

Chapter 11: Rubella

Laura Zimmerman, MPH; Susan Reef, MD

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%–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. Postauricular occipital and posterior cervical lymphadenopathy is characteristic and precedes the rash by 5–10 days. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. Rare complications include thrombocytopenic purpura and encephalitis.

When infection occurs during pregnancy, especially during the first trimester, the risk of fetal infection may be as high as 90%, often resulting in congenital rubella syndrome (CRS). Consequences of CRS include abortions, miscarriages, stillbirths, and severe birth defects. Up to 20% of the infants born to mothers infected during the first half of pregnancy have CRS. The most common congenital defects are cataracts, heart defects, hearing impairment, and developmental delay. See Chapter 12, “Congenital Rubella Syndrome,” for more details.

II. Background

The number of reported cases of rubella in the United States has declined more than 99%, from 57,686 cases in 1969 to 176 cases in 2000, with even fewer cases in 2001. The proportion of cases among adults aged ≥ 20 years has risen from 29% of cases in 1991 to 79% of cases in 2000. In 2000, 138 (83%) reported rubella cases of known race or ethnicity were among persons of Hispanic ethnicity.¹ Despite routine rubella vaccination among children, rubella outbreaks occurred in the 1990s and 2000 among members of religious communities that traditionally refuse vaccination^{2,3} and among adults from countries without a history of routine rubella vaccination programs.

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

III. Importance of rapid case identification

Prompt identification of suspected, probable, or confirmed cases of rubella is important to avoid exposure of susceptible pregnant women. Rapid case identification and investigations are also important so that control measures can be initiated to prevent the spread of the disease.

IV. Importance of surveillance

Surveillance data are used to identify groups of persons or areas in which additional disease control efforts (such as immunization) are required to reduce disease incidence and to evaluate the effectiveness of disease prevention programs and policies.

V. Disease reduction goals

The proposed Healthy People 2010 objectives include a goal to eliminate indigenous rubella and CRS in the United States by the year 2010.⁴

VI. Case definitions

The following case definition for rubella has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 1997.⁵

Clinical case definition

Rubella is an illness that has all of the following characteristics:

- Acute onset of generalized maculopapular rash
- Temperature > 99°F (37.2°C), if measured
- Arthralgia or arthritis, lymphadenopathy, or conjunctivitis

Laboratory criteria for diagnosis

Laboratory criteria for diagnosis consist of the following:

- Positive serologic test for rubella immunoglobulin M (IgM) antibody
- Significant rise between acute and convalescent-phase titers in serum rubella immunoglobulin G antibody level by any standard serologic assay
- Isolation of rubella virus
- Detection of virus by reverse transcription polymerase chain reaction (RT-PCR)

Case classification

Suspected: Any generalized rash illness of acute onset.

Probable: A case that meets the clinical case definition, has no or noncontributory serologic or virologic testing, and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed: A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case.

Comment: Serum rubella IgM test results that are false positives have been reported in persons with other viral infections (e.g., acute infection with Epstein-Barr virus [infectious mononucleosis], recent cytomegalovirus infection, and parvovirus infection) or in the presence of rheumatoid factor.^{6,7} Patients who have laboratory evidence of recent measles infection are excluded.

Asymptomatic confirmed. A case in an asymptomatic person that is laboratory-confirmed and epidemiologically linked to a laboratory-confirmed case that is clinically consistent with rubella.

Importation status

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

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

- Importation from another country: Onset of rash is within 14–23 days of entering the United States.
- Importation from another state: To establish, obtain documentation that the case-patient had face-to-face contact with a case of rubella outside the state or was out of the state for the entire period when infection could have occurred (i.e., within 14–23 days before rash onset).

VII. Laboratory testing

The only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, a significant rise in IgG antibody from paired acute and convalescent sera, a positive viral culture for rubella, or detection of the virus by RT-PCR.

Diagnostic tests used to confirm acute or recent rubella infection or CRS include serologic testing and virus cultures. Because many rash illnesses may mimic rubella infection and 20%–50% of rubella infections may be subclinical, laboratory testing is the only way to confirm the diagnosis. Acute rubella infection can be confirmed by the presence of serum rubella IgM, a significant rise in IgG antibody titer in acute and convalescent serum specimens, positive rubella virus culture, or detection of the rubella virus by RT-PCR. Sera should be collected as early as possible (within 7–10 days) after onset of illness, and again at least 7–14 days (preferably 14–21 days) later. IgM antibodies may not be detectable before day 5 after rash onset. In case of a negative rubella IgM and IgG in specimens taken before day 5, repeat serologic testing. Virus may be isolated from 1 week before to 2 weeks after rash onset. However, maximum viral shedding is up to day 4 after rash onset.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections or positive heterophile test (indicating infectious mononucleosis) or

with a positive rheumatoid factor (indicating rheumatologic disease).^{6,7} When a false-positive rubella IgM is considered, a rheumatoid factor, parvovirus IgM, and heterophile test should be used to rule out a false-positive rubella IgM test result.

Immunity to rubella may be documented by the presence of serum IgG rubella-specific antibodies by enzyme immunoassay, hemagglutination inhibition, latex agglutination, and immunofluorescent antibody assays.

For additional information on laboratory testing for the surveillance of vaccine-preventable diseases, see Chapter 19, “Laboratory Support for Surveillance of Vaccine-Preventable Diseases.”

Serologic testing

The serologic tests available for laboratory confirmation of rubella infections and immunity vary among laboratories. The following tests are widely available and may be used to screen for rubella immunity, for laboratory confirmation of disease, or both. The state health department can provide guidance on available laboratory services and preferred tests.

Clinical diagnosis of rubella is unreliable and should NOT be considered in assessing immune status.

Enzyme immunoassay (EIA). Most of the diagnostic testing done for rubella antibodies use 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; indirect assays are also acceptable.

Hemagglutination inhibition (HI) test. This once was the standard and most commonly used technique and allows for either screening or diagnosis (if paired acute and convalescent sera are tested). A four-fold rise or greater in HI antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody indicative of primary infection.

Latex agglutination (LA) test. The 15-minute LA test appears to be sensitive and specific for screening when performed by experienced laboratory personnel.

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 to avoid false-positive results due to complexes with rheumatoid antibody.

Virus isolation

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS cases (see **Appendix 15**). The best results come from throat swabs. Efforts should be made to obtain clinical specimens for virus isolation from all cases (or from at least some cases in each outbreak) at the time of the initial investigation. Virus may be isolated from 1 week before to 2 weeks after rash onset. However, maximum viral shedding occurs up to day 4 after rash onset.

Molecular typing

Rubella virus isolates are very important for surveillance. Molecular epidemiologic surveillance provides important information on:

- Origin of the virus
- Virus strains circulating in the U.S.
- Whether these strains have become endemic in the U.S.

In obtaining specimens for rubella molecular typing, collect throat swabs within 4 days of rash onset. Specimens for molecular typing from CRS cases should be collected as soon as possible after diagnosis. Appropriate specimens from CRS cases for molecular typing include throat swabs, cerebrospinal fluid, and cataracts from surgery. Strains 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)

There has been extensive evaluation of RT-PCR for detection of rubella virus in clinical specimens, documenting its usefulness.^{8,9} 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.¹⁰ 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, schools, 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 to the National Notifiable Diseases Surveillance System by the state health department via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS), once available.

Reporting should not be delayed because of incomplete information or laboratory confirmation; following completion of case investigations, data previously submitted to NETSS or NEDSS should be updated with the available new information.

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

Information to Collect

- Demographic information
 - Name
 - Address
 - Age
 - Sex
 - Ethnicity

continued on the next page

Information to collect (con't.)

- Race
- Country of birth
- Length of time in U.S.

- Reporting Source
 - County
 - Earliest date reported

- Clinical
 - Hospitalizations and duration of stay
 - Date of illness onset
 - Duration of rash
 - Symptoms
 - Fever
 - Arthralgia or arthritis
 - Lymphadenopathy
 - Conjunctivitis
 - Complications
 - Encephalitis
 - Arthralgia or arthritis
 - Thrombocytopenia
 - Outcome (case survived or died)
 - Date of death

- Laboratory
 - Virus isolation
 - Serology

- If female, pregnancy history
 - If pregnant, pregnancy status
 - Number of weeks gestation at onset of illness
 - Prior evidence, date of serological immunity, or both
 - Prior diagnosis and date of rubella
 - Date and specific titer result of prior serum rubella IgG titer
 - Number and dates of previous pregnancies and location (e.g. state or country) of these pregnancies
 - Pregnancy outcome, when available (e.g., termination, CRS, normal infant)

- Vaccine Information
 - Number of doses of rubella-containing vaccine received
 - Dates of vaccination
 - If not vaccinated, reason

continued on the next page

Information to collect (con't.)

- Epidemiological
 - Transmission setting (infection acquired in daycare, school, workplace)
 - Relationship to outbreak (Is case part of an outbreak or is it a sporadic case?)
 - Source of exposure and travel history (indigenous case or imported; if imported, international out-of-state import; include state name, country name, and dates of travel)

IX. Vaccination

Live attenuated rubella virus vaccine is recommended for persons ≥ 12 months of age unless one of these conditions applies: a medical contraindication such as severe immunodeficiency or pregnancy; documented evidence of rubella immunity as defined by serological evidence (e.g., a positive serum rubella IgG); documented immunization with at least one dose of rubella vaccine on or after first birthday; or birth before 1957 (except women who could become pregnant). Clinical diagnosis of rubella is unreliable and should **not** be considered in assessing immune status.

With use of combined measles-mumps-rubella (MMR) for measles vaccination under the currently recommended two-dose schedule, most children and adolescents now receive two doses of rubella vaccine. Rubella vaccine, as MMR, is recommended at 12–15 months of age. A second dose of MMR is recommended at 4–6 years of age.¹¹

Health-care providers who treat women of childbearing age should routinely determine rubella immunity and vaccinate those who are susceptible and not pregnant. Women found to be susceptible during pregnancy should be vaccinated immediately post-partum.¹¹

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 prior to conception 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.¹²

Data were available on 680 live births to susceptible women who were inadvertently vaccinated 3 months before or during 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 who were vaccinated 1–2 weeks before to 4–6 weeks after conception, the maximal theoretical risk is 1.3%.¹²

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. Additional guidelines for enhancing surveillance are given in Chapter 16, “Enhancing Surveillance.”

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

Although only 200 cases of rubella and 11 cases of CRS were reported in 2000 and 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, (i.e., 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. Thus, many persons 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.

Expanding laboratory testing

Serologic tests for measles and rubella should be done sequentially. All suspected cases of measles that have a negative serum measles IgM test should be tested for rubella IgM and IgG. All suspected cases of rubella should be tested for serum rubella IgM and if negative, and measles is suspected, tested for measles IgM.

Searching laboratory records

Audits of laboratory records may provide reliable evidence of previously unreported serologically confirmed or culture-confirmed cases of rubella. This activity is particularly important during outbreaks in order to better define the scope of disease transmission in an area.

Conducting active surveillance

In outbreak settings, active surveillance for rubella should be maintained for at least two incubation periods following rash onset of the last case. Two incubation periods allow for the identification of transmission from a subclinical case. Surveillance for CRS should be implemented when confirmed or probable rubella cases are documented in a setting where pregnant women might have been exposed.

Monitoring surveillance indicators

Regular monitoring of surveillance indicators, including time intervals between diagnosis and reporting and completeness of reporting, may identify specific areas of the surveillance and reporting system that need improvement. Indicators that should be monitored include:

- The proportion of confirmed cases reported to the NNDSS with complete information
- The median interval between rash onset and notification of a public health authority, for confirmed cases
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of confirmed cases among women of child-bearing age with known pregnancy status

XI. Case investigation

The goal of rubella case investigation is to prevent exposure of susceptible pregnant women to rubella and thereby prevent cases of CRS. It is essential that potentially susceptible, exposed pregnant women be identified, evaluated, and counseled. The Rubella Surveillance Worksheet (see **Appendix 16**) may be used as a guideline in conducting a case investigation as well as *MMWR Recommendations and Reports*, “Control and Prevention of Rubella: Evaluation and Management of Suspected Outbreaks, Rubella in Pregnant Women, and Surveillance for Congenital Rubella Syndrome.”¹³ (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5012a1.htm>)

Establishing a diagnosis of rubella

Because clinical diagnosis of rubella is unreliable, cases must be laboratory confirmed, especially if the reported cases are not epidemiologically linked to a laboratory-confirmed case.

The occurrence of a rubella-like illness in recently vaccinated persons can pose particular difficulties in the outbreak setting. Ten percent of recipients of rubella-containing vaccine may develop fever and rash approximately 1 week after vaccination, and vaccination of susceptible persons results in production of IgM antibody that cannot be distinguished from that resulting from natural infection. Persons vaccinated within 7 days of a rubella-like illness who are IgM positive should be classified as confirmed cases of wild-type rubella if they are epidemiologically linked to a laboratory-confirmed case. Molecular typing techniques can distinguish between vaccine and wild virus rash for those vaccinated 7–10 days before rash onset. Specimens for molecular typing should be obtained within 4 days of rash.

Obtaining accurate pregnancy status for adult women

All women of childbearing age who are contacts of a case should have their pregnancy status determined. If a pregnant woman is infected with rubella, immediate medical consultation is necessary. If a pregnant woman is susceptible to rubella, precautions should be taken to prevent any exposure to persons infected with rubella; these activities may include ensuring rubella immunity of household contacts and isolation of women from settings where rubella virus has been identified.¹³

(<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5012a1.htm>)

Obtaining accurate and complete immunization histories

Rubella case investigations should include complete immunization histories that document any doses of rubella-containing vaccine.

Identifying the source of infection

Efforts should be made to identify the source of infection for every confirmed case of rubella. Case-patients or their caregivers should be asked about contact with other known cases; in outbreak settings, such histories may often be obtained. Since many rubella cases (20%–50%) are asymptomatic, identification of a source will not always be possible. When no history of contact with a known case can be elicited, opportunities for exposure to unidentified cases in high-risk populations should be sought. Investigating sources of exposure should be directed to the place and time period in which transmission would have occurred. Such exposures may occur in colleges or universities, workplaces, and communities where unvaccinated persons congregate.

Assessing potential for transmission and identify contacts

In recent outbreaks, transmission has occurred in households, communities, workplaces, and prisons. As part of the case investigation, the potential for further transmission should be assessed, and contacts (particularly susceptible pregnant women) of the case-patient during the infectious period (7 days before to 7 days after the onset of rash) should be identified.

Obtaining specimens for virus isolation

Efforts should be made to obtain clinical specimens (throat swabs and urine) for virus isolation from all cases (or from at least some cases in each outbreak) at the time of the initial investigation. These specimens for isolation of rubella virus should be obtained within 4 days after rash onset. Isolates are essential for tracking the epidemiology of rubella in the United States, now that rubella virus may no longer continuously circulate in this country. By comparing isolates from new case-patients to other virus samples, the origin of particular virus types in this country can be tracked.¹⁰ Furthermore, this information may help to document the interruption of indigenous transmission. See **Appendix 15** for the procedure to follow in collection of specimens.

Conducting laboratory evaluation of exposed pregnant women

When a pregnant woman is exposed to rubella, a blood specimen should be taken as soon as possible and tested for rubella IgG and IgM antibody. The specimen should be stored for possible retesting. A positive IgM response indicates recent or acute infection. A positive IgG result performed at the time of exposure most likely indicates immunity. If there is no IgG or IgM response, a second specimen should be taken 3 to 4 weeks later and tested concurrently for IgG with the first specimen.¹¹ If the response is still negative, a third specimen should be obtained at 6 weeks, and again tested for IgG concurrently with the first. An IgG negative result at 6 weeks indicates that infection has not occurred. A negative response on the first specimen and a positive response on the second or third specimen indicate that infection has occurred. As long as the exposure to rubella continues, it is important to continue testing for IgG and IgM responses.

Establishing pregnancy outcome registry for women diagnosed with rubella during pregnancy

All pregnant women infected with rubella during pregnancy should be followed to document the pregnancy outcome (e.g., termination, CRS, normal infant). Outcomes that are documented should be reported to the CDC.

XII. Outbreak control

Aggressive response to rubella outbreaks may interrupt disease transmission and will increase vaccination coverage among persons who might otherwise not be protected. The main strategies are to define at-risk populations, to ensure that susceptible persons are rapidly vaccinated (or excluded from exposure if a contraindication to vaccination exists), and to maintain active surveillance to permit modification of control measures if the situation changes.

Control measures should be implemented as soon as at least one case of rubella is confirmed in a community. In settings where pregnant women may be exposed, control measures should begin as soon as rubella is suspected and should not be postponed until laboratory confirmation. All persons at risk who cannot readily provide laboratory evidence of immunity or a documented history of vaccination on or after their first birthday should be considered susceptible and should be vaccinated if no contraindications exist.

In schools and other educational institutions, exclusion of persons without valid evidence of immunity may limit disease transmission and may help rapidly raise the vaccination level in the target population. All persons who have been exempted from rubella vaccination for medical, religious, or other reasons also should be excluded from attendance. Exclusion should continue until 3 weeks after the onset of rash of the last reported case in the outbreak setting.

Mandatory exclusion and vaccination of adults should be practiced in rubella outbreaks in medical settings because pregnant women may be exposed.

All persons at risk who cannot readily provide laboratory evidence of immunity or a documented history of vaccination on or after their first birthday should be considered susceptible and should be vaccinated if no contraindications exist.

References

1. CDC. Rubella and congenital rubella syndrome--United States, 1994-1997. *MMWR Morb Mortal Wkly Rep.* 1997;46:350-354.
2. CDC. Rubella and congenital rubella syndrome--United States, January 1, 1991-May 7, 1994. *MMWR Morb Mortal Wkly Rep.* 1994;43:391, 397-391, 401.
3. Mellinger AK, Cragan JD, Atkinson WL, et al. High incidence of congenital rubella syndrome after a rubella outbreak. *Pediatr Infect Dis J.* 1995;14:573-578.
4. United States Department of Health and Human Services. *Healthy People 2010: With understanding and improving health.* 2000; Washington, D.C.: U.S. Government Printing Office.
5. CDC. Case definitions for infectious conditions under public health surveillance. *MMWR Recomm Rep.* 1997;46:1-55.
6. Kurtz JB, Anderson MJ. Cross-reactions in rubella and parvovirus specific IgM tests. *Lancet.* 1985;2:1356.
7. Morgan-Capner P. False positive tests for rubella-specific IgM. *Pediatr Infect Dis J.* 1991;10:415-416.
8. Bosma TJ, Corbett KM, O'Shea S, et al. PCR for detection of rubella virus RNA in clinical samples. *J Clin Microbiol.* 1995;33:1075-1079.
9. del Mar MM, de Ory F, Moreno M, et al. Simultaneous detection of measles virus, rubella virus, and parvovirus B19 by using multiplex PCR. *J Clin Microbiol.* 2002;40:111-116.
10. Roush S, Birkhead G, Koo D, et al. Mandatory reporting of diseases and conditions by health care professionals and laboratories. *JAMA.* 1999;282:164-170.
11. Watson JC, Hadler SC, Dykewicz CA, et al. Measles, mumps, and rubella--vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 1998;47:1-57.
12. CDC. Revised ACIP recommendation for avoiding pregnancy after receiving a rubella-containing vaccine. *MMWR Morb Mortal Wkly Rep.* 2001;50:1117.
13. CDC. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR Recomm Rep.* 2001;50:1-23. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5012a1.htm>