Chapter 15: Congenital Rubella Syndrome

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I. Disease Description

Congenital rubella syndrome (CRS) is an illness resulting from rubella virus infection during pregnancy. When rubella infection occurs during early pregnancy, serious consequences—such as miscarriages, stillbirths, and a constellation of severe birth defects in infants can result. The risk of congenital infection and defects is highest during the first 12 weeks of gestation and decreases after the 12th week of gestation with defects rare after the 20th week of gestation.[1–3] Common congenital defects of CRS include cataracts, congenital heart disease, hearing impairment, and developmental delay. 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. See Chapter 14, "Rubella," for more information on rubella infection.

II. Background

The link between congenital cataracts and maternal rubella infection was first made in 1941 by Australian ophthalmologist, Norman Gregg, who had noticed an unusual number of infants with cataracts following a rubella epidemic in 1940. In the absence of vaccination, rubella is an endemic disease with epidemics every 6 to 9 years. If rubella infections occurred among non-immune pregnant women, CRS cases can occur. During the 1962–1965 global rubella pandemic, an estimated 12.5 million rubella cases occurred in the United States, resulting in 2,000 cases of encephalitis, 11,250 therapeutic or spontaneous abortions, 2,100 neonatal deaths, and 20,000 infants born with CRS.[4]

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was and continues to be to prevent congenital rubella infections, including CRS.[5] Following vaccine licensure, the number of reported cases of CRS in the United States declined dramatically to <1 case per year or 4 cases total during 2005–2011 (CDC, unpublished data). In 28 (85%) of the 33 cases occurring during 1998–2011, the mother was born outside the United States. Of the 33 CRS cases occurring during this time, 16 (48%) were known importations (CDC, unpublished data). In 2004, an independent panel of internationally recognized experts in public health, infectious diseases, and immunizations reviewed the available data on rubella epidemiology and unanimously agreed that rubella elimination (i.e., the absence of year round endemic transmission) was achieved in the United States.[5]

Although rubella has been eliminated in the United States, it continues to be endemic in many parts of the world. It is estimated that more than 100,000 infants are born with CRS annually worldwide.[6] According to a survey of the member countries in the World Health Organization (WHO), the number of countries that have incorporated rubella-containing vaccines into their routine national immunization programs increased from 83 (13% of the birth cohort) in 1996 to 130 countries (40% of the birth cohort) in 2010. As of October 2010, the WHO Region of the Americas and European Region have established rubella elimination goals for the year 2010 and 2015, respectively; the Western Pacific Region has established targets for accelerated rubella control and CRS prevention goal (<1 case per 100,000) by 2015; and the Eastern Mediterranean Region has established a goal of CRS prevention without a target date for countries that have introduced national rubella vaccination programs.[7] In addition, in 2011, WHO recommended for all countries that are providing two doses of measles vaccine and have not introduced rubella vaccine, to consider including rubella-containing vaccine in their immunization program.[8] In 2010, the Pan American Health Organization (PAHO) announced that the Region of the Americas had achieved the rubella and CRS elimination goals set in 2003 based on surveillance data. Although regional documentation of elimination is ongoing, an expert panel unanimously agreed in December 2011 that CRS elimination has been maintained in the United States.[7, 9]

III. Maintenance of Elimination

The United States has established and achieved the goal of eliminating indigenous rubella transmission and CRS. Elimination of endemic rubella was documented and verified in the United States in 2004.[5] However, because of international travel and countries without routine rubella vaccination, imported cases of rubella and CRS cases are likely. To maintain elimination, the United States should continue to maintain high vaccination rates among children, ensure that women of childbearing age, particularly women born outside of the United States, are vaccinated, and maintain good surveillance for both rubella and CRS.

IV. Vaccination

See Chapter 14, "Rubella," for information on vaccination with rubella-containing vaccines.

V. Case Definition

Case definition for case classification

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) and published in 2009.[10]

Suspected: An infant who does not meet the criteria for a probable or confirmed case but who has one or more of the following findings:

- cataracts,
- congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment,
- pigmentary retinopathy,
- purpura,
- hepatosplenomegaly,
- jaundice,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

Probable: An infant who does not have laboratory confirmation of rubella infection but has at least two of the following, without a more plausible etiology:

- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

OR

An infant who does not have laboratory confirmation of rubella infection but has at least one or more of the following, without a more plausible etiology:

- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

AND one or more of the following:

- purpura,
- hepatosplenomegaly,
- jaundice,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

Confirmed: An infant with at least one of the symptoms clinically consistent with congenital rubella syndrome listed above; and laboratory evidence of congenital rubella infection demonstrated by:

- isolation of rubella virus, or
- detection of rubella-specific immunoglogulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

Infection only: An infant without any clinical symptoms or signs of rubella but with laboratory evidence of infection demonstrated by:

- isolation of rubella virus, or
- detection of rubella-specific immunoglogulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

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.

Epidemiologic classification of internationally-imported and U.S.-acquired

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 subclassified into four groups as described in the rubella case classification section in Chapter 14, "Rubella."

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.

VI. Laboratory Testing

Diagnostic tests used to confirm CRS include serologic assays and detection of rubella virus.

For additional information on laboratory testing for rubella virus, see Chapter 14, "Rubella." For additional information on use of laboratory testing in surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

Virus detection (real-time RT-PCR, RT-PCR)

Rubella virus can be detected from nasal, throat, urine, and blood specimens from infants with CRS. Efforts should be made to obtain clinical specimens for virus isolation from infants at the time of the initial investigation (see Appendix 15). However, because infants with CRS may shed virus from the throat and urine for a prolonged period (a year or longer), specimens obtained later may also yield rubella virus.

As with rubella infection, molecular typing is recommended because it provides important epidemiologic information to track the epidemiology of rubella in the United States now that rubella virus no longer continuously circulates in this country. By comparing virus sequences from new case-patients with virus sequences from other cases, the origin of particular virus types in this country can be tracked.[11] Furthermore, this information may help in documenting the maintenance of the elimination of endemic rubella virus transmission. Specimens for molecular typing should be obtained from patients with CRS as soon as possible after diagnosis. Appropriate specimens include throat swabs, urine, and cataracts from surgery. Specimens for virus detection and molecular typing should be sent to CDC as directed by the state health department.

Serologic testing

The serologic tests available for laboratory confirmation of CRS infections vary among laboratories. Enzyme immunoassays (EIA) are the most commonly used and widely available diagnostic test for rubella IgG and IgM antibodies. EIAs are sensitive and relatively easy to perform. EIA is the preferred testing method for IgM, using the capture technique, although indirect assays are also acceptable. In infants with CRS, IgM antibody can be detected in the infant's cord blood or serum and persists for about 6–12 months.

VII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[12] These regulations and laws list the diseases to be reported and describe those persons or groups responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

Provisional reports of CRS cases should be sent by the state health department to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8253) and to the National Notifiable Diseases Surveillance System (NNDSS). Reporting should not be delayed because of incomplete information or lack of confirmation; following completion of case investigations, data previously submitted to NNDSS should be updated with the available new information.

The *Congenital Rubella Syndrome Case Report* form (Appendix 17) is used to collect clinical and laboratory information on cases of CRS that are reported by state and local health departments. CRS cases are classified by year of patient's birth.

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth (mother)
  - Length of time in United States (mother)
- Reporting source
  - County
  - Earliest date reported
- Clinical
  - Symptoms or syndromes
    - Cataracts
    - Hearing impairment
    - Developmental delay
    - Type of congenital heart defect
    - Pigmentary retinopathy
    - Purpura
    - Radiolucent bone disease
    - Hepatosplenomegaly
    - Meningoencephalitis
    - Microcephaly
    - Other
- Outcome (infant survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses
- Laboratory (performed on both mother and infant)
  - Virus isolation
  - Genotype
  - PCR results
- Maternal history
  - Dates of rubella vaccinations
  - Number of doses of vaccine given
  - If not vaccinated, reason
  - History of documentation of rubella infection or disease during pregnancy
  - Rubella laboratory results
  - History of pregnancies within and outside the United States (including country and years of pregnancies)
- Travel outside the U.S. during pregnancy (countries visited with dates)
- Contact with foreign travelers during pregnancy
- Epidemiologic
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)
  - Source of exposure
  - Travel history

VIII. Case Investigation

Cases of U.S.-acquired CRS are sentinel events indicating the presence of rubella infections in a community that may have been previously unrecognized. The diagnosis of a single case of U.S.-acquired CRS in a community should result in intensified rubella and CRS surveillance and an investigation to determine where the mother was exposed to rubella. If the mother was exposed in a different state, state health officials should contact the other state to alert public health officials to possible rubella circulation.

Infants with CRS may present with various manifestations of the syndrome, depending on timing of the infection in pregnancy. Infants born to women infected with rubella during pregnancy should be evaluated for infection and CRS; however, depending on the gestational age of the infant at the time of the mother's infection, symptoms may not be apparent. After 20 weeks' gestation, the only defect may be hearing impairment. Furthermore, some children are infected in utero but have no congenital defects.

Laboratory confirmation should be sought in all suspected CRS cases, regardless of signs or symptoms.

Conducting active surveillance

Surveillance for CRS should be implemented when confirmed or probable rubella cases are documented in a setting where pregnant women might have been exposed.[13] Women who contract rubella while pregnant should be monitored for birth outcome, and appropriate testing should be performed on the infant after birth. Healthcare providers should be advised to evaluate infants born with conditions consistent with CRS and to collect specimens for virus detection and to perform a rubella-specific IgM antibody test on infants suspected of having CRS.

IX. Prevent Transmission from Infants with CRS

Cases of U.S.-acquired rubella have occurred among susceptible persons providing care for infants with CRS.[14] Because infants can shed the virus for prolonged periods, (up to 1 year of age or longer) infants with CRS should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained one month apart after the infant is older than three months of age are negative for rubella virus. Infants with CRS should be placed in contact isolation during any hospital admission before age one year or until the infant is no longer considered infectious. In addition, health officials should consider excluding infants with CRS from child care facilities until he or she is no longer considered infectious. Persons having contact with infants with CRS should have documented evidence of immunity to rubella (see Chapter 14, "Rubella") and caregivers of infants with CRS should be aware of the potential hazard of the infants to susceptible pregnant contacts.

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