Changing Epidemiology of Congenital Rubella Syndrome in the United States

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To describe clinical presentation and epidemiology of US infants with congenital rubella syndrome (CRS) and to identify missed opportunities for maternal vaccination, data from CRS cases reported to the National Congenital Rubella Syndrome Registry (NCRSR) from 1985 through 1996 were analyzed. Missed opportunities for maternal vaccination were defined as missed postpartum, premarital, and occupational opportunities, that is, times when rubella vaccination is recommended but was not given. From 1985 through 1996, 122 CRS cases were reported to the NCRSR. The most frequent CRS-related defect was congenital heart disease. Of the reported infants with CRS, 44% were Hispanic. Of 121 known missed opportunities for rubella vaccination among 94 mothers of infants with indigenous CRS, 98 (81%) were missed postpartum opportunities. CRS continues to occur in the United States. Hispanic infants have an increased risk of CRS. Missed opportunities for postpartum rubella vaccination were identified for 52% of indigenous CRS cases.

Rubella virus infection in adults and children usually causes a mild and self-limited illness with few complications. However, the devastating consequences of rubella were recognized in 1941 when the virus was identified as a teratogen [1]. Rubella, especially during the first trimester, can cause miscarriage or congenital rubella syndrome (CRS), which is characterized by a pattern of congenital anomalies, including nerve deafness, cataracts, cardiac abnormalities, and mental retardation. Late effects of CRS include diabetes, thyroid disease, and progressive rubella panencephalitis [2]. More than 20,000 children were born with CRS during the last major epidemic of rubella in the United States in 1965–1966 [3]. In 1982 dollars, the lifetime cost of caring for a child with CRS was estimated to be >$220,000 [4].

CRS can be prevented by routine rubella vaccination of children and all nonpregnant women of childbearing age who lack rubella immunity and is one of the few preventable birth defect syndromes. The first rubella vaccine was licensed for use in the United States in 1969. Wide use of vaccine has reduced the incidence of rubella and CRS by >99% from pre−vaccine era levels. In 1995, only 128 rubella cases and 6 cases of CRS were reported by state health departments to the US Centers for Disease Control and Prevention (CDC)’s National Notifiable Disease Surveillance System and the National Congenital Rubella Syndrome Registry (NCRSR).

From 1969 to 1982, there was a 10-fold reduction in the average annual number of reported CRS cases. However, since 1982, the rate of decline in the number of CRS cases reported per year has slowed. A stable, low number of CRS cases is reported annually. Because the US Public Health Service has established a goal to eliminate indigenous CRS cases in the United States by the year 2000 [5], we reviewed the clinical presentation of recent CRS cases and the demographic characteristics of women at increased risk of delivering an infant with CRS and identified the rubella vaccination strategies that could have prevented the recently reported CRS cases.

Methods

We analyzed data from CRS cases reported from 1985 through 1996 to the NCRSR, a passive surveillance system. Since its initiation in 1969, the NCRSR has been maintained at the National Immunization Program, CDC, and receives reports of US-born infants with CRS from state and local health departments. Cases are classified by year of birth, rather than the year the case was reported.

In the NCRSR, 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 (i.e., 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. This includes at least one of the following—cataracts or congenital glaucoma, heart defect, hearing loss, or pigmentary retinopathy—plus another of the above signs or purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, or radiolucent bone disease.

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The NCRSR collects clinical and demographic data about infants with CRS and their mothers. Questions were asked about whether prenatal care was obtained, whether rubella was diagnosed during pregnancy, and whether the pregnancy was complicated by rubella symptoms such as fever, rash, lymphadenopathy, arthritis or arthralgia, and respiratory infections. We examined the clinical characteristics of CRS cases that were associated with earlier diagnosis by comparing clinical findings among infants diagnosed at <1 month of age with those diagnosed at >1 month of age by Pearson χ². In addition, age and self-reported race and ethnicity of the mothers were examined and compared with demographic characteristics of all women giving birth in the United States in 1990.

Since 1984, CRS cases have been classified as imported or indigenous. An imported case of CRS is defined as CRS in a US 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, the mother must have been outside of the United States throughout the 21 days before conception and the first 20 weeks of her pregnancy for the case to be considered an imported case. All CRS cases that do not satisfy the above criteria are classified as indigenous cases.

Self-reported rubella vaccination history is obtained, but the date of vaccination, age at vaccination, and the rubella vaccine strain administered are not collected. Vaccination history is not confirmed by provider verification or medical record review.

In 1984, the Advisory Committee on Immunization Practices (ACIP) outlined an approach to expand existing efforts for rubella vaccination of susceptible adolescents and young adults, particularly women of childbearing age [6]. Key components included recommendations for premarital screening and vaccination of rubella-susceptible women, prenatal screening with postpartum vaccination of rubella-susceptible women, and college and work site vaccination programs for students, health care workers, and women of childbearing age employed in day care centers, schools, colleges, prisons, companies, government offices, and industries [6]. We considered these situations potential opportunities for rubella vaccination of adult women, and we classified missed opportunities for vaccination as missed occupational, missed premarital, or missed postpartum opportunities. Missed opportunities for rubella vaccination were assessed only for indigenous CRS cases.

Data on duration of marriage (<1 year vs. ≥1 year) was used as a proxy to evaluate the effectiveness of premarital screening programs. If a woman was married for >1 year when she delivered an infant with CRS, she would have had time to undergo premarital rubella susceptibility testing and follow-up rubella vaccination before becoming pregnant. According to ACIP guidelines, at least 3 months should elapse between receipt of rubella vaccine and conception [7]. Data were analyzed with SAS (SAS Institute, Cary, NC) software for Windows, version 6.08.

Results

From 1985 through 1996, 106 (87%) confirmed CRS cases and 16 (13%) probable CRS cases were reported to the NCRSR. A mean of 10 infants with confirmed or probable rubella were born per year (range, 0–34; figure 1).

Three clusters of confirmed CRS have been reported since 1985 and account for 51 (42%) of the 122 reported cases. All three clusters followed rubella outbreaks. An outbreak of rubella in New York City in 1985 contributed to a cluster of 8 CRS cases in 1986 [8]. A second cluster of 21 cases of CRS in Southern California in 1990 followed a multi-county outbreak of rubella in 1989 [9]. A third CRS cluster of 22 cases in 1991–1992 followed a 1991 rubella outbreak among the Amish in Pennsylvania [10, 11].

The most frequently occurring CRS-related defect among infants reported to the NCRSR was congenital heart disease, which was reported in 86 (71%) of 122 CRS cases; of these, 62 (72%) had a patent ductus arteriosus (table 1). Other common signs of CRS were hearing loss, low birth weight or very low birth weight, and congenital cataracts. From 1985 through 1996, 106 (87%) confirmed CRS cases for which occupation was reported were not employed during pregnancy, and 16 (13%) probable CRS cases were reported to the NCRSR.

The median age of the mothers of an infant with CRS was 23 years (range, 15–38). Among the 111 mothers of infants with CRS of known race, 88 (79%) were white, 13 (12%) were black, and 10 (9%) were other. This is not significantly different from the racial distribution for all births for 1990 (table 2) [12]. In contrast, ethnicity was associated with risk of CRS, with Hispanic infants at significantly increased risk. From 1985 to 1996, 44% of the reported cases of infants with CRS were born to Hispanic women, compared with Hispanic women delivering 15% of all births in the United States (1990 data), [12] for a relative risk of 2.9 (P < .001).

Since 1985, 94 (78%) mothers of infants with CRS acquired rubella within the United States, and 27 (22%) of 121 CRS cases with known exposure status were imported. Since 1991, the NCRSR has collected data on country of rubella exposure. From 1991 to 1996, 7 (64%) of 11 mothers of infants with imported CRS were exposed to rubella in Mexico. In addition, there was 1 imported case of CRS each from Germany, Poland, the Dominican Republic, and Sri Lanka.

From 1985 to 1996, 33 (27%) of 122 mothers of infants with CRS reported they were tested for rubella immunity before becoming pregnant. The self-reported rubella vaccination history was known for 52 (55%) of the mothers of infants with indigenous CRS. Of these, 17 (33%) stated that they had been vaccinated for rubella.

Sixty-nine (83%) of 83 mothers of infants with indigenous CRS for whom occupation was reported were not employed outside of the home. Only 3 (4%) women worked in occupations for which the ACIP has recommended rubella vaccination [7]. In addition, 1 16-year-old mother of an infant with CRS was a student in a state that required rubella vaccination for
students in kindergarten through grade 12. This also represents a missed opportunity for vaccination.

Among mothers of indigenous cases for whom the duration of marriage was reported, 45% had been married >1 year at the time they delivered the infant with CRS. Seventy-seven (87%) of 89 mothers of infants with indigenous CRS for whom information was obtained reported receiving prenatal care. Forty-six (52%) of 87 mothers of infants with indigenous CRS with completed information reported having one or more previous live-born children (table 3).

Thirty (32%) of 94 mothers had 1 missed opportunity and 28 (30%) had >1 missed opportunity. A total of 121 known missed opportunities for rubella vaccination were identified among 94 mothers of infants with indigenous CRS. Of these, 98 (81%) were missed postpartum opportunities, 19 (16%) were missed premarital opportunities, and 4 (3%) were missed workplace opportunities.

**Discussion**

Since a safe and effective rubella vaccine was licensed in the United States nearly 30 years ago, the number of CRS cases has declined by >99%. However, elimination of indige-

**Table 1.** Clinical characteristics of CRS cases reported to National Congenital Rubella Syndrome Registry, United States, 1985–1996 (n = 122).

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease (any congenital)</td>
<td>86 (70.5)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>62 (50.8)</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>22 (18.0)</td>
</tr>
<tr>
<td>Other congenital heart conditions</td>
<td>36 (29.5)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>73 (59.8)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>70 (57.4)</td>
</tr>
<tr>
<td>Very low birth weight (&lt;1500 g)</td>
<td>15 (12.3)</td>
</tr>
<tr>
<td>Low birth weight (1500–2500 g)</td>
<td>55 (45.1)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>52 (42.6)</td>
</tr>
<tr>
<td>Purpura</td>
<td>45 (36.9)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>43 (35.2)</td>
</tr>
<tr>
<td>Spleenomegaly</td>
<td>42 (34.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41 (33.6)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>28 (23.0)</td>
</tr>
<tr>
<td>Radiolucent bone disease</td>
<td>24 (19.7)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>18 (14.8)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>15 (12.3)</td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>10 (8.2)</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>9 (7.4)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (3.3)</td>
</tr>
</tbody>
</table>

**Table 2.** Characteristics of mothers of infants with reported CRS, United States, 1985–1996 (n = 122).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of mothers of infants with CRS (with known data)</th>
<th>% of all US mothers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>20 (16.8)</td>
<td>12.5</td>
</tr>
<tr>
<td>20–24</td>
<td>55 (46.2)†</td>
<td>26.2</td>
</tr>
<tr>
<td>25–29</td>
<td>30 (25.2)</td>
<td>30.7</td>
</tr>
<tr>
<td>30–39</td>
<td>14 (11.8)†</td>
<td>29.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13 (11.7)</td>
<td>16.5</td>
</tr>
<tr>
<td>Other</td>
<td>10 (9.0)</td>
<td>4.4</td>
</tr>
<tr>
<td>White</td>
<td>88 (79.3)</td>
<td>79.1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>51 (44.0)†</td>
<td>14.5</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>65 (56.0)†</td>
<td>84.5</td>
</tr>
</tbody>
</table>

† Proportion statistically different (P < .05) from all US mothers giving birth in 1990, based on binomial distribution.
How many Hispanic women in this series were immigrants. With vaccination of susceptible women misses the increasing through 1996, the proportion of infants with CRS born to Hispanic women (18%) was higher than the proportion of Hispanic women in the population (7%) [17]. We found that from 1985 through 1996, the proportion of infants with CRS born to Hispanic women increased even further, to 44%. It is unknown how many Hispanic women in this series were immigrants. However, studies from the United Kingdom reported an increased risk among women who were recent immigrants [21, 22]. Women immigrating to the United States from countries where rubella immunity is not routinely acquired early in life either by vaccination or infection may have lower rubella immunity rates than do US-born women, but we were unable to test this hypothesis because data on maternal immigration status was not collected. However, only 20% of the world’s population reside in countries or areas that currently use rubella vaccine [23].

From surveillance data, indigenous transmission of rubella appears to have been interrupted in the United States at least once [19]. Strategies to prevent reintroduction in the future include promoting better rubella control outside of the United States and decreasing the number of rubella-susceptible persons in the United States.

We evaluated three strategies recommended by the ACIP to prevent rubella transmission and CRS cases: vaccination of employees, premarital screening, and prenatal screening and postpartum vaccination. Outbreaks of rubella have been reported in health care settings in which transmission to susceptible staff [24–26] or patients has been documented [27–30]. In addition, transmission has been described in offices, banks, prisons, and other occupational settings [19, 31]. Therefore, ACIP has recommended rubella vaccination for employees of medical facilities (including volunteers, trainees, nurses, and physicians), as well as persons employed in day care centers, schools, colleges, prisons, companies, government offices, and industrial sites [7]. However, from 1985 through 1996, only 3 mothers of reported CRS cases were employed in any of the above-listed occupations (1 nurse, 1 nurse’s aide, and 1 child care provider). Of those with reported occupation, the majority (83%) of mothers of infants with CRS were not employed outside of the home, so implementation of vaccination programs at the work site would not have reached these rubella-susceptible women.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation for which rubella vaccination is recommended</td>
<td>4 (4.3)*</td>
<td>79 (84.9)</td>
<td>11 (11.7)</td>
</tr>
<tr>
<td>Married ≥1 year at the time of delivery</td>
<td>19 (20.2)</td>
<td>23 (24.5)</td>
<td>52 (54.8)</td>
</tr>
<tr>
<td>≥1 previous live-born children</td>
<td>46 (48.9)</td>
<td>41 (43.6)</td>
<td>7 (7.4)</td>
</tr>
</tbody>
</table>

NOTE. n excludes 1 infant with CRS for whom importation status was not reported.

* Includes 1 mother of infant with CRS who listed occupation as “student.”

Table 3. Number (%) of mothers of infants with indigenous CRS by characteristic related to missed opportunities, United States, 1985–1996 (n = 94).
A third strategy identified by ACIP to target rubella-susceptible women of childbearing age is to screen women during prenatal visits and to vaccinate nonimmune women immediately postpartum. Numerous studies have demonstrated that postpartum rubella vaccination is safe and effective [37–44]. Consistent prenatal rubella susceptibility screening with postpartum immunization would have been the most effective of the three ACIP strategies and could have prevented 56% of the reported CRS cases from 1985 through 1996. However, this strategy remains only partially implemented. A 1992 study found that only 32 (57%) of 56 surveyed hospitals in Los Angeles routinely offered vaccination to rubella-susceptible postpartum women before discharge, and only 2 (6%) of 32 hospitals performing induced abortions provided screening and rubella vaccination [45]. If rubella vaccination was routinely offered to women after all pregnancies, including those ending in stillbirths or elective or spontaneous abortions, even more CRS cases would have been prevented.

From physician surveys, the most common reasons reported for failing to provide postpartum rubella vaccinations were reluctance to use the vaccine, difficulty in obtaining follow-up, and negative titer not noticed by medical staff [46, 47]. A policy requiring rubella vaccination of women without documented rubella immunity before discharge from the hospital, birthing center, or abortion clinic could decrease the risk of patients being lost to follow-up or negative titers not being noticed by the medical staff.

Rubella vaccine efficacy is estimated to be 95% [3], and there is no evidence that protective immunity wanes. Therefore, we believe that the infants with CRS were delivered primarily to unvaccinated women, especially since 86% of the mothers of infants with CRS had a self-reported vaccination history that was negative or unknown. However, 17 (14%) of the 122 women in our case series reported having been previously vaccinated with rubella vaccine, but this was not confirmed by vaccine record review. Vaccine failure or reinfecation is rare [48, 49] and is unlikely to have occurred in all 17 women with self-reported rubella vaccination.

The incidence of CRS has decreased since the 1960s, but cases have continued to occur annually. Public health officials, private providers, and hospital infection control personnel should work to ensure that persons without documentation of rubella immunity, especially women of childbearing age, are identified and offered rubella vaccination. Serologic testing of unvaccinated persons for rubella immunity before rubella vaccination is not necessary and may be a barrier to vaccination because it unnecessarily postpones an opportunity to administer vaccine. Unless otherwise contraindicated, rubella vaccination should be offered by health care providers during any routine primary care and family planning; at sexually transmitted disease clinics, travel clinics, and postpartum visits; and to unvaccinated persons who lack other evidence of rubella immunity, especially nonpregnant women of childbearing age and foreign-born persons.

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