During the 1990s, the characteristics (ie, age distribution, sex, and race/ethnicity) of rubella cases changed significantly (TABLE 1). In 1990, incidence was higher among children younger than 15 years than among persons aged 15 to 44 years (0.63 and 0.13 per 100000, respectively); however, since the mid 1990s, incidence has increased among persons aged 15 to 44 years to 0.24 in 1998 (range in 1996 through 1999, 0.16 to 0.24 per 100000) and decreased among children younger than 15 years to 0.08 in 1998 (range in 1996 through 1999, 0.03 to 0.08 per 100000). In 1990, children younger than 15 years accounted for 69% of cases (338/488), declining to a low in 1997 of 11% (20/181). Since 1996, the highest percentage of cases occurred among persons aged 20 to 29 years, with a high in 1999 of 49% (131/269).

This shift to adults began earlier in California; in 1990, although ages for the suspected California cases were not reported to the NNDSS, an investigation revealed that the majority of the 411 reported cases occurred among persons aged 20 years or older.

The age shift was accompanied by a shift in the distribution of cases by sex. Since the mid 1990s, significantly fewer cases were reported among women than among men ($P<.001$). However, every year since 1992, more than 50% of the cases among women occurred among those of childbearing age (15-44 years). In 1996 through 1999, rubella was reported in 281 women of childbearing age; of these, 71 (26%) were pregnant at the time of rash onset. Of 50 women with known data on trimester, 27 (54%) were in their first trimester, 9 (18%) were in their second trimester, and 14 (28%) were in their third trimester.

In the 1990s, a shift in the distribution of cases by race/ethnicity occurred. Since the mid 1990s, most of the reported cases occurred among persons of Hispanic ethnicity; of these persons, most were born outside the United States. In 1992, incidence among Hispanics was 0.06 per 100 000 and increased to a high in 1998 of 0.97 per 100 000; however, incidence among non-Hispanics was stable. When adjusting for sex and age group, Hispanic ethnicity ($P \leq .001$) remained the most significant factor. In 1998, of cases with known country of origin, 79% (231/291) were born outside the United States. Of these, 91% were from the Western Hemisphere: Mexico (43%), Guatemala (21%), El Salvador (16%), Honduras (4%), Colombia (4%), and Cuba (3%). In 1999, 65% of cases (92/141) with known country of origin occurred among persons born outside the United States. Of these, 98% were from the Western Hemisphere: Mexico (81%) and El Salvador (14%).

Laboratory Confirmation

During the 1990s, the percentage of confirmed cases increased. From 1992 through 1994, the percentage of confirmed cases increased from 28% (44/157) to 83% (188/227). In 1995, 76% were reported as confirmed, but only 50% of cases had documented laboratory confirmation, epidemiologic linkage, or both. Since 1996, at least 93% of cases are classified as confirmed each year, with at least 84% of these cases being laboratory confirmed, epidemiologically linked, or both.

Source of Exposure for Rubella Cases

During the 1990s, surveillance for source of exposure was improved and data became more complete. In 1992, 73% of reports did not include a source; however, among case reports that did, 47% (20/43) were classified as imported. From 1997 to 1999, 17% were classified as unknown source; however, among case reports with a known source, 8% were classified as imported. From 1997 through 1999, of the 55 imported cases, 52 had information on country of exposure. Countries of exposure included Mexico (33%), Japan (12%), Russia (13%), and the Philippines (8%).

Vaccination Status

Since 1996, at least 93% of case reports have included vaccination status. From 1996 through 1999, 8% to

Table 1. Characteristics of Rubella Case-Patients, United States, 1990-1999*

	Year									
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Total reported cases, No.	1124	1412	157	192	227	128	238	181	364	272
Total with known age	**488**	**1008**	**105**	**185**	**227**	**126**	**237**	**181**	**364**	**269**
Age, y										
<1	43 (8.8)	32 (3.2)	13 (12.4)	20 (10.8)	11 (4.8)	6 (4.8)	7 (3.0)	7 (3.9)	16 (4.4)	16 (6.0)
1-4	106 (21.7)	193 (19.1)	16 (15.2)	17 (9.2)	17 (7.5)	3 (2.4)	11 (4.6)	7 (3.9)	12 (3.3)	17 (6.3)
5-14	189 (38.7)	382 (37.9)	21 (20.0)	32 (17.3)	17 (7.5)	10 (7.9)	10 (4.2)	6 (3.3)	19 (5.2)	4 (1.5)
15-19	62 (12.7)	191 (18.9)	8 (7.6)	8 (4.3)	11 (4.8)	12 (9.5)	32 (13.5)	27 (14.9)	48 (13.2)	30 (11.2)
20-29	88 (18.0)	210 (20.8)	18 (17.1)	55 (29.7)	65 (28.6)	25 (19.8)	107 (45.1)	80 (44.2)	167 (45.9)	131 (48.7)
30-44	0	0	27 (25.7)	41 (22.2)	82 (36.1)	55 (43.7)	53 (22.4)	42 (23.2)	71 (19.5)	61 (22.7)
≥45	0	0	2 (1.9)	12 (6.5)	24 (10.6)	15 (11.9)	17 (7.2)	12 (6.6)	31 (8.5)	10 (3.7)
Total with known ethnicity, No.	NA	NA	**73**	**140**	**196**	**108**	**214**	**171**	**353**	**255**
Ethnicity										
Hispanic	NA	NA	14 (19.2)	36 (25.7)	78 (39.8)	60 (55.6)	137 (64.0)	112 (65.5)	294 (83.3)	198 (77.6)
Non-Hispanic	NA	NA	59 (80.8)	104 (74.3)	118 (60.2)	48 (44.4)	77 (36.0)	59 (34.5)	59 (16.7)	57 (22.4)
Total with known sex, No.	NA	NA	**105**	**182**	**227**	**126**	**238**	**181**	**363**	**271**
Sex										
Male	NA	NA	62 (59.0)	93 (51.1)	122 (53.7)	63 (50.0)	137 (57.6)	108 (59.7)	239 (65.8)	174 (62.4)
Female	NA	NA	43 (41.0)	89 (48.9)	105 (46.3)	63 (50.0)	101 (42.4)	73 (40.3)	124 (34.2)	97 (35.8)
Women of childbearing age†	NA	NA	27 (62.8)	46 (51.7)	69 (65.7)	41 (65.1)	74 (73.3)	55 (75.3)	80 (64.5)	72 (74.2)

*Data are No. (%) unless otherwise noted. NA indicates not applicable.
†Percentage of women.

14% reported receiving vaccine, 48% to 57% had never been vaccinated, and 29% to 41% reported unknown vaccination status.

For the cases in 1998 born outside the United States, most (88%) either were unvaccinated (134 [58%] of 231) or had unknown vaccination status (68 [29%] of 231). Of the 29 persons (12%) who were vaccinated, 24 (83%) were vaccinated within 14 days prior to rash onset, 7 within 7 days prior, and 7 between 7 and 14 days prior. In 1999, the same pattern was noted.

Even though rubella occurred mainly among foreign-born adults in 1998 and 1999, we stratified vaccination status by age and country of origin to evaluate the vaccination status of persons born inside the United States. In 1998, 51 cases occurred among US-born persons who were age-eligible for vaccination. Of these, 36 cases had known vaccination status and 13 of these had received vaccine. Of the 13 vaccinated persons, 8 (62%) were among children younger than 15 years. In 1999, the same pattern was noted.

CRS Cases

From 1990 through 1999, 117 cases of CRS were reported to the NCRSR (Figure 1). Of these, 110 (94%) were classified as confirmed and 7 (6%) as probable. Of the 117 infants with CRS, 66 (56%) were born during 1990 and 1991. Of these, 43 occurred in 2 clusters. The first cluster of 21 infants was associated with a multicounty rubella outbreak in southern California in 1989.[9] The second cluster was associated with a 1991 rubella outbreak among an Amish community in Pennsylvania.[10] Each year from 1992 through 1999, an average of 6 infants with CRS were born.

Mothers of infants with CRS tended to be young, Hispanic, and foreign-born. Of 113 mothers with known age, the median age was 23 years (range, 15-38 years). Among the 102 mothers whose race/ethnicity was known, 84 (82%) were white, 9 (9%) were black, and 5 (5%) were Asian/Pacific Islander. Of the 115 mothers with known ethnicity, 57 (50%) were Hispanic; overall in the United States, Hispanics accounted for 17% of all births.[11] Since 1997, 83% (20/24)of the infants with CRS were born to Hispanic women, and 21 of the 23 mothers with known country of birth were born outside the United States. The countries of the mothers' births include Mexico (n=13), Philippines (n=2), Dominican Republic (n=2), Columbia (n=1), Pakistan (n=1), Honduras (n=1), and Guyana (n=1). Only 1 of these women had received rubella-containing vaccine prior to birth of an infant with CRS.

During the beginning of the 1990s, most of the mothers were exposed to rubella in the United States; however, by the end of the decade, almost half of the cases were imported. Of the 114 cases with known import status, 75% (86/114) were classified as indigenous; that is, exposure to disease occurred in the United States. Since 1997, when complete data on country of exposure were available, 42% of CRS cases (10/24) were imported; 6 mothers (60%) were exposed in Mexico, and 1 each in the Philippines, Pakistan, Venezuela, and Honduras.

Outbreaks

From 1990 through 1999, 65 outbreaks were reported; of these, 34 (52%) occurred in 1990-1991. Settings that predominated at the beginning of the decade did not account for the majority of outbreaks by the end of the decade.

In 1990-1991, the 34 reported outbreaks accounted for 41% of cases reported (1046/2536). Common outbreak settings included religious communities (14/34), correctional facilities (9/34), and higher education institutions (4/34). The percentages of cases for each type of outbreak were 72%, 15%, and 4%, respectively. Outbreaks in religious communities were larger than those in correctional facilities (median size, 22.5 and 9.5; range, 9-128 and 5-36, respectively).

Since 1993, of the 31 outbreaks that were reported, the most predominant setting has been worksites (n=13), followed by communities (n=10) and correctional facilities (n=5). Some of these outbreaks were initially identified as workplace outbreaks, and subsequent investigation revealed spread to the community. After the 1990-1991 outbreaks, the largest outbreak in the rest of the decade occurred in Massachusetts in 1993-1994 involving 128 cases.[12] Six pregnant women were in-

Table 2. Rubella Outbreaks, United States, 1995-1999*

Year†	No. of Outbreaks	No. (%) of Total Cases‡	No. (%) of Persons Aged ≥15 y	Source of Exposure	No. (%) of Hispanics	No. of Congenital Rubella Syndrome Cases
1995	2	38 (30)	37 (97)	Community, work site	37 (97)	0
1996	5	125 (53)	122 (98)	Jails, workplaces, community, higher education	102 (83)	0
1997	9	116 (64)	104 (90)	Cruise ships, Immigration and Naturalization Services (INS) service processing centers, workplaces, community	85 (73)	1
1998	7	220 (60)	211 (96)	INS service processing centers, community, families, workplaces	199 (90)	0
1999	4	156 (57)	134 (86)	Community, workplaces	128 (82)	1

*Outbreaks are defined as 5 or more epidemiologically linked cases.
†Outbreaks classified by year of index case.
‡Percentage of cases calculated by year of rash onset.

fected, 4 of whom were in their first trimester; 3 chose to terminate their pregnancies.

Since 1995, when most cases occurred among Hispanic persons, most outbreaks also predominantly affected Hispanic adults (TABLE 2). In 1995, 2 outbreaks occurred, accounting for 30% (n=38) of reported cases among mainly Hispanic adults. Since 1996, more than half of the cases were associated with outbreaks.[13]

In 1997, country of origin data was collected in most of the outbreaks. The data show that almost all subsequent outbreaks were in the foreign-born population. In the first half of 1997, 6 outbreaks occurred; 4 of these involved workplaces, such as meat processing plants and cruise ships, that employed foreign-born workers. The fifth outbreak occurred in a community of persons in New York, NY, from the Caribbean and Guyana. One infant with CRS was born as a result of this outbreak. In late 1997, 3 outbreaks began that comprised 37% (n=135) of the 364 cases reported in 1998.[14]

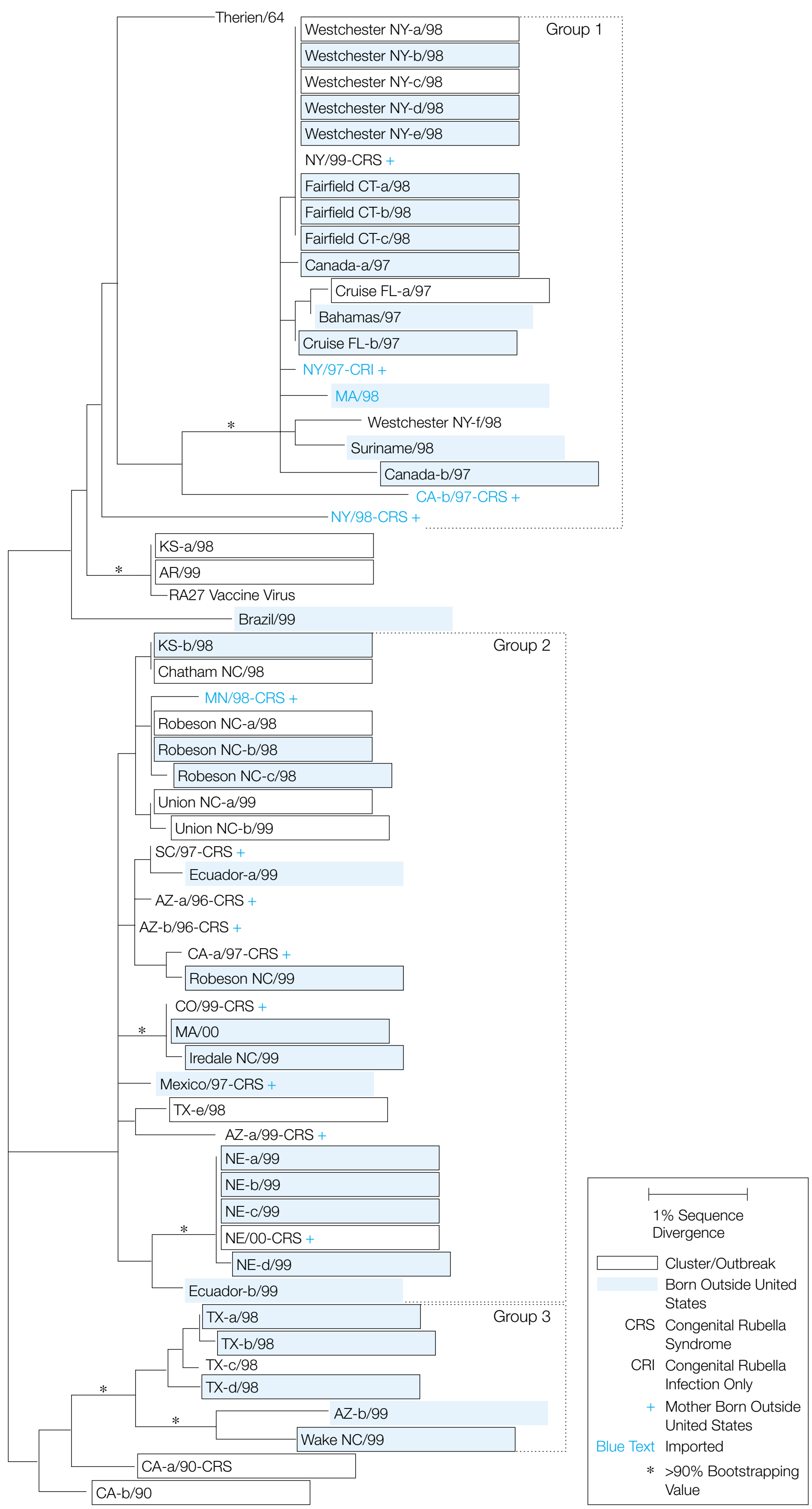
In 1999, 4 outbreaks occurred in the United States.[15] Three of the 4 were workplace-associated; however, 1 of these, which occurred in Nebraska, spread into the community, including infecting children and adults in a day-care center.[16,17] As a result of this outbreak, 1 infant with CRS was born.

In 1997-1999, despite enhanced passive and active surveillance in hospitals, health care practitioners' offices, clinics, and schools, cases of rubella were not reported among vaccinated school-aged children.

Molecular Epidemiology of Rubella and CRS

The 49 viruses isolated in the United States distribute into 3 statistically meaningful genotypic groups (FIGURE 2). Group 1 include isolates from community outbreaks in late 1997 and 1998 in New York and Connecticut,[18] 1 CRS case and 1 infection-only case in New York (the mother of the in-

Figure 2. Phylogenetic Analysis of Rubella Isolates in the Americas During the 1990s



fection-only case was exposed in Guyana), and cruise ship outbreaks in Florida in 1997. These isolates are very similar to each other and to 2 viruses obtained from an outbreak in 1997 in Manitoba and individual isolates from the English-speaking Caribbean and Suriname. Outlying viruses in this group include 2 viruses from 2 US-born infants with CRS whose mothers were exposed in the Philippines (CA/97) and Venezuela (NY/98); both mothers were born outside the United States. Another virus in group 1 (MA/98) was isolated from a case acquired in Ukraine. Two older viruses, the current US rubella vaccine virus (RA/27/3; the parent of this virus was isolated in Philadelphia, Pa, in 1964) as well as TH/US/64 (Therien strain isolated in Connecticut), a standard laboratory strain used as the "outgroup" in construction of the tree, also appear on side branches at the base of group 1. The 2 viruses that are very similar to the RA/27/3 vaccine strain (KS-a/98 and AR/99) were isolated from vaccinated persons who developed a rash after receipt of measles-mumps-rubella vaccine as part of outbreak control measures.

Viruses in group 2 include isolates from an outbreak in Kansas in 1998 (KS: 98), an outbreak in Nebraska in 1999 (NE-a/99 through NE-d/99, plus a CRS case resulting from this outbreak, NE/00), and outbreaks and clusters in North Carolina in both 1998 and 1999 (Chatham NC/98; Robeson NC-a/98 through Robeson NC-c/98; Robeson NC/99; Union NC-a/99 and Union NC-b/99; Iredale NC/99). Group 2 also includes several viruses from isolated CRS cases in Minnesota (MN/98), South Carolina (SC/97), Arizona (AZ-a/96, AZ-b/96, and AZ-a/99), California (CA/97), and Colorado (CO/99). Foreign viruses in group 2 include 2 viruses from Ecuador isolated in 1999 and a virus isolated from a CRS case in Mexico (Mexico/97); additionally, the MN/98 virus was from a CRS case whose mother contracted rubella during pregnancy in Veracruz, Mexico.

Group 3 contains viruses from cluster in North Carolina (Wake NC/99), 2 cluster/outbreaks in Texas (TX-a/98 through TX-b/98 were from the 1997-1998 Immigration and Naturalization Service outbreak, while TX-d/98 was associated with a different cluster), and 1 isolate from Arizona. Two viruses from the 1990 Los Angeles, Calif, outbreak are at the base of this group, indicating that these viruses are progenitors of current group 3 viruses and that evolution has occurred during the intervening period.

Viruses from all 3 genotypic groups were involved in clusters and outbreaks. We were successful in isolating multiple viruses from 5 clusters/outbreaks (New York–Connecticut, 1998, 8 isolates; Robeson County, North Carolina, 1998, 3 isolates; Union County, North Carolina, 1999, 2 isolates; Nebraska, 1999, 5 isolates; and the INS outbreak in Texas, 1997-1998, 2 isolates). In all of these cases, the viruses isolated from a single cluster/outbreak were genetically similar if not identical. Among the clusters/outbreaks, 1 pair of geographically isolated clusters/outbreaks was caused by identical viruses (Kansas and Chatham County, NC, in 1998) and the Robeson County cluster in 1998 and Union County outbreak in 1999 were caused by closely related viruses. However, in general, clusters and outbreaks were caused by dissimilar viruses; for example, the virus from the 1999 Robeson County cluster was more distant to the 1998 Robeson County virus than was the 1999 Union County virus. Similarly, independent clusters/outbreaks in 4 counties in North Carolina in 1999 (Union, Robeson, Iredale, and Wake) were caused by 3 distantly related group 2 viruses and 1 group 3 virus. Interestingly, some of the viruses from clusters/outbreaks were most closely related to viruses from isolated CRS cases; for example, the Iredale NC/99 and MA/00 viruses were very similar to the CO/99 CRS virus, and the Robeson NC/99 cluster virus was most closely related to 3 CRS viruses (AZ-a/96, AZ-b/96, and SC/98).

COMMENT

After the rubella resurgence in 1990-1991, the number of reported rubella cases continued to decline, as had occurred in the 1970s and 1980s.[19,20] However, since the beginning of the 1990s, the demographics of the rubella and CRS cases and the characteristics of the outbreaks have changed significantly. Rubella now occurs mainly among foreign-born Hispanic adults who are either unvaccinated or whose vaccination status is unknown, with very limited spread and circulation among the US resident population. These changes and data from the molecular typing of viruses from rubella and CRS cases suggest that the United States is on the verge of elimination of indigenous rubella and CRS. However, rubella cases continue to occur in the United States, and the threat of CRS remains, particularly among women of childbearing age who were born outside the United States. Therefore, control efforts now must focus on at-risk populations such as foreign-born adults.

The most important change in the epidemiology of rubella in the United States is that most cases now occur among Hispanics, particularly those born in countries where rubella vaccination programs do not exist or were recently implemented. This trend also has been identified in infants with CRS whose mothers were born outside the United States. In the California outbreak in 1990, one of the risk factors for infants with CRS was to have a mother who was foreign-born.

Both US-born and foreign-born individuals with rubella were more likely to be unvaccinated or have unknown vaccination status. Among the foreign-born persons vaccinated, usually as part of outbreak control measures, many were vaccinated within 2 weeks prior to rash onset. This finding demonstrates failure to vaccinate, not vaccine failure or waning immunity, to be the reason for rubella continuing in the United States. Additionally, mothers of infants with CRS were also more likely not to have been vaccinated.

In the late 1990s, as previously described in the late 1970s and 1980s, outbreaks continued to occur in settings where adults congregated,[21-26] but outbreaks occur primarily among foreign-born persons. Even though certain US populations (eg, inner city) may be undervaccinated, the lack of outbreaks in these populations suggests that surrounding herd immunity may have a protective effect. In the outbreak areas, limited spread to the unvaccinated US population demonstrates that the US program has been successful and that vaccine failure and waning immunity are not factors for rubella occurring in the United States.

Molecular typing, which provides important data on the origin of viruses from cases and outbreaks, identified 3 different groups from the 1990s. Group 1 viruses, which were isolated from 3 outbreaks (Westchester, NY, Fairfield, Conn, and a Florida cruise ship), exhibited little internal diversity. This finding suggests that a single source seeded these outbreaks. Most likely, this source came from the Caribbean because of the close relationship of this group with viruses from the Bahamas, Suriname, and Venezuela.

In groups 2 and 3, cases within clusters/outbreaks again do not exhibit high sequence diversity, which suggests that a unique source seeded each cluster/outbreak. However, viruses from different clusters/outbreaks were often diverse, indicating independent seeding of each of these outbreaks rather than endemic activity. For example, viruses from 4 cluster/outbreaks in North Carolina in 1999 (Union-a/99 and Union-b/99, Robeson/99, Iredale/99, and Wake/99) were diverse, indicating independent seeding of each of these outbreaks rather than endemic activity. However, viruses from 21998 clusters in North Carolina (Chatham/98 and Robeson-a/98, Robeson-b/98, and Robeson-c/98) were similar; thus, they could have been seeded by a single source. These 2 clusters may reflect endemic circulation, but they may also reflect multiple introductions of a single virus.

Conversely, within groups 2 and 3, there are several examples of similar viruses isolated from widely geographically separated cases (Iredale NC/99, CO/99, and MA/00), much like the group 1 pattern. This situation is consistent with multiple introductions of a single virus. Based on the inclusion of 1 virus from Mexico (Mexico/97) and 2 from Ecuador (Ecuador-a/99 and Ecuador-b/99) in group 2 and the Mexican origin of the mothers of several CRS cases (MN/98, SC/98, AZ-a/96, AZ-b/96, AZ/99, and NE/00), group 2 appears to have come from Latin America. Considering that routine vaccination began in the late 1990s in these countries, it appears that groups 2 and 3 indicate the endemic transmission that occurs in neighboring countries, which is reflected in cases that occur in the United States as a result of multiple or continuous import of viruses. It is anticipated that the number of group 2 viruses found in the United States will decline.

When a random sample of viruses isolated in the 1990s were analyzed along with viruses from the 1960s and 1970s, the resulting phylogenetic tree revealed that viruses isolated earlier are more similar to one another than they are to viruses isolated in the 1990s. This distant relationship between viruses from the 1990s and those available from the 1960s and 1970s provides no evidence for endemic circulation of prevaccine viruses in the United States. Before vaccination began in the United States, viruses similar to those in the United States circulated in Europe and Japan. After the institution of vaccination programs in these countries, distinct genotypes evolved in the United States, Europe, and Japan. A similar pattern is likely to develop in many countries in the Western Hemisphere as vaccination programs are established.

A limitation of our interpretations is the uncertain completeness of case ascertainment. Even though states have enhanced surveillance for rubella during the last 5 years, identification of cases is challenging because 20% to 50% of rubella cases are mild or asymptomatic. The pattern of viruses from molecular typing for the last 3 to 4 years is consistent with seeding from external sources, however, additional data from viruses occurring in the United States and other countries, particularly in the Western Hemisphere, are needed to substantiate this interpretation.

The primary goal of a rubella vaccination program is to eliminate congenital rubella infections. Ensuring immunity among women of childbearing age is critical. In the United States, in addition to childhood vaccination, prenatal rubella testing and postpartum vaccination will prevent some of the CRS cases; however, not all CRS cases can be prevented because less than half of the mothers have had previous pregnancies.

Some states are exploring strategies for controlling rubella in at-risk populations, including forming partnerships with employers to offer vaccination to employees and offering vaccination to at-risk women through the Special Supplemental Program for Women, Infants, and Children, which reaches approximately 40% of US mothers of neonates each year. A major challenge to the workplace approach is a high turnover rate among industries that currently employ at-risk persons.

Rubella and CRS cases that occur in the United States demand attention both nationally and regionally. As of January 2001, 44 of the 47 countries in the Americas (excluding the Dominican Republic, Peru, and Guatemala) have implemented childhood rubella vaccination programs.[27] However, most of these programs have been ongoing for fewer than 3 years. The current epidemiology in the United States demonstrates the effectiveness of a successful rubella vaccination program. If all countries in the Western Hemisphere achieve and maintain high childhood immunization coverage and ensure immunity in women of childbearing age, the goal of eliminating indigenous transmission is achievable.

Author Contributions: *Study concept and design:* Reef, Frey, Wharton.
Acquisition of data: Reef, Frey, Theall, Abernathy, Burnett.
Analysis and interpretation of data: Reef, Frey, Theall, Abernathy, Burnett, Icenogle, McCauley, Wharton.
Drafting of the manuscript: Reef, Frey, McCauley.
Critical revision of the manuscript for important intellectual content: Reef, Frey, Theall, Abernathy, Burnett, Icenogle, Wharton.

Statistical expertise: Theall, Burnett.
Obtained funding: Reef.
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