Chapter 15: Congenital Rubella Syndrome

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I. Disease Description

Rubella is a viral illness caused by a togavirus of the genus *Rubivirus* and is characterized by a mild, maculopapular rash. The rubella rash occurs in 50% to 80% of rubella-infected persons and is sometimes misdiagnosed as measles or scarlet fever. Children usually develop few or no constitutional symptoms, but adults may experience a 1–5-day prodrome of low-grade fever, headache, malaise, mild coryza, and conjunctivitis. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. When rubella infection occurs during pregnancy, especially during the first trimester, serious consequences—such as miscarriages, stillbirths, and a constellation of severe birth defects known as congenital rubella syndrome (CRS)—can result. Of the mothers infected during the first 11 weeks of gestation, 90% will deliver an infant born with CRS; the rate of CRS for infants born to women infected during the first 20 weeks of pregnancy is 20%. The most common congenital defects of CRS are cataracts, heart defects and hearing impairment.

II. Background

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.[1]

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was to prevent congenital rubella infections, including CRS. Following vaccine licensure, the number of reported cases of CRS in the United States has declined 99%, from 77 cases in 1970 to one imported case in 2004.[2, 3] During 1998–2004, 28 cases of CRS were reported to the National Congenital Rubella Syndrome Registry (NCRSR); five of these were in infants born during 2001–2004. In 26 (93%) of the 28 cases occurring during 1998–2004 in which the mother's country of birth was known, the mother was born outside the United States. Of the 24 CRS cases with known import status occurring during this time, 12 (50%) were imported.[3]

The goal of rubella vaccination is to prevent congenital rubella infection.

In 2004, an independent panel of internationally recognized experts in public health, infectious diseases and immunizations reviewed the available data on rubella occurrence and epidemiology and unanimously agreed that rubella is no longer endemic in the United States.[4]

Although rubella is no longer endemic in the United States, it continues to be endemic in many parts of the world. It is estimated that more than 100,000 cases of CRS occur annually worldwide.[5] According to a survey of the member countries in the World Health Organization, the number of countries that have incorporated rubella-containing vaccine into their routine national immunization programs increased from 65 (12% of the birth cohort) in 1996 to 116 countries (26% of the birth cohort) in 2004. As of February 2006, two WHO regions (European, The Americas) have established rubella elimination goals for the year 2010.[3]

III. Importance of Rapid Identification

Infants with CRS may shed virus for up to 1 year. Therefore, it is essential that infected infants be identified as early in life as possible in order to prevent further spread of the virus. Infected infants should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained 1 month apart after the infants is older than 3 months of age are negative for rubella virus.[6]

Early diagnosis of CRS facilitates early intervention for specific disabilities. Results of recently published reports demonstrate significant enhancement of speech and language development, and eventual success in school for children with hearing impairment if they are identified early and intervention begins immediately.[7, 8]

IV. Importance of Surveillance

The goal of rubella vaccination is to prevent congenital rubella infection. Surveillance data are used to identify groups of persons or areas in which disease control efforts such as immunization can reduce or eliminate endemic disease and to evaluate the effectiveness of disease prevention programs and policies.

V. Disease Reduction Goals

As part of the proposed *Healthy People 2010* objectives, a goal was established to eliminate U.S.-acquired rubella and CRS in the United States by the year 2010.[9]

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VI. Case Definition

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) in June 1999.[10] The case classification for importation status was approved by the CSTE in June 2006.[11]

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
- Demonstration of rubella-specific 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)
- PCR positive for rubella virus

Case classification

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

Probable: A case that is not laboratory confirmed and that 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 loss) 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 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.

VII. Laboratory Testing

Diagnostic tests used to confirm CRS include serologic assays and isolation of the virus. Laboratory confirmation can be obtained by any of the following:

- Demonstration of rubella-specific IgM antibodies in the infant's cord blood or serum. In infants with CRS, IgM antibody persists for at least 6–12 months. In some instances, IgM may not be detected until at least 1 month of age; thus, infants with symptoms consistent with CRS who test negative shortly after birth should be retested at 1 month of age.[6]
- Documentation of persistence of serum rubella IgG titer beyond the time expected from passive transfer of maternal IgG antibody (i.e., rubella titer that does not decline at the expected rate of a twofold dilution per month).
- Isolation of rubella virus, which may be shed from the throat and urine for a year or longer.
- Detection of rubella virus by reverse transcription polymerase chain reaction (RT-PCR).

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."

Serologic testing

The serologic tests available for laboratory confirmation of CRS infections vary among laboratories. The following tests are widely available and may be used for screening for laboratory confirmation of disease. The state health department can provide guidance on available laboratory services and preferred tests. For additional information on laboratory testing for rubella virus, see Chapter 14, "Rubella."

Enzyme immunoassay (EIA). Most diagnostic testing done for rubella antibodies uses some variation of the EIA, which is sensitive, widely available, and relatively easy to perform. EIA, using the capture technique, is the preferred testing method for IgM. Indirect assays are also acceptable.

Immunofluorescent antibody (IFA) assay. IFA is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay; complexes due to rheumatoid antibody or IgG antibodies can lead to a false-positive result.

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine the origin of the virus, the virus strains circulating in the U.S., and whether these strains are no longer endemic in the U.S.

Virus isolation

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS patients (best results come from throat swabs). 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 for a prolonged period, specimens obtained later may also yield rubella virus. Infants with CRS should be considered infectious until two cultures of clinical specimens obtained 1 month apart after the infant is older than 3 months of age are negative for rubella virus.

Molecular typing

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine 1) the origin of the virus, 2) virus strains circulating in the United States, and 3) whether these strains are no longer endemic in the United States.[12] Specimens for molecular typing should be obtained from patients with CRS as soon as possible after diagnosis. Appropriate specimens include throat swabs, cerebrospinal fluid, and cataracts from surgery. Specimens for virus isolation should be sent to CDC for molecular typing as directed by the state health department.

Reverse transcription polymerase chain reaction

Extensive evaluations have documented the usefulness of PCR for detection of rubella virus in clinical specimens.[13–15] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by RT-PCR

VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[16] 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 facilities, and other institutions. Persons reporting should contact the state health department for reporting requirements specific to that state.

Reporting to CDC

Within 14 days of the initial report to the state or local health department , provisional reports of rubella and CRS cases should be sent by the state health department to CDC via the National Electronic Telecommunications System for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS). Reporting should not be delayed because of incomplete information or lack of confirmation.

In addition, each possible and confirmed case of CRS should be reported to the National Congenital Rubella Syndrome Registry (NCRSR), National Center for Immunization and Respiratory Diseases (NCIRD) at (404) 639-8253. The Congenital Rubella Sydrome 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. NCRSR cases are classified by year of patient's birth. Although case report forms should be as complete as possible, lack of complete information should not delay the reporting.

Information to collect

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
- Outcome (infant survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses
- Laboratory (performed on both mother and infant)
  - Virus isolation
  - Dates and results of previous serologic tests for rubella immunity
  - Serology
- Maternal history
  - Dates of rubella vaccinations
  - Number of doses of vaccine given
  - If not vaccinated, reason
  - History of documentation of rubella infection during pregnancy
  - History of pregnancies within and outside the United States (including country and years of pregnancies)
- Epidemiologic
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)
  - Source of exposure
  - Travel history

IX. Vaccination

Because birth defects are noted in 3%–5% of all births, confusion about the etiology of birth defects may result if vaccine is administered during pregnancy. In 2001, the Advisory Committee on Immunization Practices (ACIP) reviewed data from several sources indicating that no cases of CRS had been identified among infants born to women who were vaccinated against rubella within 3 months of or early in pregnancy. On the basis of these data, ACIP changed its recommendation regarding the time period for avoiding pregnancy after receipt of a rubella-containing vaccine from 3 months to 28 days.[17]

Data were available on 680 live births to susceptible women who were inadvertently vaccinated within 3 months prior to conception or early in pregnancy. No infant was born with CRS. However, a small theoretical risk of CRS of not greater than 0.5% cannot be ruled out. Limiting the analysis to the 293 infants born to susceptible mothers vaccinated 1–2 weeks before to 4–6 weeks after conception, the maximal theoretical risk is 1.3%.[17]

X. Enhancing Surveillance

Guidelines for enhancing surveillance are contained in Chapter 18, "Enhancing Surveillance," as well as in the MMWR report entitled "Control and Prevention of Rubella: Evaluation and Management of Suspected Outbreaks. Rubella in Pregnant Women, and Surveillance for Congenital Rubella Syndrome."[6] In addition, the following activities may be undertaken to improve the detection and reporting of cases and to improve the comprehensiveness and quality of surveillance for rubella and CRS.

Promote awareness that rubella and CRS still occur in the United States.

Although only 10 rubella cases and one imported CRS case were reported in 2004, it is likely that not all cases were identified. Efforts should continue to promote physicians' awareness of the possibility of rubella and CRS, especially when evaluating patients with suspected measles who have negative serologic tests for acute measles infection (negative serum measles IgM).

Promote awareness of groups at high risk for rubella infection and CRS births.

Rubella vaccine is not administered routinely in many countries, and in others rubella vaccine was only recently added to the childhood immunization schedule.[3, 5] Thus, many persons born outside the United States or who received childhood immunizations in other countries may have never received rubella vaccine. Healthcare providers should have a heightened index of suspicion for rubella and CRS births among persons from countries without a history of routine rubella vaccination programs.

Conduct 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.[6] Women who contract rubella while pregnant should be monitored for birth outcome, and a rubella-specific IgM antibody test should be performed on the infant after birth. Healthcare providers should be advised to evaluate infants born with conditions consistent with CRS and to perform a rubella-specific IgM antibody test on infants suspected of having CRS.

Search laboratory records.

Audits of laboratory records may provide reliable evidence of previously unreported serologically confirmed or culture-confirmed cases of congenital rubella syndrome. Infants with CRS have been identified by including the serologic results for toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH) agents in audits of laboratory records. This may be particularly useful in hospitals serving high-risk populations.

Compare other data sets and identify speciality schools and clinics.

After a rubella outbreak has occurred, surveillance for CRS can be enhanced in several ways. Birth defects registries may reveal unreported CRS cases.[2] In addition, children with CRS whose cases were never reported may be enrolled in schools for the deaf or blind. Pediatric specialty clinics caring for children with mental retardation, congenital heart defects, congenital deafness and hearing impairment, congenital cataracts, or growth retardation may be a source of unreported CRS patients.

Review hospital discharge data and linkages with newborn hearing screening programs.

Reviewing hospital discharge data in high-risk areas has proved useful in identifying undiagnosed cases of CRS.[18] Infants with discharge codes consistent with CRS may then be categorized according to the CRS case definition, allowing for greater insight into the rates

of CRS in high-risk populations. Furthermore, if newborn hearing screening is performed routinely, infants identified with hearing deficiencies or progressive hearing loss may also be tested for CRS, since hearing impairment is the most common single defect associated with CRS.

XI. Case Investigation

The diagnosis of a single case of CRS in a community should trigger intensified rubella and CRS surveillance.

Cases of U.S.-acquired CRS are sentinel events indicating the presence of rubella infections in the 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. The classic presentation for CRS is cataracts, hearing impairment, and congenital heart disease (especially patent ductus arteriosus or peripheral pulmonic stenosis). Infants born to women infected with rubella 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, cord blood or serum to be tested for rubella IgM and urine and throat specimens for viral isolation should be obtained. In the event of a negative IgM result from a specimen taken within 1 month of birth, a second specimen should be obtained and tested once the infant is at least 1 month of age. A CRS case report form (see Appendix 17) should be completed.

Efforts should be made to obtain clinical specimens (throat swabs and urine) for virus isolation from all case-patients. These isolates are essential for tracking the epidemiology of rubella in the United States now that it is believed rubella virus no longer continuously circulates in this country. By comparing isolates from new case-patients with other rubella virus samples, the origin of particular virus types in this country can be tracked.[12] See Appendix 15 for the procedure for collection of specimens.

XII. Preventing Transmission From Infants With CRS

Cases of U.S.-acquired rubella have occurred among susceptible persons providing care for infants with CRS.[19] Infants with CRS can shed the virus for prolonged periods, up to 1 year of age or longer in some cases. Persons having contact with infants with CRS should be immune to rubella. Infants with CRS should be placed in contact isolation. These precautions should be enforced during any admission before the first birthday, unless two cultures of throat and urine specimens obtained 1 month apart after the infant is older than 3 months are negative for virus.[6]

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