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Rubella

Rubella

The name rubella is derived from Latin, meaning “little red.” Rubella was initially considered to be a variant of measles or scarlet fever and was called “third disease.” It was not until 1814 that it was first described as a separate disease in the German medical literature, hence the common name “German measles.” In 1914, Hess postulated a viral etiology based on his work with monkeys. Hiro and Tosaka in 1938 confirmed the viral etiology by passing the disease to children using filtered nasal washings from persons with acute cases.

Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first reported recognition of congenital rubella syndrome (CRS). Rubella virus was first isolated in 1962 by Parkman and Weller. The first rubella vaccines were licensed in 1969.

Rubella Virus

Rubella virus is classified as a togavirus, genus *Rubivirus*. It is most closely related to group A arboviruses, such as eastern and western equine encephalitis viruses. It is an enveloped RNA virus, with a single antigenic type that does not cross-react with other members of the togavirus group. Rubella virus is relatively unstable and is inactivated by lipid solvents, trypsin, formalin, ultraviolet light, low pH, heat, and amantadine.

Pathogenesis

Following respiratory transmission of rubella virus, replication of the virus is thought to occur in the nasopharynx and regional lymph nodes. A viremia occurs 5–7 days after exposure with spread of the virus throughout the body. Transplacental infection of the fetus occurs during viremia. Fetal damage occurs through destruction of cells as well as mitotic arrest.

Clinical Features

Acquired Rubella

The incubation period of rubella is 14 days, with a range of 12–23 days. Symptoms are often mild, and up to 50% of infections may be subclinical or inapparent. In children, rash is usually the first manifestation and a prodrome is rare. In older children and adults, there is often a 1–5 day prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms preceding the rash. The rash of rubella is maculopapular and occurs 14–17 days after exposure. The

Rubella

- From Latin meaning "little red"
- Discovered in 18th century - thought to be variant of measles
- First described as distinct clinical entity in German literature
- Congenital rubella syndrome (CRS) described by Gregg in 1941

Rubella Virus

- Togavirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, ultraviolet light, low pH, and heat

Rubella Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Viremia 5-7 days after exposure with spread to tissues
- Placenta and fetus infected during viremia

Rubella Clinical Features

- Incubation period 14 days (range 12-23 days)
- Prodrome of low-grade fever
- Maculopapular rash 14-17 days after exposure
- Lymphadenopathy in second week

Rubella Complications

Arthralgia or arthritis	
adult female	up to 70%
children	rare
Thrombocytopenic	
purpura	1/3,000 cases
Encephalitis	1/6,000 cases
Neuritis	rare
Orchitis	rare

Epidemic Rubella – United States, 1964-1965

- 12.5 million rubella cases
- 2,000 encephalitis cases
- 11,250 abortions (surgical/spontaneous)
- 2,100 neonatal deaths
- 20,000 CRS cases
 - deaf - 11,600
 - blind - 3,580
 - mentally retarded - 1,800

rash usually occurs initially on the face and then progresses from head to foot. It lasts about 3 days and is occasionally pruritic. The rash is fainter than measles rash and does not coalesce. The rash is often more prominent after a hot shower or bath. Lymphadenopathy may begin a week before the rash and last several weeks. Postauricular, posterior cervical, and suboccipital nodes are commonly involved.

Arthralgia and arthritis occur so frequently in adults that they are considered by many to be an integral part of the illness rather than a complication. Other symptoms of rubella include conjunctivitis, testalgia, or orchitis. Forschheimer spots may be noted on the soft palate but are not diagnostic for rubella.

Complications

Complications of rubella are not common, but they tend to occur more often in adults than in children.

Arthralgia or arthritis may occur in up to 70% of adult women who contract rubella, but it is rare in children and adult males. Fingers, wrists, and knees are often affected. Joint symptoms tend to occur about the same time or shortly after appearance of the rash and may last for up to 1 month; chronic arthritis is rare.

Encephalitis occurs in one in 6,000 cases, more frequently in adults (especially in females) than in children. Mortality estimates vary from 0 to 50%.

Hemorrhagic manifestations occur in approximately one per 3,000 cases, occurring more often in children than in adults. These manifestations may be secondary to low platelets and vascular damage, with thrombocytopenic purpura being the most common manifestation. Gastrointestinal, cerebral, or intrarenal hemorrhage may occur. Effects may last from days to months, and most patients recover.

Additional complications include orchitis, neuritis, and a rare late syndrome of progressive panencephalitis.

Congenital Rubella Syndrome

Prevention of CRS is the main objective of rubella vaccination programs in the United States.

A rubella epidemic in the United States in 1964–1965 resulted in 12.5 million cases of rubella infection and about 20,000 newborns with CRS. The estimated cost of the epidemic was \$840 million. This does not include the emotional toll on the families involved. The estimated

lifetime cost of one case of CRS today is estimated to be in excess of \$200,000.

Infection with rubella virus can be disastrous in early gestation. The virus may affect all organs and cause a variety of congenital defects. Infection may lead to fetal death, spontaneous abortion, or premature delivery. The severity of the effects of rubella virus on the fetus depends largely on the time of gestation at which infection occurs. As many as 85% of infants infected in the first trimester of pregnancy will be found to be affected if followed after birth. While fetal infection may occur throughout pregnancy, defects are rare when infection occurs after the 20th week of gestation. The overall risk of defects during the third trimester is probably no greater than that associated with uncomplicated pregnancies.

Congenital infection with rubella virus can affect virtually all organ systems. Deafness is the most common and often the sole manifestation of congenital rubella infection, especially after the fourth month of gestation. Eye defects, including cataracts, glaucoma, retinopathy, and microphthalmia may occur. Cardiac defects such as patent ductus arteriosus, ventricular septal defect, pulmonic stenosis, and coarctation of the aorta are possible. Neurologic abnormalities, including microcephaly and mental retardation, and other abnormalities, including bone lesions, splenomegaly, hepatitis, and thrombocytopenia with purpura may occur.

Manifestations of CRS may be delayed from 2 to 4 years. Diabetes mellitus appearing in later childhood occurs frequently in children with CRS. In addition, progressive encephalopathy resembling subacute sclerosing panencephalitis has been observed in some older children with CRS. Children with CRS have a higher than expected incidence of autism.

Infants with CRS may have low titers by hemagglutination inhibition (HI) but may have high titers of neutralizing antibody that may persist for years. Reinfection may occur. Impaired cell-mediated immunity has been demonstrated in some children with CRS.

Laboratory Diagnosis

Many rash illnesses can mimic rubella infection, and as many as 50% of rubella infections may be subclinical. The only reliable evidence of acute rubella infection is a positive viral culture for rubella or detection of rubella virus by polymerase chain reaction, the presence of rubella-specific IgM antibody, or demonstration of a significant rise in IgG antibody from paired acute- and convalescent-phase sera.

Congenital Rubella Syndrome

- Infection may affect all organs
- May lead to fetal death or premature delivery
- Severity of damage to fetus depends on gestational age
- Up to 85% of infants affected if infected during first trimester

Congenital Rubella Syndrome

- Deafness
- Cataracts
- Heart defects
- Microcephaly
- Mental retardation
- Bone alterations
- Liver and spleen damage

Rubella Laboratory Diagnosis

- Isolation of rubella virus from clinical specimen (e.g., nasopharynx, urine)
- Positive serologic test for rubella IgM antibody
- Significant rise in rubella IgG by any standard serologic assay (e.g., enzyme immunoassay)

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from rubella and CRS patients. Virus may be isolated from the pharynx

1 week before and until 2 weeks after rash onset. Although isolation of the virus is diagnostic of rubella infection, viral cultures are labor intensive, and therefore not done in many laboratories; they are generally not used for routine diagnosis of rubella. Viral isolation is an extremely valuable epidemiologic tool and should be attempted for all suspected cases of rubella or CRS. Information about rubella virus isolation can be found on the CDC website at http://www.cdc.gov/ncidod/dvrd/revb/measles/surv_rubellavirus.htm.

Serology is the most common method of confirming the diagnosis of rubella. Acute rubella infection can be serologically confirmed by a significant rise in rubella antibody titer in acute- and convalescent-phase serum specimens or by the presence of serum rubella IgM. Serum should be collected as early as possible (within 7–10 days) after onset of illness, and again 14–21 days (minimum of 7) days later.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections, with a positive heterophile test for infectious mononucleosis, or with a positive rheumatoid factor.

The serologic tests available for laboratory confirmation of rubella infections vary among laboratories. The state health department can provide guidance on available laboratory services and preferred tests.

Enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive, widely available, and relatively easy to perform. It can also be modified to measure IgM antibodies. Most of the diagnostic testing done for rubella antibodies uses some variation of ELISA.

Hemagglutination inhibition (HI) test was once the “standard” and most commonly used technique. It is sensitive and simple to perform and allows for either screening or diagnosis (if paired acute- and convalescent-phase sera are tested). A fourfold rise or greater in HI-derived 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.

Immunofluorescent antibody 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.

Epidemiology

Occurrence

Rubella occurs worldwide.

Reservoir

Rubella is a human disease. There is no known animal reservoir. Although infants with CRS may shed rubella virus for an extended period, a true carrier state has not been described.

Transmission

Rubella is spread from person to person via airborne transmission or droplets shed from the respiratory secretions of infected persons. There is no evidence of insect transmission.

Rubella may be transmitted by persons with subclinical or asymptomatic cases (up to 50% of all rubella virus infections).

Temporal Pattern

In temperate areas, incidence is usually highest in late winter and early spring.

Communicability

Rubella is only moderately contagious. The disease is most contagious when the rash first appears, but virus may be shed from 7 days before to 5–7 days or more after rash onset. Infants with CRS shed large quantities of virus from body secretions for up to 1 year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

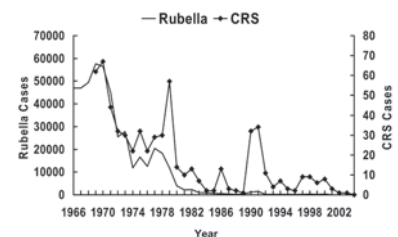
Secular Trends in the United States

Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population). Following vaccine licensure in 1969, rubella incidence declined rapidly. By 1983, fewer than 1,000 cases per year were reported (less than 0.5 cases per 100,000 population). A moderate resurgence of rubella occurred in 1990–1991, primarily due to outbreaks in California (1990) and among the Amish in Pennsylvania (1991). In 2003, a record low annual total of seven cases was reported. In October 2004, CDC convened an independent expert panel to review available rubella and CRS data. After a careful review, the panel unanimously agreed that rubella was no longer endemic in the United States.

Rubella Epidemiology

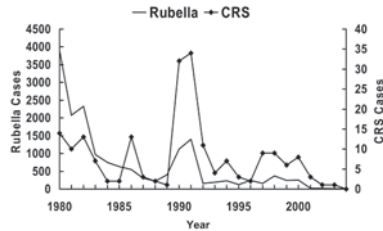
- **Reservoir** Human
- **Transmission** Respiratory
Subclinical cases may transmit
- **Temporal pattern** Peak in late winter and spring
- **Communicability** 7 days before to 5-7 days after rash onset
Infants with CRS may shed virus for a year or more

Rubella - United States, 1966-2004

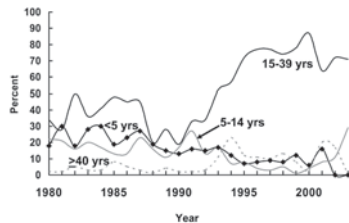


Rubella

Rubella - United States, 1980-2004



Rubella - United States, 1980-2003
Age Distribution of Reported Cases



Rubella and CRS in the United States

- Most reported rubella in the U.S. since the mid-1990s has occurred among foreign-born Hispanic adult
- Majority of CRS since 1997 occurred in children of unvaccinated women born to Hispanic women, most born in Latin America

Rubella Case Definition

- Acute onset of generalized maculopapular rash, and
- Temperature of $>99^{\circ}\text{F}$ (37.2°C), if measured, and
- Arthralgia or arthritis, lymphadenopathy, or conjunctivitis

Until recently, there was no predominant age group for rubella cases. From 1982 through 1992, approximately 30% of cases occurred in each of three age groups: younger than 5, 5–14, and 15–39 years. Adults 40 years of age and older typically accounted for less than 10% of cases. However, since 1993, persons 15–39 years of age have accounted for more than half the cases. In 2003, this age group accounted for 71% of all reported cases.

Most reported rubella in the United States since the mid-1990s has occurred among Hispanic young adults who were born in areas where rubella vaccine is routinely not given.

CRS surveillance is maintained through the National Congenital Rubella Registry, which is managed by the National Center for Immunization and Respiratory Diseases. The largest annual total of reported CRS cases to the registry was in 1970 (67 cases). An average of 5–6 CRS cases have been reported annually since 1980. Although reported rubella activity has consistently and significantly decreased since vaccine has been used in the United States, the incidence of CRS has paralleled the decrease in rubella cases only since the mid-1970s. The decline in CRS since the mid-1970s was due to an increased effort to vaccinate susceptible adolescents and young adults, especially women. Rubella outbreaks are almost always followed by an increase in CRS.

Rubella outbreaks in California and Pennsylvania in 1990–1991 resulted in 25 cases of CRS in 1990 and 33 cases in 1991. Two CRS cases were reported in 2001, and in 2004, no cases were reported. Since 1997, the mothers of the majority of infants with CRS were Hispanic women, most of whom were born in Latin American or Caribbean countries where rubella vaccine is routinely not used or has only recently begun to be used.

Classification of Rubella Cases

Clinical Case Definition of Acquired Rubella

A clinical case of rubella is defined as an illness with all of the following characteristics: 1) acute onset of generalized maculopapular rash; 2) a temperature higher than 99°F (37.2°C), if measured; and 3) arthralgia or arthritis, lymphadenopathy, or conjunctivitis. Cases meeting the measles case definition are excluded. Also excluded are cases with serology compatible with recent measles virus infection.

Case Classification of Acquired Rubella

A suspected case is any generalized rash illness of acute onset. A probable case meets the clinical case definition, has noncontributory or no serologic or virologic test results,

and is not epidemiologically linked to a laboratory-confirmed case. A confirmed case is laboratory confirmed or meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case.

Clinical Case Definition of Congenital Rubella Syndrome

The clinical case definition of CRS is an illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by symptoms from the following categories:

- A. Cataracts, congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), loss of hearing, pigmentary retinopathy
- B. Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Case Classification of Congenital Rubella Syndrome

An infection-only case is one with laboratory evidence of infection but without any clinical symptoms or signs. A suspected case has some compatible clinical findings, but does not meet the criteria for a probable case. A probable case is one that is not laboratory confirmed, has any two complications listed in category A above or one complication from category A and one from B, and lacks evidence of any other etiology. A confirmed case is a clinically consistent case that is laboratory confirmed. 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.

Rubella Vaccine

Three rubella vaccines were licensed in the United States in 1969: HPV-77:DE-5 (duck embryo), HPV-77:DK-12 (dog kidney), and GMK-3:RK53 Cendevax (rabbit kidney) strains. HPV-77:DK-12 was later removed from the market because there was a higher rate of joint complaints following vaccination with this strain. In 1979, the RA 27/3 (human diploid fibroblast) strain (Meruvax-II, Merck) was licensed and all other strains were discontinued.

Rubella Vaccine

Vaccine	Trade Name	Licensure
HPV-77:DE5	Meruvax	1969
HPV-77:DK12	Rubelogen	1969
GMK-3:RK53	Cendevax	1969
RA 27/3*	Meruvax II	1979

*Only vaccine currently licensed in U.S.

Rubella

Rubella Vaccine

- **Composition** Live virus (RA 27/3 strain)
- **Efficacy** 95% (Range, 90%-97%)
- **Duration of Immunity** Lifelong
- **Schedule** At least 1 dose
- Should be administered with measles and mumps as MMR or with measles, mumps and varicella as MMRV

Rubella Vaccine (MMR) Indications

- All infants 12 months of age and older
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on nonpregnant women of childbearing age, particularly those born outside the U.S.

Characteristics

The RA 27/3 rubella vaccine is a live attenuated virus. It was first isolated in 1965 at the Wistar Institute from a rubella-infected aborted fetus. The virus was attenuated by 25–30 passages in tissue culture, using human diploid fibroblasts. It does not contain duck, chicken or egg protein.

Vaccine virus is not communicable except in the setting of breastfeeding (see Contraindications, below), even though virus may be cultured from the nasopharynx of vaccinees.

Rubella vaccine is available as a single-antigen preparation, combined with mumps vaccine, combined with measles and mumps vaccines as MMR, or combined with mumps, rubella, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated (and for MMRV, if the vaccinee is 12 months through 12 years of age). Use of single-antigen rubella vaccine is not routinely recommended.

MMR and MMRV are supplied as a lyophilized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. The vaccine contains a small amount of human albumin, neomycin, sorbitol, and gelatin.

Immunogenicity and Vaccine Efficacy

RA 27/3 rubella vaccine is safe and more immunogenic than rubella vaccines used previously. In clinical trials, 95% or more of vaccinees aged 12 months and older developed serologic evidence of rubella immunity after a single dose. More than 90% of vaccinated persons have protection against both clinical rubella and viremia for at least 15 years. Follow-up studies indicate that one dose of vaccine confers long-term, probably lifelong, protection. Seroconversion rates are similar for single-antigen rubella vaccine, MMR, and MMRV.

Several reports indicate that viremic reinfection following exposure may occur in vaccinated persons who have low levels of detectable antibody. The frequency and consequences of this phenomenon are unknown, but it is believed to be uncommon. Rarely, clinical reinfection and fetal infection have been reported among women with vaccine-induced immunity. Rare cases of CRS have occurred among infants born to women who had documented serologic evidence of rubella immunity before they became pregnant.

Vaccination Schedule and Use

At least one dose of rubella vaccine, as combination MMR

(or MMRV) vaccine, is routinely recommended for all children 12 months of age or older. All persons born during or after 1957 should have documentation of at least one dose of MMR. The first dose of MMR should be given on or after the first birthday. Any dose of rubella-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with rubella-containing vaccine before 12 months of age should be revaccinated when the child is at least 12 months of age.

A second dose of MMR is recommended to produce immunity to measles and mumps in those who failed to respond to the first dose. Data indicate that almost all persons who do not respond to the measles component of the first dose will respond to a second dose of MMR. Few data on the immune response to the rubella and mumps components of a second dose of MMR are available. However, most persons who do not respond to the rubella or mumps component of the first MMR dose would be expected to respond to the second dose. The second dose is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although a second dose of vaccine may increase antibody titers in some persons who responded to the first dose, available data indicate that these increased antibody titers are not sustained. The combined MMR vaccine is recommended for both doses to ensure immunity to all three viruses.

The second dose of MMR vaccine should routinely be given at age 4–6 years, before a child enters kindergarten or first grade. The recommended health visit at age 11–12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR (with the first dose administered no earlier than the first birthday). The second dose of MMR may be administered as soon as 1 month (i.e., minimum of 28 days) after the first dose. The minimum interval between doses of MMRV is 3 months.

All older children not previously immunized should receive at least one dose of rubella vaccine as MMR or MMRV if 12 years of age or younger.

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles and mumps exposure may require a second dose. This second dose should be administered as combined MMR vaccine (see Measles chapter for details). Efforts should be made to identify and vaccinate susceptible adolescents and adults,

particularly women of childbearing age who are not pregnant. Particular emphasis should be placed on vaccinating both males and females in colleges, places of employment, and healthcare settings.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A healthcare worker should not provide an immunization record for a patient unless that healthcare worker has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). MMRV should not be administered to persons 13 years or older.

Rubella Immunity

Persons generally can be considered immune to rubella if they have documentation of vaccination with at least one dose of MMR (or MMRV) or other live rubella-containing vaccine administered on or after their first birthday, have serologic evidence of rubella immunity, or were born before 1957. Persons who have an "equivocal" serologic test result should be considered rubella-susceptible. Although only one dose of rubella-containing vaccine is required as acceptable evidence of immunity to rubella, children should receive two doses of MMR vaccine according to the routine childhood vaccination schedule.

Birth before 1957 provides only presumptive evidence of rubella immunity; it does not guarantee that a person is immune to rubella. Because rubella can occur in some unvaccinated persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant. Only a positive serologic test for rubella antibody or documentation of appropriate vaccination should be accepted for women who may become pregnant.

Rubella Immunity

- Documentation of one dose of rubella-containing vaccine on or after the first birthday
- Serologic evidence of immunity
- Birth before 1957 (except women of childbearing age)

Rubella Immunity

- Birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant
- Only serology or documented vaccination should be accepted

Healthcare workers born before 1957 also should not be presumed to be immune. Medical facilities should consider recommending at least one dose of MMR vaccine to unvaccinated healthcare workers born before 1957 who do not have laboratory evidence of rubella immunity. Rubella vaccination or laboratory evidence of rubella immunity is particularly important for healthcare workers who could become pregnant, including those born before 1957. This recommendation is based on serologic studies which indicate that among hospital workers born before 1957, 5%–9% had no detectable measles antibody.

Clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status. Because many rash illnesses may mimic rubella infection and many rubella infections are unrecognized, the only reliable evidence of previous rubella infection is the presence of serum rubella IgG antibody. Laboratories that regularly perform antibody testing are generally the most reliable because their reagents and procedures are strictly standardized.

Occasionally, a person with a history of documented rubella vaccination is found to have a negative serum IgG by ELISA. Such persons may be given a dose of MMR vaccine and do not need to be retested for serologic evidence of rubella immunity.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. If the return and timely vaccination of those screened cannot be assured, vaccination should be done without prior testing. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity.

Neither rubella vaccine nor immune globulin is effective for postexposure prophylaxis of rubella. Vaccination after exposure is not harmful and may possibly avert later disease.

Adverse Reactions Following Vaccination

Rubella vaccine is very safe. Most adverse reactions reported following MMR vaccination (such as fever and rash) are attributable to the measles component. The most common complaints following rubella vaccination are fever, lymphadenopathy, and arthralgia. These adverse reactions only occur in susceptible persons and are more common in adults, especially in women.

Joint symptoms, such as arthralgia (joint pain) and arthri-

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rubella Vaccine Arthropathy

- Acute arthralgia in about 25% of vaccinated, susceptible adult women
- Acute arthritis-like signs and symptoms occurs in about 10% of recipients
- Rare reports of chronic or persistent symptoms
- Population-based studies have not confirmed an association with rubella vaccine

tis (joint redness and/or swelling), are associated with the rubella component of MMR. Arthralgia and transient arthritis occur more frequently in susceptible adults than in children and more frequently in susceptible women than in men. Acute arthralgia or arthritis is rare following vaccination of children with RA 27/3 vaccine. By contrast, approximately 25% of susceptible postpubertal females develop acute arthralgia following RA 27/3 vaccination, and approximately 10% have been reported to have acute arthritis-like signs and symptoms. Rarely, transient peripheral neuritic complaints, such as paresthesias and pain in the arms and legs, have been reported.

When acute joint symptoms occur, or when pain or paresthesias not associated with joints occur, the symptoms generally begin 1–3 weeks after vaccination, persist for 1 day to 3 weeks, and rarely recur. Adults with acute joint symptoms following rubella vaccination rarely have had to disrupt work activities.

Data from studies in the United States and experience from other countries using the RA 27/3 strain rubella vaccine have not supported an association between the vaccine and chronic arthritis. One study among 958 seronegative immunized and 932 seronegative unimmunized women aged 15–39 years found no association between rubella vaccination and development of recurrent joint symptoms, neuropathy, or collagen disease.

The ACIP continues to recommend the vaccination of all adult women who do not have evidence of rubella immunity.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of rubella vaccine or to a vaccine component (e.g., gelatin, neomycin), should generally not be vaccinated with MMR.

Women known to be pregnant or attempting to become pregnant should not receive rubella vaccine. Although there is no evidence that rubella vaccine virus causes fetal damage (see next section), pregnancy should be avoided for 4 weeks (28 days) after rubella or MMR vaccination.

Persons with immunodeficiency or immunosuppression, resulting from leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, or aerosolized steroid preparations is not a contraindication to rubella vaccination. Persons whose immunosuppressive therapy

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated. Rubella vaccine should be considered for persons with asymptomatic or mildly symptomatic HIV infection.

Persons with moderate or severe acute illness should not be vaccinated until the illness has improved. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to rubella vaccination.

Receipt of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to rubella vaccine. Vaccine should be given 2 weeks before, or deferred for at least 3 months following administration of an antibody-containing blood product. If rubella vaccine is given as combined MMR, a longer delay may be necessary before vaccination. For more information, see Chapter 2, General Recommendations on Immunization.

Previous administration of human anti-Rho(D) immune globulin (RhoGam) does not generally interfere with an immune response to rubella vaccine and is not a contraindication to postpartum vaccination. However, women who have received anti-Rho immune globulin should be serologically tested 6–8 weeks after vaccination to ensure that seroconversion has occurred.

Although vaccine virus may be isolated from the pharynx, vaccinees do not transmit rubella to others, except occasionally in the case of the vaccinated breastfeeding woman. In this situation, the infant may be infected, presumably through breast milk, and may develop a mild rash illness, but serious effects have not been reported. Infants infected through breastfeeding have been shown to respond normally to rubella vaccination at 12–15 months of age. Breastfeeding is not a contraindication to rubella vaccination and does not alter rubella vaccination recommendations.

Rubella Vaccination of Women of Childbearing Age

Women who are pregnant or who intend to become pregnant within 4 weeks should not receive rubella vaccine. ACIP recommends that vaccine providers ask a woman if she is pregnant or likely to become pregnant in the next 4 weeks. Those who are pregnant or intend to become pregnant should not be vaccinated. All other women should be vaccinated after being informed of the theoretical risks of vaccination during pregnancy and the importance of not becoming pregnant during the 4 weeks following vaccination. ACIP does not recommend routine pregnancy screening of women before rubella vaccination.

Vaccination of Women of Childbearing Age

- Ask if pregnant or likely to become so in next 4 weeks
- Exclude those who say "yes"
- For others
 - explain theoretical risks
 - vaccinate

Vaccination in Pregnancy Study 1971-1989

- 321 women vaccinated
- 324 live births
- No observed CRS
- 95% confidence limits 0%-1.2%

If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccination, she should be counseled about the concern for the fetus (see below), but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of the pregnancy.

When rubella vaccine was licensed, concern existed about women being inadvertently vaccinated while they were pregnant or shortly before conception. This concern came from the known teratogenicity of the wild-virus strain. To determine whether CRS would occur in infants of such mothers. CDC maintained a registry from 1971 to 1989 of women vaccinated during pregnancy. This was called the Vaccine in Pregnancy (VIP) Registry.

Although subclinical fetal infection has been detected serologically in approximately 1%–2% of infants born to susceptible vaccinees, regardless of the vaccine strain, the data collected by CDC in the VIP Registry showed no evidence of CRS occurring in offspring of the 321 susceptible women who received rubella vaccine and who continued pregnancy to term. The observed risk of vaccine-induced malformation was 0%, with a maximum theoretical risk of 1.6%, based on 95% confidence limits (1.2% for all types of rubella vaccine). Since the risk of the vaccine to the fetus appears to be extremely low, if it exists at all, routine termination of pregnancy is not recommended. Individual counseling for these women is recommended. As of April 30, 1989, CDC discontinued the VIP registry.

The ACIP continues to state that because of the small theoretical risk to the fetus of a vaccinated woman, pregnant women should not be vaccinated.

Vaccine Storage and Handling

MMR and MMRV vaccines must be shipped with refrigerant to maintain a temperature of 50°F (10°C) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (35°–46°F [2°–8°C]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature. MMRV must be shipped to maintain a temperature of -4°F (-20°C) or colder at all times. MMRV must be stored at an average temperature of 5°F (-15°C) or colder at all times.

After reconstitution, MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine is not used within 8 hours, it must be discarded. MMRV must be administered within 30 minutes of reconstitution.

Strategies to Decrease Rubella and CRS

Although the number of CRS cases is low, rubella transmission continues to occur, and increased in 1989 and 1990. The elimination of CRS will require several interventions:

- Achievement and maintenance of high immunization levels.
- Intensive surveillance of rubella and CRS.
- Prompt outbreak control when rubella occurs.

Vaccination of Susceptible Postpubertal Females

Elimination of indigenous rubella and CRS can be maintained by continuing efforts to vaccinate susceptible adolescents and young adults of childbearing age, particularly those born outside the United States. These efforts should include vaccinating in family planning clinics, sexually transmitted disease (STD) clinics, and as part of routine gynecologic care; maximizing use of premarital serology results; emphasizing immunization for college students; vaccinating women postpartum and postabortion; immunizing prison staff and, when possible, prison inmates, especially women inmates; offering vaccination to at-risk women through the special supplemental program for Women, Infants and Children (WIC); and implementing vaccination programs in the workplace, particularly those employing persons born outside the United States.

Hospital Rubella Programs

Emphasis should be placed on vaccinating susceptible hospital personnel, both male and female (e.g., volunteers, trainees, nurses, physicians.) Ideally, all hospital employees should be immune. It is important to note that screening programs alone are not adequate. Vaccination of susceptible staff must follow.

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