

Varicella is an acute infectious disease caused by varicella-zoster virus (VZV). Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Rudolf Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. In 1954, Thomas Weller used cell culture to isolate VZV from vesicular fluid of patients with varicella or zoster. A live, attenuated varicella vaccine was developed in Japan in the 1970s. The vaccine virus was developed from virus isolated by Michiaki Takahashi from vesicular fluid from an otherwise healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988, and in the United States in 1995 for persons age 12 months or older. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in the United States for persons age 12 months through 12 years.

## Varicella-Zoster Virus

VZV is a DNA virus and is a member of the herpesvirus group. Like other herpesviruses, VZV persists in the body as a latent infection after the primary (first) infection; VZV persists in sensory nerve ganglia. Primary infection with VZV results in varicella. Latent infection can reactivate resulting in herpes zoster (shingles). The virus has a short survival time in the environment.

## Pathogenesis

VZV enters the host through the respiratory tract and conjunctiva. It replicates at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia occurs 4 to 6 days after infection and disseminates the virus to other organs, such as the liver, spleen, and sensory ganglia. Further replication occurs in the viscera, followed by a secondary viremia, with viral infection of the skin. Virus can be cultured from mononuclear cells of an infected person from 5 days before to 1 to 2 days after the appearance of the rash.

## Clinical Features

The incubation period is 14 to 16 days after exposure, with a range of 10 to 21 days. The incubation period may be prolonged (e.g., up to 28 days or more) in those who have received postexposure prophylaxis with varicella specific immune globulin.

### Varicella

- Acute infectious disease caused by varicella-zoster virus (VZV)
- Distinguished from smallpox at the end of the 19th century
- Live, attenuated varicella vaccine developed in 1970s
- Varicella and MMRV vaccines licensed for use in the U.S. in 1995 and 2005, respectively

### Varicella-Zoster Virus (VZV)

- Herpesvirus (DNA)
- Primary infection results in varicella (chickenpox)
- Reactivation of latent infection results in herpes zoster (shingles)
- Short survival in environment

### Varicella Pathogenesis

- Enters through respiratory tract and conjunctiva
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 4 to 6 days after infection
- Multiple organs infected during viremia
- Secondary viremia with viral skin infection after replication

### Varicella Clinical Features

- Incubation period 14 to 16 days (range, 10 to 21 days)
- Prolonged incubation period if received postexposure prophylaxis with varicella specific immune globulin

## Primary Infection (Varicella)

- Rash often first sign of disease in children; adults may have 1 to 2 days of fever and malaise before rash
- In unvaccinated individuals, generalized and pruritic rash progresses rapidly
- Clinical course in healthy children is mild; adults may have more severe disease
- Recovery usually results in lifetime immunity

## Primary Infection (Varicella)

A mild prodrome may precede the onset of a rash. Adults may have 1 to 2 days of fever and malaise prior to rash onset, but in children the rash is often the first sign of disease.

In individuals who have not received varicella vaccine, the rash is generalized and pruritic and progresses rapidly (within 24 hours) from macules to papules to vesicular lesions before crusting. The rash usually appears first on the scalp, face or trunk, and then spreads to the extremities; the highest concentration of lesions is on the trunk. Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1 to 4 mm in diameter. The vesicles are superficial and delicate and contain clear fluid on an erythematous base. Vesicles may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in all stages of development at the same time. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 250 to 500 lesions in 2 to 4 successive crops.

The clinical course in healthy children is generally mild, fever (up to 102°F) and other systemic symptoms (e.g., malaise, headache) usually resolve within 2 to 4 days after onset of the rash. Adults may have more severe disease and have a higher incidence of complications. Immunocompromised children may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Persons infected with human immunodeficiency virus (HIV) are also at risk for severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of varicella is uncommon; it is more common in immunocompromised persons. As with other viral diseases, re-exposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Breakthrough varicella is defined as varicella due to infection with wild-type VZV occurring more than 42 days after varicella vaccination; breakthrough infection can occur after 1 or 2 doses of vaccine. With decreasing incidence of varicella overall and increasing varicella vaccination coverage, more than half of varicella cases reported during the mature phase of the vaccination program are breakthrough varicella cases. Breakthrough varicella is less severe than varicella in unvaccinated persons, with the median number of skin lesions commonly less than 50; vesicular lesions are less common and the lesions are commonly papules that do not progress to vesicles. Varicella in vaccinated persons is

typically shorter in duration and has a lower incidence of fever than in unvaccinated persons. However, about 25% to 30% of breakthrough varicella cases in vaccinees who received one dose have clinical features more similar to those in unvaccinated children, and complications with visceral dissemination, hospitalizations, or death, although uncommon, have been reported.

## Complications

Acute varicella is generally mild and self-limited, but it may be associated with complications. Secondary bacterial infections of skin lesions with *Staphylococcus* or *Streptococcus* (primarily invasive group A) are the most common cause of hospitalization and outpatient medical visits and can lead to death. Pneumonia following varicella is usually viral but may be bacterial. Primary viral pneumonia is uncommon among immunocompetent children but is the most common complication in adults. Secondary bacterial pneumonia is more common in children younger than age 1 year. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Encephalitis is an infrequent complication of varicella (1 per 50,000 cases of varicella in unvaccinated children) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common central nervous system manifestation (1 per 4,000 cases of varicella in unvaccinated children) and generally has a good outcome. Reye syndrome may follow varicella, although this outcome has become very rare with the recommendation to not use aspirin or other salicylates to reduce fever in children with varicella. Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and hepatitis.

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than age 15 years and infants younger than age 1 year. In the prevaccine era, approximately 10,500 persons with varicella required hospitalization each year. Hospitalization rates were approximately 1 to 2 per 1,000 cases among healthy children and 14 per 1,000 cases among adults. The fatality rate for varicella was approximately 1 per 100,000 cases among children age 1 through 14 years, 6 per 100,000 cases among persons age 15 through 19 years, and 21 per 100,000 cases among adults. Most deaths occur in immunocompetent children and adults. Since 1995, when the varicella vaccination program was implemented, hospitalizations and deaths from varicella have declined in the United States 93% and 94%, respectively.

### Varicella Complications

- Bacterial infection of skin lesions
- Pneumonia
- Central nervous system manifestations
- Reye syndrome (rare)

Immunocompromised persons have a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster. Severe and even fatal varicella has been reported in otherwise healthy children on high-dose corticosteroids (e.g., 2 milligrams per kilogram per day or more of prednisone or equivalent) for treatment of asthma and other illnesses.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate, with a fatality ratio as high as 30% if antivirals are not given. This severe disease is the result of fetal exposure to VZV without the benefit of passive maternal antibody. The usual interval from onset of rash in a mother to onset in her neonate is 9 to 15 days but it can be as short as 2 days. Infants born to mothers with onset of maternal varicella more than 5 days prior to delivery usually have a benign course, attributed to passive transfer of maternal antibody across the placenta.

### **Congenital VZV Infection**

- Results from maternal infection in the first 20 weeks of gestation
- Associated with newborn limb hypoplasia, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, microcephaly, and low birth weight

### **Congenital VZV Infection**

Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with abnormalities in the newborn, including hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, microcephaly, and low birth weight. This constellation of abnormalities, collectively known as congenital varicella syndrome, was first recognized in 1947. The risk of congenital abnormalities from primary maternal varicella infection is very low (less than 2%). Children infected with VZV in utero may develop herpes zoster early in life without having had extrauterine varicella. Isolated case-reports of congenital varicella syndrome have been reported in women infected after 20 weeks of gestation with the latest occurring at 28 weeks of gestation. Rare reports of congenital birth defects following maternal zoster exist, but whether they represent congenital varicella syndrome is unclear.

### **Laboratory Testing**

Laboratory testing, whenever possible, or epidemiological linkage to a typical case or laboratory-confirmed case, should be sought to confirm or rule out varicella. Rapid VZV identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. Laboratory techniques in use allow differentiation of wild-type and vaccine strains of VZV.

Polymerase chain reaction (PCR) is the method of choice for laboratory diagnosis of varicella. Real-time PCR methods are

widely available and are the most sensitive and specific of the available tests. Results are available within several hours. If real-time PCR is unavailable, the direct fluorescent antibody (DFA) method can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling.

Skin lesions are the preferred sample for laboratory confirmation of varicella. Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens for PCR. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative.

PCR testing that discriminates between vaccine and wild-type VZV is available free of charge through the specialized reference laboratories at CDC and the American Public Health Laboratory Association Vaccine Preventable Diseases Reference Centers.

For diagnosis of acute varicella infection, serologic confirmation includes a significant rise in varicella immune globulin class G (IgG) by any standard serologic assay. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels.

A variety of serologic tests for varicella antibody are available commercially to assess disease-induced immunity. Commercial enzyme-linked immunosorbent assays (ELISAs) are recommended for the purpose of screening. There is evidence to suggest that the latex agglutination method, another method to test for serologic IgG, may give false-positive results that could mistakenly categorize a susceptible person as immune.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease and commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination. Therefore, routine testing for varicella immunity following vaccination is not recommended.

## Epidemiology

### Occurrence

Varicella occurs worldwide. In countries in temperate climates, it is primarily a childhood disease, with most children infected by age 10 years. In tropical areas, children acquire varicella at older ages and therefore a higher proportion of young adults remain susceptible, resulting in a higher proportion of cases occurring among adults. The reason(s) for this difference in age distribution are not known with certainty.

### Varicella Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person
  - Direct contact with vesicular fluid or inhalation of aerosols
- Temporal pattern
  - Peak in winter and early spring
- Communicability
  - 1 to 2 days before onset of rash until all lesions have formed crusts

## Reservoir

VZV, the virus that causes both varicella (chickenpox) and zoster (shingles), is an exclusively human pathogen. No animal or insect source or vector is known to exist.

## Transmission

VZV transmission occurs person-to-person by direct contact with vesicular fluid or by inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster. Transmission may also occur from infected respiratory tract secretions of patients with varicella that might also be aerosolized. Skin lesions are considered the major source of transmissible VZV. Transmission of VZV would cause varicella, not zoster, in a VZV-naïve person.

## Temporal Pattern

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. High rates of vaccination coverage in the United States have eliminated discernible seasonality of varicella. Less seasonality is also reported in tropical areas.

## Communicability

The period of communicability extends from 1 to 2 days before the onset of rash until all lesions have formed crusts. The virus has not been isolated from crusted lesions. Vaccinated persons who contract varicella may develop lesions that do not crust (macules and papules only). Isolation guidance for these persons is to restrict contact with others until no new lesions appear within a 24-hour period.

Varicella is highly contagious. Secondary attack rates among susceptible household contacts of persons with varicella are between 61% and 100%. Zoster is much less infectious as varicella, i.e., about 1/5 as infectious as varicella.

## Secular Trends in the United States

In the prevaccine era, varicella was endemic in the United States, and virtually all persons acquired varicella by adulthood. As a result, the number of cases occurring annually was estimated to approximate the birth cohort, or about 4 million per year. The majority of cases (approximately 90%) occurred among children younger than age 15 years. In the 1990s, the highest age-specific incidence of varicella was among children age 1 to 4 years, who accounted for 39% of all cases. This age distribution was probably a result of earlier exposure to VZV in preschool and child care settings. Adults age 20 years or older accounted for only 7% of cases.

### Varicella Secular Trends in the United States

- Virtually all persons acquired varicella by adulthood before vaccine
- Since vaccine, varicella incidence has declined an average of 97%
  - Decline has occurred in all age groups

The incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly since implementation of the national varicella vaccination program in 1995. Overall, varicella incidence declined an average of 97% from prevaccine years (from 1993–1995 to 2013–2014) based on data from four states that have been continuously reporting varicella to the National Notifiable Diseases Surveillance System (NNDSS) since before the varicella vaccination program. Cases declined in all age groups, including infants who are not eligible for vaccination and adults whose rates of vaccination are low, indicating community protection benefits of the vaccination program. The second dose of varicella vaccine was added to the national program in 2007. During the 2-dose era, data from 40 states that reported varicella cases to NNDSS have shown an 85% decline in varicella incidence from 2005–2006 to 2013–2014, with the greatest declines among children age 5 to 14 years (85% to 89%).

One-dose varicella vaccine coverage among children age 19 through 35 months has been 90% to 91% since 2007; varicella vaccination coverage of at least 2 doses among adolescents age 13 through 17 years without a history of varicella has been greater than 85% since 2016.

## Varicella Vaccines

Two live, attenuated VZV-containing vaccines for the prevention of varicella are licensed for use in the United States. VAR (Varivax) vaccine is single-antigen varicella vaccine and MMRV (ProQuad) vaccine is a combination measles, mumps, rubella, and varicella vaccine.

## Characteristics

VAR vaccine is derived from the Oka strain of VZV. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages. The vaccine is reconstituted with sterile water and contains gelatin. VAR vaccine is administered by the subcutaneous route. Each dose of VAR vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

MMRV vaccine contains measles, mumps, and rubella virus of equal titer and identical to those in the MMR vaccine. The titer of Oka Varicella-Zoster virus is higher in MMRV vaccine than in VAR, a minimum of 9,772 plaque-forming units (PFU) versus 1,350 PFU, respectively. The vaccine is reconstituted with sterile water and contains gelatin. MMRV vaccine is administered by the subcutaneous route. Each dose of MMRV vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

### Varicella Vaccines

- VAR (Varivax)
- MMRV (ProQuad)

### Varicella Vaccine Characteristics

- Live, attenuated vaccines
- VAR contains neomycin and gelatin
- MMRV contains neomycin and gelatin
- Administered by subcutaneous injection

## Varicella Vaccination Schedule

- 2-dose series at age 12 through 15 months and age 4 through 6 years
- Minimum age for dose 1 is 12 months
- Minimum interval for dose 1 to 2 is:
  - 3 months for children age 12 months–12 years (although a 4-week interval is valid)
  - 4 weeks for persons age 13 years and older (VAR only)
- Discuss risks and benefits of MMRV versus separate VAR
  - Separate MMR and VAR vaccines preferred for dose 1 in ages 12 through 47 months
  - MMRV preferred for dose 2 and dose 1 at age 48 months or older

## Vaccination Schedule and Use

VAR or MMRV can be used to implement the vaccination recommendations for prevention of varicella. VAR vaccine (Varivax) is licensed for use in persons age 12 months or older. MMRV (ProQuad) is licensed for use in children age 12 months through 12 years.

### VAR (Varivax)

VAR vaccine is licensed for use in persons age 12 months or older. It is administered as a 2-dose series. Dose 1 is recommended for children age 12 through 15 months. Dose 2 is recommended at age 4 through 6 years at the same visit as the second dose of MMR vaccine, but may be given as early as 3 months after dose 1 (the minimum interval for children younger than age 13 years). However, if dose 2 is administered at least 4 weeks after dose 1, it does not need to be repeated. For persons age 13 years or older, the minimum interval between doses is 4 weeks. Testing for varicella immunity following 2 doses of vaccine is not necessary because 99% of persons are seropositive after the second dose. Moreover, available commercial assays are not sensitive enough to detect antibody following vaccination in all instances. VAR vaccine has been shown to be safe and effective in healthy children when administered at the same time as MMR vaccine at separate sites and with separate syringes. If varicella and MMR vaccines are not administered at the same visit, they should be separated by at least 4 weeks. Varicella vaccine may be administered simultaneously with all other childhood vaccines.

Children with a clinician-diagnosed or verified history of typical varicella can be assumed to be immune to varicella. Serologic testing of children prior to vaccination is not warranted because the majority of children between age 12 months and 12 years without a clinical history of varicella are not immune. Prior history of varicella is not a contraindication to varicella vaccination, so when in doubt as to history, varicella vaccine should be administered. Because serologic evidence of VZV infection has been documented in 96%-97% of U.S.-born adults age 20-29 years and in 97%-99% of adults age 30 years or older tested during 1998–1999, individuals who were born in the United States before 1980 are considered to have evidence of immunity except for health-care personnel (risk of spreading VZV to high-risk patients), pregnant women (risk of transmission to fetus which might result in congenital varicella syndrome), and immunocompromised persons (risk of severe disease).

Varicella vaccine should be administered to all adolescents and adults age 13 years or older who do not have evidence of varicella immunity. Persons age 13 years or older should receive two doses of VAR vaccine separated by at least 4 weeks. If there is a lapse of more than 4 weeks after the first dose, the second dose may be administered at any time without repeating the first dose.

All health care personnel should be immune to varicella. In health care settings, serologic screening of personnel who are uncertain of their varicella history, or who claim not to have had the disease, is likely to be cost-effective. Testing for immunity following vaccination is not necessary. Seroconversion does not always result in full protection against disease, although no data regarding correlates of protection are available for adults. Vaccinated healthcare personnel exposed to VZV should be monitored daily from day 8 to 21 after exposure through the employee health or infection control program to screen for fever, skin lesions, and systemic symptoms. In addition, health care personnel should be instructed to immediately report fever, headache, or other constitutional symptoms and any skin lesions that may be atypical. The person should be placed on sick leave immediately if symptoms occur. The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact is very low, and the benefits of vaccinating susceptible health care personnel clearly outweigh this potential risk.

## MMRV (ProQuad)

MMRV vaccine is licensed for use in children age 12 months through 12 years. MMRV vaccine may be used for both dose 1 and dose 2 of measles, mumps, and rubella vaccination and varicella vaccination in children younger than age 13 years. The minimum interval between doses of MMRV is 3 months. However, if dose 2 is administered at least 4 weeks following dose 1, it does not need to be repeated.

For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 through 47 months, either separate MMR and varicella (VAR) vaccines, or MMRV vaccine, may be used. However, the risk of febrile seizures is about twice as high for children receiving MMRV vaccine versus separate MMR and VAR vaccines. Providers who are considering administering MMRV should discuss the benefits and risks of both vaccination options with the parents. Unless the parent or caregiver expresses a preference for MMRV, separate MMR vaccine and VAR vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age and for the first dose at age 48 months or older, the use of MMRV generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and VAR vaccine).

## Immunogenicity and Vaccine Efficacy

### VAR (Varivax)

After one dose of VAR vaccine, 97% of children age 12 months through 12 years develop detectable antibody titers. More than 90% of vaccine responders maintain antibody for at least 6 years. In Japanese studies, 97% of children had antibody 7 to 10 years after vaccination.

### Varicella Vaccine Efficacy

- Effectiveness:
  - 82% for dose 1
  - 92% for dose 2

Among healthy adolescents and adults age 13 years or older, an average of 78% develop antibody after dose 1, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody persisted for at least 1 year in 97% of recipients after the second dose.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccine recipients. Breakthrough infection is significantly milder than infection among unvaccinated persons, with fewer lesions (generally fewer than 50), many of which are maculopapular rather than vesicular. Most persons with breakthrough infection do not have fever. Although findings of some studies have suggested otherwise, most investigations have not identified time since vaccination as a risk factor for breakthrough varicella. Some investigations have identified asthma, use of steroids, and vaccination at younger than age 15 months as risk factors for breakthrough varicella, but other investigations did not.

Interference from live viral vaccine could reduce vaccine effectiveness. A study of 115,000 children in two health maintenance organizations during 1995 to 1999 found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of breakthrough varicella compared with those who received varicella vaccine before, simultaneously with, or more than 30 days after MMR vaccine.

Studies have shown that a second dose of varicella vaccine boosts immunity and reduces the risk of breakthrough disease in children. A meta-analysis of postlicensure estimates found the effectiveness of 1 dose of varicella vaccine to be 82% against any clinical varicella and 98% against severe disease. Two doses of vaccine demonstrated 92% effectiveness against any clinical varicella.

## MMRV (ProQuad)

MMRV vaccine was licensed on the basis of non-inferiority of immunogenicity of the antigenic components rather than the clinical efficacy. Clinical studies involving healthy children age 12 through 23 months indicated that those who received a single dose of MMRV vaccine developed similar levels of antibody to measles, mumps, rubella, and varicella as children who received MMR vaccine and VAR vaccine concomitantly at separate injection sites.

## Varicella Immunity

Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:

### Varicella Immunity

- Documentation of age-appropriate vaccination
- Laboratory evidence of immunity
- Laboratory confirmation of disease
- Birth in the U.S. before 1980
  - Exception: Health care personnel, pregnant women, and immunocompromised persons
- Health care provider diagnosis or verification of varicella disease
- History of herpes zoster based on health care provider diagnosis or verification of disease history

- Preschool-aged children (age 12 months or older): 1 dose
- School-aged children, adolescents, and adults: 2 doses
- Laboratory evidence of immunity: commercial assays can be used to assess disease-induced immunity, but they lack adequate sensitivity to reliably detect vaccine-induced immunity (i.e., they may yield false-negative results).
- Laboratory confirmation of disease
- Birth in the United States before 1980 (except for health care personnel, pregnant women, and immunocompromised persons for whom birth in the United States before 1980 should not in itself be considered evidence of immunity). Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A health care provider diagnosis or verification of varicella disease: verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended, and one of the following should be sought: a) an epidemiologic link to a typical varicella case, or b) evidence of laboratory confirmation if laboratory testing was performed at the time of acute disease. When such documentation is lacking, a person should not be considered as having a valid history of disease, because other diseases may mimic mild or atypical varicella.
- History of herpes zoster based on health care provider diagnosis or verification of disease history.

## Postexposure Prophylaxis

### VAR Vaccine

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 70% to 100% effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, after exposure. ACIP recommends the vaccine for postexposure prophylaxis within 3 through 5 days after exposure for persons age 12 months or older who do not have evidence of varicella immunity and who do not have contraindications to vaccination. If exposure to varicella does not cause infection, postexposure vaccination should induce protection against subsequent exposure. If the exposure results in infection, there is no evidence that administration of varicella vaccine during the incubation period or prodromal stage of illness

### Varicella Vaccine Postexposure Prophylaxis

- Varicella vaccine is recommended for use in persons age 12 months or older without evidence of varicella immunity within 3 through 5 days after exposure to varicella
  - 70%-100% effective if given within 3 days of exposure (possibly up to 5 days)

increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, preexposure vaccination of all health care personnel without evidence of varicella immunity is the recommended and preferred method for preventing varicella in health care settings.

Varicella outbreaks in some settings (e.g., childcare facilities and schools) can persist up to 6 months. Varicella vaccine has been used successfully to control these outbreaks. During a varicella outbreak, persons who have received one dose of varicella vaccine should receive a second dose, provided the appropriate vaccination interval has elapsed since the first dose (3 months for persons age 12 months through 12 years and at least 4 weeks for persons age 13 years or older).

### **Varicella-Zoster Immune Globulin**

A Varicella-Zoster Immune Globulin (VZIG [VariZIG]) is licensed for use in the United States for postexposure prophylaxis for persons who do not have evidence of varicella immunity and who have contraindications for varicella vaccine. VariZIG is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (IgG) that is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly.

Patient groups recommended by ACIP to receive VariZIG for postexposure prophylaxis include the following:

- Immunocompromised patients without evidence of immunity to varicella
- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after)
- Hospitalized preterm infants born at 28 weeks gestation or later whose mothers do not have evidence of immunity
- Hospitalized preterm infants born earlier than 28 weeks' gestation or who weigh 1,000 grams or less at birth, regardless of maternal history of varicella disease or vaccination
- Pregnant women without evidence of immunity to varicella

## Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications and precautions are similar for both varicella-containing vaccines. VAR vaccine and MMRV vaccine both contain minute amounts of neomycin and gelatin but do not contain egg protein. Persons with alpha-gal allergy may wish to consult their physician before receiving a vaccine that contains gelatin.

Persons who are immunosuppressed due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated with a varicella-containing vaccine. However, treatment with low-dose (e.g., less than 2 milligrams per kilogram of body weight per day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to vaccination.

The interval until immune reconstruction varies with the intensity and type of immunosuppressive therapy, radiation therapy, underlying disease, and other factors, complicating the ability to make a definitive recommendation for an interval after cessation of immunosuppressive therapy when live-virus vaccines can be administered safely and effectively. Current recommendations are for patients to be vaccinated with varicella vaccine when in remission and at least three months after cancer chemotherapy, with evidence of restored immunocompetence. Varicella vaccine (as a 2-dose regimen if there is sufficient time) should be administered to immunocompetent patients without evidence of varicella immunity, if it can be administered at least 4 weeks before initiating immunosuppressive therapy.

Other immunosuppressive medications include human immune mediators such as interleukins and colony-stimulating factors, immune modulators, and medicines such as tumor necrosis factor-alpha inhibitors and anti-B cell antibodies. Live vaccines should be withheld 3 months following such therapies, and withheld at least 6 months following therapy with anti-B cell antibodies. Some experts recommend longer than 6 months following anti-B cell antibodies.

A family history of congenital or hereditary immunodeficiency in first-degree relatives (i.e., parents and siblings), unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory, is a contraindication for MMR or MMRV vaccine.

### Varicella Vaccine Contraindications

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Immunosuppression due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy
  - Family history of congenital or heredity immunodeficiency in first-degree relatives
  - HIV infection\*
  - Hematopoietic stem cell transplant (wait 24 months)
  - Pregnancy

\*Contraindicated for MMRV; contraindicated for VAR depending on CD4 count

### Varicella Vaccine Precautions

- Precaution
  - Moderate or severe acute illness
  - Alpha-gal allergy (consult with physician)
  - Receipt of antibody-containing blood products (wait 3 to 11 months to vaccinate)
  - Need for tuberculosis testing\*
  - Receipt of specific antiviral drugs 24 hours before vaccination
  - Simultaneous use of aspirin or aspirin-containing products
  - Personal or family history of seizures of any etiology\*

\*MMRV only

Persons with severe cellular immunodeficiency resulting from infection with HIV, including persons diagnosed with acquired immunodeficiency syndrome (AIDS) should not receive varicella vaccine. HIV-infected children with CD4+ T-lymphocyte percentage of 15% or higher, and older children and adults with a CD4+ count of 200 per microliter or higher may be considered for vaccination. These persons may receive MMR vaccine and VAR vaccine, but should not receive MMRV vaccine.

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to vaccination by passively transferred antibodies, neither VAR vaccine nor MMRV vaccine (nor MMR vaccine) should be administered for 3 to 11 months after receipt of antibody-containing blood products. The interval between the antibody-containing blood product and receipt of VAR, MMR, or MMRV vaccine is determined by the type of product administered. Antibody-containing products should not be given for 2 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, vaccine recipients should either be revaccinated later at the appropriate intervals (ranging 3 to 11 months), or tested for immunity and revaccinated if seronegative.

Varicella-containing vaccines may be administered a minimum of 24 months after hematopoietic stem cell transplant to patients who do not have graft versus host disease, are considered immunocompetent, and whose last dose of intravenous immunoglobulin (IVIG) was 8 to 11 months previously. Nonimmune family members, close contacts, and health care personnel associated with the patient should be vaccinated before that time.

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccine. Children with a personal or family history of seizures of any etiology should ideally be vaccinated with separate MMR and VAR vaccines because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for VAR or MMRV vaccination. These antiviral drugs should be avoided for 14 days after vaccination if possible.

Although there is no evidence that either varicella or varicella vaccine exacerbates tuberculosis, vaccination is not recommended for persons known to have untreated active tuberculosis. Tuberculosis testing is not a prerequisite for varicella vaccination.

Simultaneous use of aspirin or aspirin-containing products is a precaution for VAR or MMRV vaccine. The manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving VAR or MMRV vaccine because of the association between aspirin use and Reye syndrome following varicella.

The need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing is a precaution for MMRV vaccine.

Prior history of varicella is not a contraindication to varicella vaccination, so when in doubt as to history, varicella vaccine should be administered.

Women known to be pregnant or attempting to become pregnant should not receive a varicella-containing vaccine.

## Vaccination in Pregnancy

Wild-type varicella poses a low risk to the fetus. Because the virulence of the attenuated virus used in the vaccine is less than that of the wild-type virus, the risk to the fetus, if any, should be even lower from vaccine virus. Because the effects of the varicella virus on the fetus are unknown, pregnant women should not be vaccinated. Nonpregnant women who are vaccinated should avoid becoming pregnant for 1 month after each injection. For persons without evidence of immunity, having a pregnant household member is not a contraindication for vaccination.

Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, varicella vaccination during pregnancy should not be considered a reason to terminate pregnancy.

To monitor the pregnancy outcomes of women inadvertently vaccinated with VZV-containing vaccines immediately before or during pregnancy, Merck and CDC established the Merck/CDC Pregnancy Registry for VZV-Containing Vaccines. From inception of the registry in 1995 through March 2012, no cases of congenital varicella syndrome and no increased prevalence of other birth defects have been detected among women vaccinated within 3 months before or during pregnancy. Although a small risk for congenital varicella syndrome cannot be ruled out, the low number of exposures being registered each year in addition to the rarity of the outcome, were too low to improve on the estimate of the risk within a reasonable timeframe. Therefore, new patient enrollment was discontinued as of October 16, 2013. Merck continues to monitor pregnancy outcomes after inadvertent exposures to VZV-containing vaccines during pregnancy or within 3 months

before conception. CDC and the Food and Drug Administration continue to monitor adverse events after vaccination with VZV-containing vaccines through the Vaccine Adverse Event Reporting System (VAERS). New cases of exposure immediately before or during pregnancy or other adverse events after vaccination with VAR vaccine or MMRV vaccine should be reported to Merck (telephone, 1-877-888-4231) and to VAERS (<https://vaers.hhs.gov/index.html>).

Postpartum vaccination of women without evidence of immunity need not be delayed because of breastfeeding. Single-antigen varicella vaccine should be administered to nursing mothers without evidence of immunity.

## Varicella Vaccine Safety

### VAR

- Rash at injection site
  - 1–3%
- Generalized rash
  - 4–6%
- Fever
  - 10–15%

### MMRV

- Fever of 102°F or higher
  - 21.5%
- Febrile seizures
  - 1 additional per 2,300 to 2,600 children age 12 through 23 months

## Vaccine Safety

The most common adverse reactions following varicella vaccine are local reactions, such as pain, soreness, erythema, and swelling. Based on information from the manufacturer's clinical trials of varicella vaccine, local reactions are reported by 19% of children and by 24% of adolescents and adults (33% following the second dose). These local adverse reactions are generally mild and self-limited. A varicella-like rash at injection site is reported by 3% of children and by 1% of adolescents and adults following the second dose. In both circumstances, a median of two lesions have been present. These lesions generally occur within 2 weeks and may be maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4% to 6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with an average of five lesions. Most of these generalized rashes occur within 3 weeks and may be mainly maculopapular.

Systemic reactions are not common. Fever within 42 days of vaccination is reported by 15% of children and 10% of adolescents and adults. The majority of these episodes of fever have been attributed to concurrent illness rather than to the vaccine.

Varicella vaccine is a live virus vaccine and may result in a latent infection, similar to that caused by wild varicella virus. Consequently, zoster caused by the vaccine virus has been reported. Not all these cases have been confirmed as having been caused by vaccine virus. The risk of zoster following vaccination was assessed among children and is much lower (~79% lower) than that following infection with wild-type virus. The majority of cases of zoster following vaccine have been mild and have not been associated with complications such as postherpetic neuralgia; however, in children cases of herpes zoster with meningitis have been reported.

In MMRV vaccine prelicensure studies conducted among children age 12 to 23 months, fever (reported as abnormal or

elevated greater than or equal to 102°F oral equivalent) was observed 5 to 12 days after vaccination in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and VAR vaccine recipients. Measles-like rash was observed in 3.0% of MMRV vaccine recipients compared with 2.1% of those receiving MMR vaccine and VAR vaccine. Two postlicensure studies indicated that one additional febrile seizure per 2,300 to 2,600 children age 12 through 23 months occurred 5 to 12 days after the first dose of MMRV vaccine, compared with children who had received the first dose of MMR vaccine and VAR vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that this increased risk exists for children age 4 to 6 years receiving the second dose of MMRV vaccine.

### **Transmission of Varicella Vaccine Virus**

Accumulated evidence supports that healthy, vaccinated persons have minimal risk for transmitting the varicella vaccine virus to contacts; through 2018 only 13 cases from 11 immunocompetent vaccine recipients have been documented, most commonly among household contacts. Transmission of vaccine virus was reported only from vaccine recipients who developed a varicella-like or herpes zoster rash after vaccination. Secondary cases of varicella caused by the vaccine virus have been typically mild. In studies of household contacts, several instances of asymptomatic seroconversion have been observed. If a vaccinated person develops a rash, it is recommended that close contact with persons who do not have evidence of varicella immunity and who are at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved. As a safeguard, medical facilities should consider precautions for personnel in whom rash occurs after vaccination. Health care personnel in whom a vaccine-related rash occurs should avoid contact with persons without evidence of immunity who are at high risk of serious complications until all lesions resolve or no new lesions appear within a 24-hour period.

### **Vaccine Storage and Handling**

For storage and handling specifics, please refer to the manufacturer. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, [www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf](http://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf).





