Chapter 12: 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, the risk of fetal infection may be as high as 90%. Consequences of congenital rubella infection include abortions, miscarriages, stillbirths, and a constellation of severe birth defects known as congenital rubella syndrome (CRS). The most common congenital defects are cataracts, heart defects, hearing impairment, and developmental delay.

II. Background

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

The number of reported cases of CRS in the United States has declined 96% from 77 cases in 1970 to 3 cases in 2001.[1-3] Two of the three infants with CRS reported in 2001 had foreign-born mothers. Between 1990 and 2001, 121 cases of confirmed CRS were reported to the National Congenital Rubella Syndrome Registry. Of the 118 cases with known import status between 1990 and 2001, 33 (28%) were imported.

Despite routine rubella vaccination among children, some rubella outbreaks continue in the U.S. These outbreaks are primarily confined to groups who traditionally refuse vaccinations and to adults from countries without a history of or with recently established routine rubella vaccination programs. Throughout the 1990s, the majority of infants with CRS were infants of mothers who fall into these categories.

Though rubella cases are at record-low levels in the United States, rubella and CRS continue to be global burdens. It is estimated that there are more than 110,000 cases of CRS annually throughout the world. With the increased use of rubella vaccine; however, the burden of rubella infection should decrease in the future. As of April, 2000, 52% of countries use rubella vaccine in their national programs.

III. Importance of rapid case identification

As infants with CRS may shed virus for prolonged periods, they should be identified as early in life as possible in order to prevent further spread of the virus. Infants with CRS may shed virus up to 1 year of age or longer and should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained 1 month apart are negative for rubella virus after age 3 months.[4]

Additionally, 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.[5,6]

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 disease incidence 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 indigenous rubella and CRS in the United States by the year 2010.[7]

VI. Case definitions

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) in June 1999.[8]

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
- Demonstration of rubella-specific immunoglobulin M (IgM) antibody
- Infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month)
- Detection of rubella virus by reverse transcription polymerase chain reaction (RT-PCR)

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.

Indigenous case: Any case that cannot be proved to be imported.

Imported case: A case that has its source outside the reporting state.

- **International importation**. Defined as CRS in a United States or non-United States citizen whose mother was outside the United States for the entire period when she may have had exposure to rubella (21 days before conception and during the first 20 weeks of gestation) or who has known exposure to risks outside the United States.

- **Importation from another state.** This classification requires documentation that the mother either had face-to-face contact with a case of rubella outside the state or was out of state for the entire period when she might have become infected (14–23 days before rash onset or 21 days before conception and during the first 20 weeks of gestation).

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 sera. 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).[4]

- Documentation of persistence of serum rubella IgG titer beyond the time expected from passive transfer of maternal IgG antibody.

- 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 19, "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 11, "Rubella."

- **Enzyme immunoassay (EIA).** Most of the diagnostic testing done for rubella antibodies uses some variation of the EIA, which is sensitive, widely available, and relatively easy to perform. EIA is the preferred testing method for IgM, using the capture technique; however, 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 isolation

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 have become endemic in the U.S.

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS cases (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 2 cultures of clinical specimens obtained 1 month apart 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 U.S., and 3) whether these strains have become endemic in the U.S.[9] 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 (RT- PCR)

In the United Kingdom, there has been extensive evaluation of PCR for detection of rubella virus in clinical specimens, documenting its usefulness.[10,11] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by RT-PCR.

VIII. Reporting

Each state and territory has regulations and/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 health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Contact your state health department for reporting requirements in your state.

Reporting to CDC

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), once available, within 14 days of the initial report to the state or local

health department. 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 Immunization Program (NIP), at (404) 639-8230. The NCRSR case report form (see **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 before case reporting, 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 of the mother
  - Length of time in U.S. of the mother

- Reporting Source
  - County
  - Earliest date reported

- Clinical
  - Symptoms or syndromes
    - Cataracts
    - Hearing impairment
    - Developmental delay
    - Type of congenital heart defect
    - Meningoencephalitis
    - Microcephaly

- Outcome (case survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses

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Information to collect (con't.)

- 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 of the U.S. (including country and years of pregnancies)

- Epidemiological
  - 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 or early in pregnancy. On the basis of these data, ACIP shortened its recommended period to avoid pregnancy after receipt of a rubella-containing vaccine from 3 months to 28 days.[13]

Data were available on 680 live births to susceptible women who were inadvertently vaccinated 3 months prior to conception or early in pregnancy. None of the infants was born with CRS. However, a small theoretical risk of 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%.[13]

X. Enhancing surveillance

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. Additional guidelines for enhancing surveillance are given in Chapter 16, "Enhancing Surveillance," as well as in the *MMWR Recommendations and Reports* issue, "Control and Prevention of

Rubella: Evaluation and Management of Suspected Outbreaks, Rubella in Pregnant Women, and Surveillance for Congenital Rubella Syndrome."[4]

Promoting awareness that rubella and CRS still occur in the U.S.

Although only 19 cases of rubella and 2 cases of CRS were reported in 2001, 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).

Promoting awareness of high-risks groups 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.[14] Thus, many persons born outside the United States or who received childhood immunizations in other countries may never have had the opportunity to receive rubella vaccine. Health-care providers should have a heightened index of suspicion of rubella and CRS births in individuals from countries without a history of routine rubella vaccination programs.

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.[4] 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. Health-care 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.

Searching 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 serological 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.

Comparing other data sets

Birth defects registries may reveal unreported CRS cases.[1] 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, and growth retardation may be a source of

unreported CRS patients. These activities should be undertaken following rubella outbreaks as part of enhancing surveillance for CRS.

Reviewing hospital discharge data and linkages with newborn hearing screening programs

Reviewing hospital discharge data in high-risk areas has proven useful in identifying undiagnosed cases of CRS.[15] 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 routinely performed, infants identified through screening with hearing deficiencies or progressive hearing loss may also be tested for CRS, as hearing impairment is the most common single defect associated with CRS.

XI. Case investigation

Cases of indigenous CRS are sentinel events indicating the presence of rubella infections in the community which may have been previously unrecognized. The diagnosis of a single case of indigenous 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 them to possible rubella circulation.

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

Infants with CRS may present with different 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, symptoms may not be apparent depending on the gestational age of the infant at the time of the mother's infection. After 20 weeks gestation, the only defect may be hearing impairment. Also, 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, a cord blood or sera 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 cases. 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.[9] See **Appendix 15** for the procedure for collection of specimens.

XII. Preventing transmission from infants with CRS

Cases of indigenous rubella have occurred among susceptible persons providing care for infants with CRS.[16] Infants with CRS can shed the virus for prolonged periods of time, 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 are negative for virus after age 3 months.[4]

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