104 - 212 Rubella (German Measles)

212 Rubella (German Measles)

Acknowledgment The authors acknowledge the substantial contributions of Kaitlin Rainwater-Lovett, who coauthored prior editions of this chapter. ■ ■FURTHER READING De Swart RL, Moss WJ: The immunological basis for immunization series: Module 7: Measles. Update 2020. Geneva: World Health Organization, 2020. Griffin DE: Measles immunity and immunosuppression. Curr Opin Virol 46:9, 2020. Hübschen JM et al: Measles. Lancet 399:678, 2022. Mina MJ et al: Measles virus infection diminishes preexisting antibod ies that offer protection from other pathogens. Science 366:599, 2019. Minta AA et al: Progress toward measles elimination—Worldwide, 2000–2022. MMWR Morb Mortal Wkly Rep 72:1262, 2023. Moss WJ: Measles. Lancet 380:2490, 2017. Moss WJ et al: Feasibility assessment of measles and rubella eradica tion. Vaccine 39:3544, 2021. Phadke VK et al: Vaccine refusal and measles outbreaks in the US. JAMA 324:1344, 2020. Strebel PM, Orenstein WA: Measles. N Engl J Med 381:349, 2019. World Health Organization: Measles vaccines: WHO position paper—April 2017. Wkly Epidemiol Rec 92:205, 2017. Alan C. Ou, Ludmila M. Perelygina,

Laura A. Zimmerman, Susan E. Reef

Rubella (German Measles) Rubella was historically viewed as a variant of measles or scarlet fever. After an epidemic of rubella in Australia in the early 1940s, the ophthalmologist Norman Gregg noticed the occurrence of congenital cataracts among infants whose mothers had reported rubella during early pregnancy, and congenital rubella syndrome (CRS; see “Clinical Manifestations,” below) was first described. Not until 1962 was a sepa rate viral agent for rubella isolated. ■ ■ETIOLOGY Rubella virus is a member of the Matonaviridae family the genus Rubivirus. This single-strand RNA enveloped virus measures 40–80 nm in diameter. Its nucleocapsid consists of ~10-kb positive-sense RNA genome surrounded by a protein shell composed of a core protein and a single-layer lipoprotein envelope with spike-like projections contain ing two glycoproteins, E1 and E2. There is only one antigenic type of rubella virus, and humans are its only known reservoir. ■ ■PATHOGENESIS AND PATHOLOGY Although the pathogenesis of postnatal (acquired) rubella has been well documented, data on pathology are limited because of the mild ness of the disease. Rubella virus is spread from person to person via respiratory droplets. Primary implantation and replication in the nasopharynx are followed by spread to the lymph nodes. Subsequent viremia occurs, which in pregnant women often results in infection of the placenta. Placental virus replication may lead to infection of fetal organs. The pathology of CRS in the infected fetus is well defined, with almost all organs found to be infected; however, the pathogenesis of CRS is only

poorly delineated. In tissue, infections with rubella virus have diverse effects, ranging from no obvious impact to cell destruction. The hallmark of fetal infection is a chronic infection with persistence throughout fetal development in utero and for up to 1 year after birth. Individuals with acquired rubella may shed virus from 7 days before rash onset to ~5–7 days thereafter. Both clinical and subclinical

infections are considered contagious. Infants with CRS may shed large quantities of virus from bodily secretions, particularly from the throat and in the urine, up to 1 year of age. Outbreaks of rubella, including some in nosocomial settings, have originated with index cases of CRS. Thus, only individuals immune to rubella virus should have contact with infants who have CRS or who are congenitally infected with rubella virus but are not showing signs of CRS.

■ ■EPIDEMIOLOGY The largest recent rubella epidemic in the United States took place in 1964–1965, when an estimated 12.5 million cases occurred, resulting in ~20,000 cases of CRS. Since the introduction of the routine rubella vac cination program in the United States in 1969, the number of rubella cases reported each year has dropped by >99%; the rate of vaccination coverage with rubella-containing vaccine (RCV) has been >90% among children 19–35 months old since 1996. In the United States, a goal for the elimination of rubella and CRS by 2000 was set in 1989. Interrup tion of endemic transmission of rubella virus was achieved by 2001. In 2004, a panel of experts agreed unanimously that rubella was no longer an endemic disease in the United States. The criteria used to document lack of endemic transmission included low disease incidence, high nationwide rubella antibody seroprevalence, outbreaks that were few and contained (i.e., small numbers of cases), and lack of endemic virus transmission (as assessed by genetic sequencing). Although interrup tion of endemic transmission has been sustained since 2001, rubella virus importations continue to occur, and cases continue to develop among susceptible persons. During 2010−2022, 66 cases of rubella were reported; 71% of these cases were in persons 20−49 years old— an age group that includes women of childbearing age. During this period, 13 cases of CRS were reported, all from foreign-born mothers. Therefore, health care providers should remain vigilant, considering the possibility of rubella virus infection in adults (especially those emi grating or returning from countries without rubella control programs) and recognizing the potential for CRS among their infants. CHAPTER 212 Rubella (German Measles) The Global Measles and Rubella Strategic Framework 2021–2030 envisions a “world free from measles and rubella” with the goal to “achieve and sustain the regional measles and rubella elimination goals.” By 2023, five of the six World Health Organization (WHO) regions had rubella elimination goals (see “Prevention” below). Although rubella and CRS are no longer endemic in the WHO Region of the Americas, they remain important public health problems globally. The number of rubella cases reported worldwide in 2000 was ~700,000; this figure declined to 17,407 in 2022. However, the number of rubella cases may be underestimated because cases are often mild, patients may not seek care, cases may not be recognized or may not be reported, and, in some countries, cases are identified through measles surveillance systems that are not specific for rubella. Despite a continued increase in the number of countries with rubella vaccination programs, 25% of the world’s children remained unvaccinated against rubella in 2022. In 2010, it was estimated that 105,000 cases of CRS occurred annually globally. ■ ■CLINICAL FEATURES Acquired Rubella Acquired rubella commonly presents with a generalized maculopapular rash that usually lasts up to 3 days (Fig. 212-1), although as many as 50% of cases may be subclinical or without rash. When the rash occurs, it is usually mild and may be dif ficult to detect in persons with darker skin. In younger children, rash is usually the first sign

of illness. However, in older children and adults, a 1- to 5-day prodrome often precedes the rash and may include lowgrade fever, malaise, and upper respiratory symptoms. The incubation period is 14 days (range, 12–23 days). Lymphadenopathy, particularly occipital and postauricular, may be noted during the second week after exposure. Although acquired rubella is usually thought of as a benign disease, arthralgia and arthritis are common in infected adults, particularly women. Thrombocytope nia and encephalitis are less common complications. Congenital Rubella Syndrome The most serious consequence of rubella virus infection can develop when a woman becomes infected

FIGURE 212-1 Mild maculopapular rash of rubella in a child. during pregnancy, particularly during the first trimester. The resulting complications may include miscarriage, fetal death, premature deliv ery, or live birth with congenital defects. Infants infected with rubella virus in utero may have myriad physical defects (Table 212-1), which most commonly relate to the eyes, ears, and heart. This constellation of severe birth defects is known as CRS. In addition to permanent manifestations, there are a host of transient physical manifestations, including thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis, “blueberry muffin syndrome”). Some infants may be born with congenital rubella virus infection but have no apparent signs or symptoms of CRS and are referred to as “infants with congenital rubella virus infection only.” PART 5 Infectious Diseases ■ ■DIAGNOSIS Acquired Rubella Clinical diagnosis of acquired rubella is difficult because of the mimicry of many illnesses with rashes, the varied clini cal presentations, and the high rates of subclinical and mild disease. Illnesses that may be similar to rubella in presentation include scarlet fever, roseola, toxoplasmosis, fifth disease, measles, Zika, and illnesses with suboccipital and postauricular lymphadenopathy. Thus, labora tory documentation of rubella virus infection is considered the only reliable way to confirm acute disease. Laboratory assessment of rubella virus infection is conducted by serologic and virus detection methods. For acquired rubella, serologic diagnosis is most common and depends on the demonstration of IgM antibodies in an acute-phase serum specimen or a fourfold rise in IgG antibody titer between acute- and convalescent-phase specimens. To TABLE 212-1 Common Transient and Permanent Manifestations in Infants with Congenital Rubella Syndrome TRANSIENT MANIFESTATIONS PERMANENT MANIFESTATIONS Hepatosplenomegaly Interstitial pneumonitis Thrombocytopenia with purpura/ petechiae (e.g., dermal erythropoiesis or “blueberry muffin syndrome”) Hemolytic anemia Bony radiolucencies Intrauterine growth retardation Adenopathy Meningoencephalitis Hearing impairment/deafness Congenital heart defects (patent ductus arteriosus, pulmonary arterial stenosis) Eye defects (cataracts, cloudy cornea, microphthalmos, pigmentary retinopathy, congenital glaucoma) Microcephaly Central nervous system sequelae (mental and motor delay, autism)

detect a rise in IgG antibody titer indicative of acute disease, the acutephase serum specimen should be collected within 7–10 days after onset of illness and the convalescent-phase specimen ~14–21 days after the first specimen. The enzyme-linked immunosorbent assay IgM capture technique is considered most accurate for serologic diagnosis, but the indirect IgM assays also are acceptable. After rubella virus infection, IgM antibody may be detectable for up to 6 weeks. In case of a negative result for IgM in specimens taken earlier than day 5 after rash onset, serologic testing should be repeated. Although uncommon, reinfection with rubella virus is possible, and IgM antibodies may be present. In this instance, IgG avidity testing is used in conjunction with IgG testing to distinguish primary rubella infection from reinfection. The detection of low-avidity antibodies in a patient’s serum indicates recent infection. The presence of mature (high-avidity)

IgG antibodies most likely indicates an infection occur ring at least 2 months previously. Avidity testing may be particularly useful in diagnosing rubella in pregnant women and assessing the risk of CRS. Rubella virus is typically detected in the nasopharynx during the prodromal period and for as long as 2 weeks after rash onset. However, viral specimens (nasopharyngeal swabs are preferred but throat swabs or urine are also acceptable) should be collected as soon after symptom onset as possible, preferably 1–3 days after onset, but no later than 7 days after onset. Rubella is usually diagnosed by viral RNA detection in a reverse-transcriptase polymerase chain reaction (RT-PCR) assay; rubella virus isolation can also be used to diagnose rubella. Congenital Rubella Syndrome The classic triad of CRS—clinical manifestations of cataracts, hearing impairment, and heart defects—is seen in ~10% of infants with CRS. Infants may present with differ ent combinations of defects depending on when infection occurs during gestation. Hearing impairment is the most common single defect of CRS. However, as with acquired rubella, laboratory diag nosis of congenital infection is highly recommended, particularly because most features of the clinical presentation are nonspecific and may be associated with other intrauterine infections. Early diagnosis of CRS allows the prompt implementation of infection control measures and facilitates appropriate medical intervention for specific disabilities. Diagnostic tests used to confirm CRS include serologic assays and virus detection. In an infant with congenital infection, serum IgM anti bodies are normally present for up to 6 months but may be detectable for up to 1 year after birth. In some instances, IgM may not be detect able until 1 month of age; thus, infants who have symptoms consistent with CRS but who test negative shortly after birth should be retested at 1 month. A rubella serum IgG titer persisting beyond the time expected after passive transfer of maternal IgG antibody (i.e., a rubella titer that does not decline at the expected rate of a twofold dilution per month) is another serologic criterion used to confirm CRS. In congenital infection, rubella virus is detected most commonly from nasopharyngeal and throat swabs and urine. Infants with con genital rubella may excrete virus for up to 1 year, but specimens for RT-PCR are most likely to be positive if obtained within the first 6 months after birth. Rubella virus in infants with CRS can also be detected by virus culture. Rubella Diagnosis in Pregnant Women In the United States, screening for rubella IgG antibodies is recommended as part of routine prenatal care. Pregnant women with a positive IgG antibody serologic test are considered immune. Susceptible pregnant women should be vaccinated postpartum. A susceptible pregnant woman exposed to rubella virus should be tested for IgM antibodies and, if positive, confirmed by testing for low-avidity IgG antibodies to determine whether she was infected during pregnancy. Pregnant women with evidence of acute infec tion must be clinically monitored, and gestational age at the time of maternal infection must be determined to assess the possibility of risk to the fetus. Among women infected with rubella virus during the first 10 weeks of gestation, the risk of delivering an infant with CRS is 90%. The risk of birth defects declines with infection later in gestation, and fetal defects are rarely associated with maternal

rubella after the 16th week of gestation, although sensorineural hear ing deficit may occur with infection as late as 20 weeks. Because of the potential for false-positive results, rubella IgM antibody testing is not recommended for pregnant women with no history of illness or contact with a rubella-like illness. TREATMENT Rubella No specific therapy is available for rubella virus infection. Symptombased treatment for various manifestations, such as fever and arthral gia, is appropriate. Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis. Although immunoglobulin may modify or suppress symptoms, it can create an unwarranted sense of secu rity: infants with congenital

rubella have been born to women who received immunoglobulin shortly after exposure. Administration of immunoglobulin should be considered only if a pregnant woman who has been exposed to a person with rubella will not consider termina tion of the pregnancy under any circumstances. In such cases, IM administration of 20 mL of immunoglobulin within 72 h of rubella exposure may reduce—but does not eliminate—the risk of rubella. ■ ■PREVENTION After the isolation of rubella virus in the early 1960s and the occur rence of a devastating rubella pandemic in 1964–1965, a vaccine for rubella was developed and licensed in 1969. The majority of rubellacontaining vaccines (RCVs) used worldwide are combined measles and rubella (MR) or measles, mumps, and rubella (MMR) formulations. A tetravalent measles, mumps, rubella, and varicella (MMRV) vaccine is available but is not widely used. Available rubella-containing vaccines are live attenuated vaccine virus. The public health burden of rubella virus infection is measured primarily through the occurrence of CRS cases among women who were infected during pregnancy. The 1964–1965 rubella epidemic in Vaccine intro - Rubella vaccine by Country - 2022 Yes Yes (Partial) No Not applicable 4000 km FIGURE 212-2 Countries using rubella vaccine in national childhood immunization schedules, 2022. Disclaimer—The boundaries and names shown and the designations used on this map do not imply the expression or any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area nor of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted or dashed lines on maps represent approximate border lines for which there may not be full agreement. (Reproduced with permission from the World Health Organization; 2024.)

the United States resulted in >30,000 infections during pregnancy. CRS occurred in ~20,000 infants born alive, including >11,000 infants who were deaf, >3500 infants who were blind, and almost 2000 infants with intellectual disability. The medical cost of this epidemic exceeded $1.5 billion. It has been estimated that the lifetime medical costs for children with CRS range from $11,255 in low-income countries to $934,000 in high-income countries.

In most countries, there are few data to document the epidemiology of CRS, but clusters of CRS cases have been reported in developing coun tries. Before the introduction of routine immunization against rubella in the United States, the incidence of CRS was 0.1–0.2 case per 1000 live births during endemic periods and 1–4 cases per 1000 live births dur ing epidemic periods. Where rubella virus is circulating and women of childbearing age are susceptible, CRS cases will continue to occur. The most effective method of preventing acquired rubella and CRS is through vaccination with an RCV. One dose induces seroconversion in ≥95% of persons ≥1 year of age. Immunity is considered long-term and is probably lifelong. The most commonly used vaccine globally is the RA27/3 virus strain. The recommendation for routine rubella vac cination schedules in the United States is a first dose of MMR vaccine at 12–15 months of age and a second dose at 4–6 years. Other persons recommended to receive a dose of a rubella-containing vaccine include adolescents and adults without documented evidence of immunity, individuals in congregate settings (e.g., college students, military per sonnel, childcare and health care workers), international travelers, and susceptible women before and after pregnancy. Because of the theoretical risk of transmission of live attenuated rubella vaccine virus to the developing fetus, women known to be pregnant should not receive RCV. In addition, pregnancy should be avoided for 28 days after receipt of RCV. In follow-up studies of ~3000 unknowingly pregnant women who received rubella vaccine, no infant was born with CRS. Receipt of RCV during pregnancy is not ordinarily a reason to consider termination of the pregnancy. CHAPTER 212 In 2022, 175 (90%) of the 194 member countries of the WHO rec ommended inclusion of RCV in the routine childhood vaccination schedule (Fig. 212-

2). Goals for the elimination of rubella and CRS Rubella (German Measles)

Revision #1
Created 2026-01-06 16:32:35 UTC by Omar Ayman
Updated 2026-01-06 16:32:35 UTC by Omar Ayman