

Varicella

Varicella is an acute infectious disease caused by varicella zoster virus (VZV). The recurrent infection (herpes zoster, also known as shingles) has been recognized since ancient times. Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by von Bokay, when children without evidence of varicella immunity acquired varicella after contact with herpes zoster. VZV was isolated from vesicular fluid of both chickenpox and zoster lesions in cell culture by Thomas Weller in 1954. Subsequent laboratory studies of the virus led to the development of a live attenuated varicella vaccine in Japan in the 1970s. The vaccine was licensed for use in the United States in March 1995. The first vaccine to reduce the risk of herpes zoster was licensed in May 2006.

Varicella Zoster Virus

VZV is a DNA virus and is a member of the herpesvirus group. Like other herpesviruses, VZV has the capacity to persist in the body after the primary (first) infection as a latent infection. VZV persists in sensory nerve ganglia. Primary infection with VZV results in chickenpox. Herpes zoster (shingles) is the result of recurrent infection. The virus is believed to have a short survival time in the environment.

Pathogenesis

VZV enters through the respiratory tract and conjunctiva. The virus is believed to replicate at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia occurs 4–6 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 or 2 days after the appearance of the rash.

Clinical Features

The incubation period is 14–16 days after exposure, with a range of 10–21 days. The incubation period may be prolonged in immunocompromised patients and those who have received postexposure treatment with a varicella antibody-containing product.

Varicella Zoster Virus

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

Varicella Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Repeated episodes of viremia
- Multiple tissues, including sensory ganglia, infected during viremia

Varicella Clinical Features

- Incubation period 14-16 days (range 10-21 days)
- Mild prodrome for 1-2 days
- Rash generally appears first on head; most concentrated on trunk
- Successive crops over several days with lesions present in several stages of development

Primary Infection (Chickenpox)

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.

The rash is generalized and pruritic and progresses rapidly from macules to papules to vesicular lesions before crusting. The rash usually appears first on the head, then on the trunk, and then the extremities; the highest concentration of lesions is on the trunk (centripetal distribution). Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1–4 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 several stages of development. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 200–500 lesions in 2 to 4 successive crops.

The clinical course in healthy children is generally mild, with malaise, pruritus (itching), and temperature up to 102°F for 2–3 days. Adults may have more severe disease and have a higher incidence of complications. Respiratory and gastrointestinal symptoms are absent. Children with lymphoma and leukemia may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Children infected with human immunodeficiency virus also may have severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of chickenpox is not common, but it can happen, particularly in immunocompromised persons. As with other viral diseases, reexposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Recurrent Disease (Herpes Zoster)

Herpes zoster, or shingles, occurs when latent VZV reactivates and causes recurrent disease. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with recurrent disease include aging, immunosuppression, intrauterine exposure to VZV, and having had varicella at a young age (younger than 18 months). In immunocompromised persons, zoster may disseminate, causing generalized skin lesions and central nervous system, pulmonary, and hepatic involvement.

Herpes Zoster (Shingles)

- Reactivation of varicella zoster virus
- Associated with:
 - aging
 - immunosuppression
 - intrauterine exposure
 - varicella at younger than 18 months of age

The vesicular eruption of zoster generally occurs unilaterally in the distribution of a sensory nerve. Most often, this involves the trunk or the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. There are few systemic symptoms.

Complications

Varicella

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* are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. Pneumonia following varicella is usually viral but may be bacterial. Secondary bacterial pneumonia is more common in children younger than 1 year of age. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common and generally has a good outcome. Encephalitis is an infrequent complication of varicella (estimated 1.8 per 10,000 cases) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children.

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.

In the prevaccine era, approximately 11,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately 2–3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella were reported each year. Most deaths occur in immunocompetent children and adults. Since 1996, the number of hospitalizations and deaths from varicella has declined more than 90%.

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than 15 years of age and infants younger than 1 year of age. For instance,

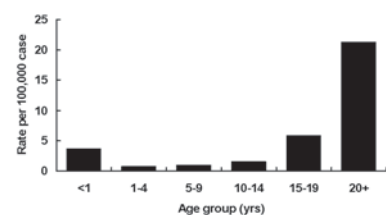
Varicella Complications

- Bacterial infection of skin lesions
- Pneumonia (viral or bacterial)
- Central nervous system manifestations
- Reye syndrome
- Hospitalization: 2-3 per 1,000 cases
- Death: 1 per 60,000 cases
- Postherpetic neuralgia (complication of zoster)

Groups at Increased Risk of Complications of Varicella

- Persons older than 15 years
- Infants younger than 1 year
- Immunocompromised persons
- Newborns of women with rash onset within 5 days before to 2 days after delivery

Varicella Fatality Rate—United States, 1990-1994



*Deaths per 100,000 cases. Meyer et al, J Infect Dis 2000;182:383-90

among children 1–14 years of age, the fatality rate of varicella is approximately 1 per 100,000 cases, among persons 15–19 years, it is 2.7 per 100,000 cases, and among adults 30–49 years of age, 25.2 per 100,000 cases. Adults account for only 5% of reported cases of varicella but approximately 35% of mortality.

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.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate and a fatality rate as high as 30%. This severe disease is believed to result from fetal exposure to varicella virus without the benefit of passive maternal antibody. Infants born to mothers with onset of maternal varicella 5 days or more prior to delivery usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

Herpes Zoster

Postherpetic neuralgia, or pain in the area of the occurrence that persists after the lesions have resolved, is a distressing complication of zoster. There is currently no adequate therapy available. Postherpetic neuralgia may last a year or longer after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Congenital VZV Infection

Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with a variety of abnormalities in the newborn, including low birth weight, hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, and microcephaly. 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 appears to be very low (less than 2%). Rare reports of congenital birth defects following maternal zoster exist, but virologic confirmation of maternal lesions is lacking.

Congenital Varicella Syndrome

- Results from maternal infection during pregnancy
- Low birth weight, atrophy of extremity with skin scarring, eye and neurologic abnormalities
- Risk appears to be low (less than 2%)
- Period of risk may extend through first 20 weeks of pregnancy

Laboratory Diagnosis

Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary. Varicella incidence has declined dramatically as a result of routine varicella immunization in the United States. This has had the combined effect of increasing the number of atypical cases (either vaccine adverse events or breakthrough wild-type infection in immunized persons) and of reducing physicians' experience in diagnosing varicella. As a result, the need for laboratory confirmation of varicella has increased.

Varicella zoster virus may be isolated in tissue culture. The most frequent source of isolation is vesicular fluid. Laboratory techniques allow differentiation of wild-type and vaccine strains of VZV.

Rapid varicella virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. VZV polymerase chain reaction (PCR) is the method of choice for rapid clinical diagnosis. Real-time PCR methods are widely available and are the most sensitive and specific method 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.

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. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions because positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative. Additional information concerning virus isolation and strain differentiation can be found at http://www.cdc.gov/vaccines/pubs/surv-manual/downloads/chpt14_varicella.pdf

A reliable history of chickenpox has been found to be a valid measure of immunity to varicella because the rash is distinctive and subclinical cases are unusual. As a result, serologic testing of children is generally not necessary. However, serologic testing may be useful in adult vaccination programs. A variety of serologic tests for varicella antibody are available. Available tests include complement fixation (CF), indirect fluorescent antibody (IFA), fluorescent antibody to membrane antigen (FAMA), neutralization, indirect hemagglutination (IHA), immune

Varicella Laboratory Diagnosis

- Isolation of varicella virus from clinical specimen
- Rapid varicella virus identification using PCR (preferred, if available) or DFA
- Significant rise in varicella IgG by any standard serologic assay (e.g., enzyme immunoassay)

adherence hemagglutination (IAHA), radioimmunoassay (RIA), latex agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive and specific, simple to perform, and widely available commercially. A commercially available LA is sensitive, simple, and rapid to perform. LA is generally more sensitive than commercial ELISAs, although it can result in false-positive results, leading to failure to identify persons without evidence of varicella immunity. This latter concern can be minimized by performing LA as a dilution series. Either of these tests would be useful for screening for varicella immunity.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease. Commercial antibody assays, particularly the LA test, may not be sensitive enough to detect vaccine-induced antibody in some recipients. Because of the potential for false-negative serologic tests, routine postvaccination serologic testing is not recommended. For diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella 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. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or e-mail vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

Epidemiology

Occurrence

Varicella and herpes zoster occur worldwide. Some data suggest that in tropical areas, varicella infection occurs more commonly among adults than children. The reason(s) for this difference in age distribution are not known with certainty, but may be related to lack of childhood varicella infection in rural populations.

Reservoir

Varicella is a human disease. No animal or insect source or vector is known to exist.

Transmission

Infection with VZV occurs through the respiratory tract. The most common mode of transmission of VZV is believed to be person to person from infected respiratory tract secretions. Transmission may also occur by respiratory contact with airborne droplets or by direct contact or inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster.

Varicella Epidemiology

- **Reservoir** Human
- **Transmission** Airborne droplet
Direct contact with lesions
- **Temporal pattern** Peak in winter and early spring (U.S.)
- **Communicability** 1-2 days before to 4-5 days after onset of rash
May be longer in immunocompromised

Temporal Pattern

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. In the United States, incidence is highest between March and May and lowest between September and November. Less seasonality is reported in tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year.

Communicability

The period of communicability extends from 1 to 2 days before the onset of rash through the first 4 to 5 days, or until lesions have formed crusts. Immunocompromised patients with varicella are probably contagious during the entire period new lesions are appearing. The virus has not been isolated from crusted lesions.

Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 of 10 susceptible household contacts of persons with varicella will become infected).

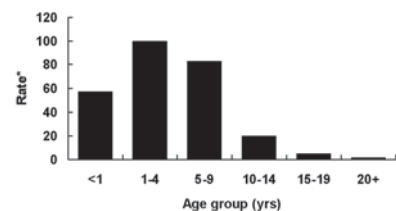
Secular Trends in the United States

Varicella

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 approximately 4 million per year. Varicella was removed from the list of nationally notifiable conditions in 1981, but some states continued to report cases to CDC. The majority of cases (approximately 85%) occurred among children younger than 15 years of age. The highest age-specific incidence of varicella was among children 1–4 years of age, 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. Children 5–9 years of age accounted for 38% of cases. Adults 20 years of age and older accounted for only 7% of cases (National Health Interview Survey data, 1990–1994).

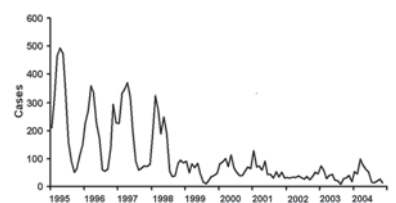
Data from three active varicella surveillance areas indicate that the incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly since licensure of vaccine in 1995. In 2004, varicella vaccination coverage among children 19–35 months in two of the active surveillance areas was estimated to be 89% and 90%. Compared with 1995, varicella cases declined 83%–93% by 2004. Cases declined most among children aged 1–4 and 5–9 years, but a decline occurred in all age groups including infants and adults, indicating reduced transmission of the

Varicella Age-Specific Incidence United States, 1990-1994



*Rate per 100,000 population. National Health Interview Survey data

Varicella Cases by Month Antelope Valley, CA, 1995-2004



Reduction in Age-Specific Varicella Incidence Rate Varicella Active Surveillance Project Sites, 1995 to 2004

Age group	Antelope Valley, CA* (%)	West Philadelphia (%)
< 1	83	77
1-4	94	89
5-9	83	95
10-14	49	98
15-19	65	78
20+	81	67
Total	83	93

*2003 population used for rate calculations

Varicella in the United States

- Increasing proportion of cases are a result of breakthrough infection
- Outbreaks reported in schools with high varicella vaccination coverage
- Persons with breakthrough infection may transmit virus

Herpes Zoster

- 500,000 to 1 million episodes occur annually in the United States
- Lifetime risk of zoster estimated to be at least 20%
- 50% of persons living until age 85 years will develop zoster

Varicella-Containing Vaccines

- Varicella vaccine (Varivax)
 - approved for persons 12 months and older
- Measles-mumps-rubella-varicella vaccine (ProQuad)
 - approved for children 12 months through 12 years
- Herpes zoster vaccine (Zostavax)
 - approved for persons 60 years and older

virus in these groups. The reduction of varicella cases is the result of the increasing use of varicella vaccine. Varicella vaccine coverage among 19–35-month-old children was estimated by the National Immunization Survey to be 88% in 2005.

Despite high one-dose vaccination coverage and success of the vaccination program in reducing varicella morbidity and mortality, varicella surveillance indicates that the number of reported varicella cases appears to have plateaued. An increasing proportion of cases represent breakthrough infection (chickenpox occurring in a previously vaccinated person). In 2001–2005, outbreaks were reported in schools with high varicella vaccination coverage (96%–100%). These outbreaks had many similarities: all occurred in elementary schools; vaccine effectiveness was within the expected range (72%–85%); the highest attack rates occurred among the younger students; each outbreak lasted about 2 months; and persons with breakthrough infection transmitted the virus although the breakthrough disease was mild. Overall attack rates among vaccinated children were 11%–17%, with attack rates in some classrooms as high as 40%. These data indicate that even in settings where almost everyone was vaccinated and vaccine performed as expected, varicella outbreaks could not be prevented with the current one-dose vaccination policy. These observations led to the recommendation in 2006 for a second routine dose of varicella vaccine.

Herpes Zoster

Herpes zoster is not a notifiable condition. An estimated 500,000 to 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 20%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster.

Vaccines Containing Varicella Virus

Three varicella-containing vaccines are now approved for use in the United States: varicella vaccine (Varivax), combination measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad), and herpes zoster vaccine (Zostavax).

Characteristics

Varicella Vaccine

Varicella vaccine (Varivax, Merck) is a live attenuated viral vaccine, derived from the Oka strain of VZV. The vaccine virus was isolated by Takahashi in the early 1970s from vesicular fluid from an otherwise healthy child with varicella

disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988. It was licensed in the United States in 1995 for persons 12 months of age and older. 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 reconstituted vaccine contains small amounts of sucrose, processed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, and potassium chloride, and trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine is reconstituted with sterile water and contains no preservative.

Measles-Mumps-Rubella-Varicella Vaccine

In September 2005, the Food and Drug Administration (FDA) licensed a combined live attenuated measles-mumps-rubella and varicella vaccine (ProQuad, Merck) for use in persons 12 months through 12 years of age. The attenuated measles, mumps, and rubella vaccine viruses in MMRV are identical and of equal titer to those in the measles-mumps-rubella (MMR) vaccine. The titer of Oka/Merck varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 ($3.99 \log^{10}$) plaque-forming units (PFU) versus 1,350 PFU ($\sim 3.13 \log^{10}$), respectively. Each 0.5-mL dose contains a small quantity of sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride; potassium phosphate dibasic; residual components of MRC-5 cells (DNA and protein) neomycin, bovine calf serum, and other buffer and media ingredients. The vaccine is reconstituted with sterile water and contains no preservative.

Herpes Zoster Vaccine

In May 2006, the FDA approved herpes zoster vaccine (Zostavax, Merck) for use in persons 60 years of age and older. The vaccine contains the same Oka/Merck varicella zoster virus used in varicella and MMRV vaccines but at a much higher titer (a minimum of 19,400 PFU versus 1,350 PFU in varicella vaccine). Each 0.65-mL dose contains a small amount of sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride; residual components of MRC-5 cells including (DNA and protein); neomycin and bovine calf serum. The vaccine is reconstituted with sterile water and contains no preservative.

Varicella Vaccine Immunogenicity and Efficacy

- Detectable antibody
 - 97% of children 12 months-12 years following 1 dose
 - 99% of persons 13 years and older after 2 doses
- 70%-90% effective against any varicella disease
- 95%-100% effective against severe varicella disease

Varicella Breakthrough Infection

- Immunity appears to be long-lasting for most recipients
- Breakthrough disease much milder than in unvaccinated persons
- No consistent evidence that risk of breakthrough infection increases with time since vaccination

Varicella Breakthrough Infection

- Retrospective cohort study of 115,000 children vaccinated in 2 HMOs (January 1995 through December 1999)
- Risk of breakthrough varicella 2.5 times higher if varicella vaccine administered less than 30 days following MMR
- No increased risk if varicella vaccine given simultaneously or more than 30 days after MMR

MMWR 2001;50(47):1058-61

Immunogenicity and Vaccine Efficacy

Varicella Vaccine

After one dose of single-antigen varicella vaccine, 97% of children 12 months to 12 years of age 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. Vaccine efficacy is estimated to be 70%–90% against infection, and 90%–100% against moderate or severe disease.

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

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. Breakthrough infection is significantly milder, 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, but not all, recent investigations have identified the presence of asthma, use of steroids, and vaccination at younger than 15 months of age as risk factors for breakthrough varicella. Breakthrough varicella infection could be a result of several factors, including interference of vaccine virus replication by circulating antibody, impotent vaccine resulting from storage or handling errors, or inaccurate recordkeeping.

Interference from live viral vaccine administered before varicella vaccine could also reduce vaccine effectiveness. A study of 115,000 children in two health maintenance organizations during 1995–1999 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.

Studies have shown that a second dose of varicella vaccine boosts immunity and reduces breakthrough disease in children.

MMRV Vaccine

MMRV vaccine was licensed on the basis of equivalence of immunogenicity of the antigenic components rather than the clinical efficacy. Clinical studies involving healthy children age 12–23 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 and varicella vaccines concomitantly at separate injection sites.

Herpes Zoster Vaccine

The primary clinical trial for zoster vaccine included more than 38,000 adults 60 to 80 years of age with no history of prior shingles. Participants were followed for a median of 3.1 years after a single dose of vaccine. Compared with the placebo group, the vaccine group had 51% fewer episodes of zoster. Efficacy was highest for persons 60–69 years of age (64%) and declined with increasing age. Efficacy was 18% for participants 80 years or older. Vaccine recipients who developed zoster generally had less severe disease. Vaccine recipients also had about 66% less postherpetic neuralgia, the pain that can persist long after the shingles rash has resolved. The duration of reduction of risk of zoster is not known.

Vaccination Schedule and Use

Varicella Vaccine

Varicella virus vaccine is recommended for all children without contraindications at 12 through 15 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella.

A second dose of varicella vaccine should be administered at 4 through 6 years of age, at the same visit as the second dose of MMR vaccine. The second dose may be administered earlier than 4 through 6 years of age if at least 3 months have elapsed following the first dose (i.e., the minimum interval between doses of varicella vaccine for children younger than 13 years is 3 months). However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated. A second dose of varicella vaccine is also recommended for persons older than 4 through 6 years of age who have received only one dose. Varicella vaccine doses administered to persons younger than 13 years should be separated by at least 3 months.

Herpes Zoster Vaccine Efficacy

- Compared with placebo group vaccine group had:
 - 51% fewer episodes of zoster
 - Lower efficacy for older recipients
 - Less severe disease
 - 66% less postherpetic neuralgia

NEJM 2005;352(22):2271-84.

Varicella Vaccine Recommendations Children

- Routine vaccination at 12-15 months of age
- Routine second dose at 4-6 years of age
- Minimum interval between doses of varicella vaccine for children younger than 13 years of age is 3 months

All varicella-containing vaccines should be administered by the subcutaneous route. Varicella 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 28 days. Varicella vaccine may also be administered simultaneously (but at separate sites with separate syringes) with all other childhood vaccines. ACIP strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 through 15 months of age.

Children with a clinician-diagnosed or verified history of typical chickenpox can be assumed to be immune to varicella. Serologic testing of such children prior to vaccination is not warranted because the majority of children between 12 months and 12 years of age without a clinical history of chickenpox are not immune. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella vaccine should be administered to all adolescents and adults 13 years of age and older who do not have evidence of varicella immunity (see Varicella Immunity section). Persons 13 years of age and older should receive two doses of varicella 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.

Assessment of varicella immunity status of all adolescents and adults and vaccination of those who lack evidence of varicella immunity are desirable to protect these individuals from the higher risk of complications from acquired varicella. Vaccination may be offered at the time of routine healthcare visits. However, specific assessment efforts should be focused on adolescents and adults who are at highest risk of exposure and those most likely to transmit varicella to others.

The ACIP recommends that all healthcare personnel be immune to varicella. In healthcare 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 varicella immunity following two 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. Seroconversion does not always result in full protection

Varicella Vaccine Recommendations Adolescents and Adults

- All persons 13 years of age and older without evidence of varicella immunity
- Two doses separated by at least 4 weeks
- Do not repeat first dose because of extended interval between doses

Varicella Vaccine Recommendations Healthcare Personnel

- Recommended for all susceptible healthcare personnel
- Prevacination serologic screening probably cost-effective
- Postvaccination testing not necessary or recommended

against disease, although no data regarding correlates of protection are available for adults. If a vaccinated health-care provider is exposed to VZV, the employee should be monitored daily from day 10 to day 21 after exposure through the employee health or infection control program to determine clinical status (screen for fever, skin lesions, and systemic symptoms). Persons with varicella may be infectious starting 2 days before rash onset. In addition, the healthcare worker should be instructed to immediately report fever, headache, or other constitutional symptoms and any skin lesions (which 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 appears to be very low (see Transmission of Varicella Vaccine Virus section), and the benefits of vaccinating susceptible healthcare providers clearly outweigh this potential risk. Transmission of vaccine virus appears to occur primarily if and when the vaccinee develops a vaccine-associated rash. As a safeguard, institutions may wish to consider protocols for personnel who develop a rash following vaccination (e.g., avoidance of contact with persons at high risk of serious complications, such as immunosuppressed persons who do not have evidence of varicella immunity).

MMRV Vaccine

MMRV vaccine is indicated for vaccination against measles, mumps, rubella and varicella in children 12 months through 12 years of age. Persons 13 years of age and older should not receive MMRV. When used, MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination. MMRV may be used for both the first and second doses of MMR and varicella in children younger than 13 years. The minimum interval between doses of MMRV is 3 months. However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated.

Herpes Zoster Vaccine

As of February 2008, ACIP recommendations for the use of herpes zoster varicella vaccine have not been published. Recommendations included here are provisional until published in *Morbidity and Mortality Weekly Report*. Publication of these recommendations is expected by mid-2008.

Zoster vaccine is approved by FDA for persons 60 years and older. A single dose of zoster vaccine is recommended for

MMRV Vaccine

- Approved for children 12 months through 12 years of age (to age 13 years)
- Do not use for persons 13 years and older
- May be used for both first and second doses of MMR and varicella vaccines
- Minimum interval between doses is 3 months

Herpes Zoster Vaccine*

- Approved for a single dose among persons 60 years and older
- May vaccinate regardless of prior history of herpes zoster (shingles)
- Persons with a chronic medical condition may be vaccinated unless a contraindication or precaution exists for the condition

*provisional recommendations as of January 2007

Varicella Vaccine Postexposure Prophylaxis

- Varicella vaccine is recommended for use in persons without evidence of varicella immunity after exposure to varicella
 - 70%-100% effective if given within 72 hours of exposure
 - not effective if administered more than 5 days after exposure but will produce immunity if not infected

adults 60 years of age and older whether or not they report a prior episode of herpes zoster. Persons with a chronic medical condition may be vaccinated unless a contraindication or precaution exists for the condition (see Contraindications and Precautions to Vaccination).

Postexposure Prophylaxis

Varicella 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 use in persons who do not have evidence of varicella immunity following exposure to varicella. 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 increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, preexposure vaccination of all healthcare workers without evidence of varicella immunity is the recommended and preferred method for preventing varicella in healthcare settings.

Varicella outbreaks in some settings (e.g., child care facilities and schools) can persist up to 6 months. Varicella vaccine has been used successfully to control these outbreaks. The ACIP recommends a second dose of varicella vaccine for outbreak control. 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 aged 12 months to 12 years and at least 4 weeks for persons aged 13 years of age and older).

MMRV Vaccine

MMRV vaccine may be used as described for varicella vaccine, and for measles as described in Chapter 10, Measles.

Herpes Zoster Vaccine

Exposure to a person with either primary varicella (chickenpox) or herpes zoster does not cause zoster in the exposed person. Herpes zoster vaccine has no role in the postexposure management of either chickenpox or zoster and should not be used for this purpose.

Varicella Immunity

In 2006, the ACIP approved a revised definition for evidence of immunity to varicella (as of January 2007 this recommendation has not yet been published, but will be published with the two-dose vaccine recommendation by mid-2007). Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:
 - Preschool-aged children 12 months of age or older: one dose
 - School-aged children, adolescents, and adults: two doses
- Laboratory evidence of immunity or laboratory confirmation of disease. 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).
- Born in the United States before 1980. For healthcare providers and pregnant women, birth before 1980 should not be considered evidence of immunity. Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A healthcare 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 atypical varicella.
- History of herpes zoster based on healthcare provider diagnosis.

Adverse Reactions Following Vaccination

Varicella Vaccine

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.

Varicella Immunity

- Written documentation of age-appropriate vaccination
- Laboratory evidence of immunity or laboratory confirmation of disease
- Born in the United States before 1980
- Healthcare provider diagnosis or verification of varicella disease
- History of herpes zoster based on healthcare provider diagnosis

Varicella Vaccine Adverse Reactions

- Local reactions (pain, erythema)
 - 19% (children)
 - 24% (adolescents and adults)
- Generalized rash – 4%-6%
 - may be maculopapular rather than vesicular
 - average 5 lesions
- Systemic reactions not common
- Adverse reactions similar for MMRV

In both circumstances, a median of two lesions have been present. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4%–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 most are 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, mostly among vaccinated children. Not all these cases have been confirmed as having been caused by vaccine virus. The risk of zoster following vaccination appears to be less 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.

MMRV Vaccine

The clinical trial of MMRV compared events that occurred within 42 days of receiving either MMRV or MMR and varicella vaccine separately in different anatomic sites. The frequencies of local reactions and generalized varicella-like rash were similar to those described for varicella vaccine. A temperature of 102°F or higher within 42 days of vaccination was more common in the MMRV group (22%) than in the group that received MMR and varicella vaccine at different sites (15%). A measles-like rash also occurred more frequently in MMRV recipients (3%) than in the group receiving separate injections (2.1%). Both fever and measles-like rash usually occurred 5–12 days following vaccination.

Herpes Zoster Vaccine

In the largest clinical trial of zoster vaccine, local reactions (erythema, pain or tenderness, and swelling) were the most common adverse reaction reported by vaccine recipients (34%), and were reported more commonly than by placebo recipients (6%). A temperature of 101°F or higher within 42 days of vaccination occurred at a similar frequency among both vaccine (0.8%) and placebo (0.9%) recipients. No serious adverse reactions were identified during the trial.

Zoster Following Vaccination

- Most cases in children
- Not all cases caused by vaccine virus
- Risk from vaccine virus less than from wild-type virus
- Usually a mild illness without complications such as postherpetic neuralgia

Herpes Zoster Vaccine Adverse Reactions

- Local reactions – 34% (pain, erythema)
- No increased risk of fever
- No serious adverse reactions identified

Contraindications and Precautions to Vaccination

Contraindications and precautions are similar for all varicella-containing vaccines. Persons with a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of vaccine should not receive varicella vaccine. Varicella, MMRV, and zoster vaccines all contain minute amounts of neomycin and hydrolyzed gelatin but do not contain egg protein or preservative.

Persons with immunosuppression 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 (less than 2 mg/kg/day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

Single-antigen varicella vaccine may be administered to persons with impaired humoral immunity (e.g., hypogammaglobulinemia). However, the blood products used to treat humoral immunodeficiency may interfere with the response to vaccination. Recommended spacing between administration of the blood product and receipt of varicella vaccine should be observed (see Chapter 2, General Recommendations on Immunization, for details).

Persons with moderate or severe cellular immunodeficiency resulting from infection with human immunodeficiency virus (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 and single-antigen varicella vaccines, but should not receive MMRV. Zoster vaccine should not be administered to persons who are immunosuppressed for any reason.

Women known to be pregnant or attempting to become pregnant should not receive a varicella-containing vaccine. To date, no adverse outcomes of pregnancy or in a fetus have been reported among women who inadvertently received varicella vaccine shortly before or during pregnancy. Although the manufacturer's package insert states otherwise, ACIP recommends that pregnancy be avoided for 1 month following receipt of varicella vaccine.

The ACIP recommends prenatal assessment and postpartum vaccination for varicella. Women should be assessed during a prenatal healthcare visit for evidence of varicella immunity.

Varicella-Containing Vaccines Contraindications and Precautions

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

Varicella Vaccine Use in Immunocompromised Persons

- MMRV not approved for use in persons with HIV infection
- Do not administer zoster vaccine to immunosuppressed persons

Varicella Vaccination in Pregnancy Registry

800.986.8999

Upon completion or termination of pregnancy, women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the healthcare facility. The second dose should be administered at least 4 weeks later at the postpartum or other healthcare visit. Standing orders are recommended for healthcare settings where completion or termination of pregnancy occurs to ensure administration of varicella vaccine.

The manufacturer, in collaboration with CDC, has established a Varicella Vaccination in Pregnancy registry to monitor the maternal–fetal outcomes of pregnant women inadvertently given varicella vaccine. The telephone number for the Registry is 800-986-8999.

Vaccination of persons with moderate or severe acute illnesses should be postponed until the condition has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse event, such as fever. Minor illness, such as otitis media and upper respiratory infections, concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to varicella vaccine. 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 skin testing is not a prerequisite for varicella vaccination.

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 varicella vaccination by passively transferred antibodies, varicella or MMRV vaccine should not be administered for 3–11 months after receipt of antibody-containing blood products. ACIP recommends applying the same intervals used to separate antibody-containing products and MMR to varicella vaccine (see chapter 2, General Recommendations on Immunization, and Appendix A for additional details). Immune globulin should not be given for 3 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, the vaccinees should either be revaccinated or tested for immunity at least 3 months later (depending on the antibody-containing product administered) and revaccinated if seronegative.

Recent receipt of an antibody-containing blood product is not a precaution to use of herpes zoster vaccine.

No adverse events following varicella vaccination related to the use of salicylates (e.g., aspirin) have been reported to date. However, the manufacturer recommends that

vaccine recipients avoid the use of salicylates for 6 weeks after receiving varicella or MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Transmission of Varicella Vaccine Virus

Available data suggest that transmission of varicella vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported, but in few instances has the secondary clinical illness been shown to be caused by vaccine virus. Several cases of suspected secondary transmission have been determined to have been caused by wild varicella virus. In studies of household contacts, several instances of asymptomatic seroconversion have been observed. It appears that transmission occurs mainly, and perhaps only, when the vaccinee develops a rash. If a vaccinated child 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.

Transmission of varicella vaccine virus from recipients of zoster vaccine has not been reported.

Vaccine Storage and Handling

Varicella vaccine is very fragile, and all vaccines that contain it must be handled with extreme care. To maintain potency, all varicella-containing vaccines must be stored frozen at an average temperature of 5°F (-15°C). Household freezers, including frost-free models, manufactured since the mid-1990s are acceptable for storage of these vaccines. Refrigerators with ice compartments that are not tightly enclosed or are enclosed with unsealed, uninsulated doors (i.e., small dormitory-style refrigerator/freezer combinations) are not capable of maintaining the required storage temperature. Regardless of the type of freezer, providers should check the adequacy of their freezer storage before obtaining vaccine by monitoring and verifying the temperature of their freezer.

The vaccine diluent should be stored separately at room temperature or in the refrigerator. The vaccine should be reconstituted according to the directions in the package insert and only with the diluent supplied (or with the diluent supplied for MMR vaccine), which does not contain preservative or other antiviral substances that might inactivate the vaccine virus. Once reconstituted, all varicella-containing vaccines must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

Transmission of Varicella Vaccine Virus

- Transmission of vaccine virus is a rare event
- Transmission appears to occur only if the vaccinee develops a rash
- Transmission of vaccine virus from recipients of zoster vaccine has not been reported

Varicella-Containing Vaccine Storage and Handling

- Store frozen at 5°F (-15°C) or lower at all times
- Store diluent at room temperature or refrigerate
- Discard if not used within 30 minutes of reconstitution

**Varicella Vaccine
Information
800-9VARIVAX**

Single antigen varicella (varivax) and MMR may be stored at refrigerator temperature for up to 72 hours. Vaccine stored in the refrigerator cannot be refrozen and must be discarded after 72 hours at this temperature.

Mishandled varicella vaccine should be clearly marked and replaced in the freezer separate from properly handled vaccine. The manufacturer must be contacted for recommendations before any mishandled vaccine is used. The Merck Vaccine Division varicella information telephone number is 800-9VARIVAX (800-982-7482).

Zoster vaccine cannot be stored at refrigerator temperature at any time.

Because of the lability of varicella vaccine, transport of the vaccine from a central clinic or storage area to an off-site clinic can be difficult. If off-site transport is attempted, a properly insulated container should be used, the vaccine should be transported on dry ice, and the temperature should be monitored continuously, to ensure that the appropriate storage temperature is maintained (see Appendix C).

Varicella Zoster Immune Globulin

In 2004, the only U.S.-licensed manufacturer of varicella zoster immune globulin (VZIG) (Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts) discontinued production of VZIG. The supply of the licensed VZIG product was depleted in early 2006. In February 2006, an investigational (not licensed) VZIG product, VariZIG (Cangene Corporation, Winnipeg, Canada) became available under an investigational new drug application (IND) submitted to the FDA. This product can be requested from the sole authorized U.S. distributor, FFF Enterprises (Temecula, California), for patients who have been exposed to varicella and who are at increased risk for severe disease and complications.

The investigational VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). Unlike the previous product, the investigational product is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly. As with any product used under IND, patients must be informed of potential risks and benefits and must give informed consent before receiving the product.

Patients without evidence of immunity to varicella (i.e., without history of disease or age-appropriate vaccination) who are at high risk for severe disease and complications,

who have been exposed to varicella, and from whom informed consent has been obtained, are eligible to receive the IND application product under an expanded access protocol. The patient groups recommended by ACIP to receive VariZIG include the following:

- Immunocompromised patients
- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after)
- Preterm infants born at 28 weeks gestation or later who are exposed during the neonatal period and whose mothers do not have evidence of immunity
- Preterm infants born earlier than 28 weeks' gestation or who weigh 1,000g or less at birth and were exposed during the neonatal period, regardless of maternal history of varicella disease or vaccination
- Pregnant women

Addition information concerning the acquisition and use of this product is available in the March 3, 2006, edition of *Morbidity and Mortality Weekly Report*, available at <http://www.cdc.gov/MMWR/preview/MMWRhtml/mm5508a5.htm>

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Varicella

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