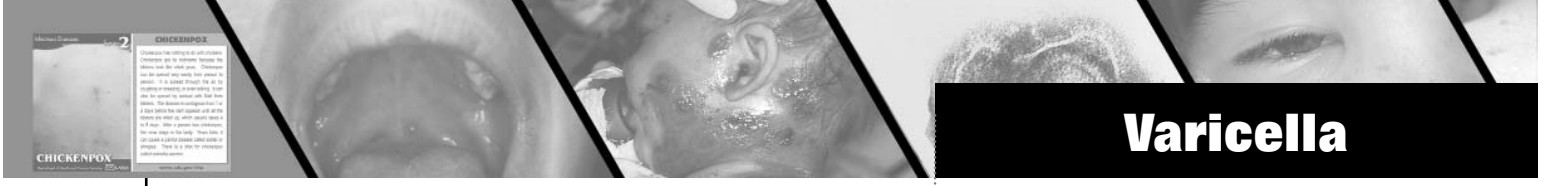


Varicella

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 healthy children and adults in the United States in March 1995.

Varicella

- Acute viral illness
- Zoster described in premedieval times
- Varicella not differentiated from smallpox until end of 19th century
- Infectious nature demonstrated in 1875

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 outside the infected host.

Varicella Zoster Virus

- Herpesvirus (DNA)
- Primary infection results in varicella (chickenpox)
- Recurrent infection results in herpes zoster (shingles)
- Short survival in 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 following the appearance of the rash.

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

Clinical Features

The **incubation period** is from 14 to 16 days from exposure, with a range of 10–21 days. The incubation period may be prolonged in immunocompromised patients and those who have received varicella zoster immune globulin (VZIG). The incubation period may be up to 28 days after receipt of VZIG.

Varicella Clinical Features

- Incubation period 14-16 days (range 10-21 days)
- Mild prodrome for 1-2 days
- Generally appear first on head; most concentrated on trunk
- Successive crops (2-4 days) of pruritic vesicles

Varicella

Primary Infection (Chickenpox)

A mild **prodrome** may precede the onset of a rash. Adults may have 1–2 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 scalp, then on the trunk, and then the extremities, with the highest concentration of lesions 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 fever 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 may also 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 this 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.

The vesicular eruption of zoster generally occurs unilaterally in the distribution of a dermatome supplied by a dorsal root

Herpes Zoster

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

or extramedullary cranial nerve sensory ganglion. Most often, this involves the trunk or the area of the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the segment involved. There are few systemic symptoms. Postherpetic neuralgia, or pain in the area of the recurrence which persists after the lesions have resolved, is a distressing complication of zoster, with no adequate therapy currently available. Postherpetic neuralgia may last as long as a year after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Complications

Acute varicella is generally mild and self-limited, but it may be associated with complications. The most common complications of varicella include **secondary bacterial infections** of skin lesions, dehydration, pneumonia, and central nervous system (CNS) involvement. 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.

Varicella Complications

- Bacterial infection of lesions
- CNS manifestations
- Pneumonia (rare in children)
- Hospitalization ~3 per 1,000 cases
- Death ~1 per 60,000 cases

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.

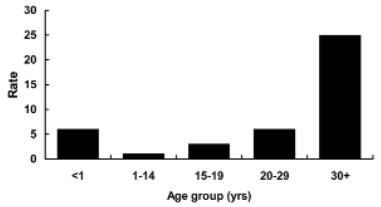
Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related 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 clinical 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 immunologically normal children and adults.

Varicella Fatality Rate in Healthy Persons



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, 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.

Groups at Increased Risk of Complications of Varicella

- Healthy adults
- Immunocompromised persons
- Newborns of mothers with rash onset within 5 days before to 48 hours after delivery

Immunocompromised persons have a high risk of acquiring serious varicella infection and 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.

Perinatal Infection

The onset of maternal varicella from 5 days before to 48 hours 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.

Congenital Varicella Syndrome

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

Congenital VZV Infection

Primary 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 during the first trimester 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. Intrauterine infection with VZV, particularly after 20 weeks' gestation, is associated with zoster in those infants at an earlier age; the exact risk is unknown.

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 such, the need for laboratory confirmation of varicella is on the increase.

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)

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 zoster virus identification. Rapid 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 more widely available than in the past 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/nip/publications/surv-manual/

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 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 and 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 email vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

Epidemiology

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

Occurrence

Varicella and herpes zoster occur worldwide. Some data suggest that varicella infection is less common in childhood in tropical areas, where chickenpox occurs more commonly among adults. 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.

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.

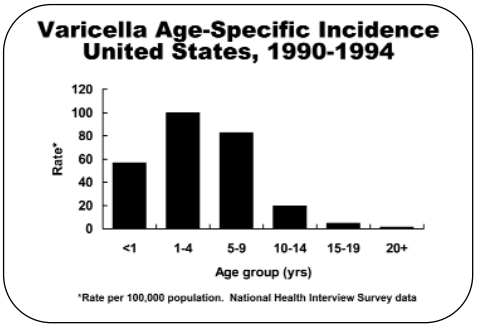
Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 of 10 susceptible household contacts of persons with varicella will become infected).

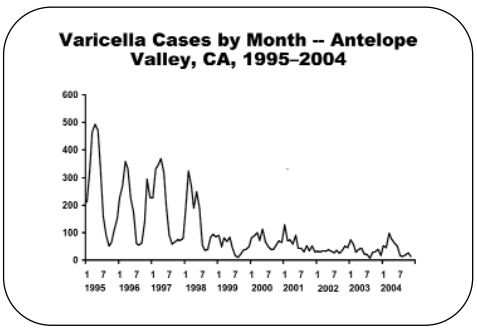
Secular Trends in the United States

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.

In the prevaccine era, 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





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

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 virus in these groups.

Herpes Zoster

Herpes zoster is not a notifiable condition. An estimated 300,000 episodes of zoster occur annually. Ninety-five percent of these episodes are first occurrences, and 5% are recurrences. The risk of zoster increases with increasing age. By age 80, almost 15% of persons will have experienced at least one episode of zoster.

Varicella Vaccine

Varicella Vaccine

- Composition — Live virus (Oka/Merck strain)
- Efficacy — 95% (Range, 65%-100%)
- Duration of Immunity — >7 years
- Schedule — 1 Dose (<13 years of age)

May be administered simultaneously with measles, mumps, and rubella (MMR) vaccine

Characteristics

Varicella zoster vaccine 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. 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 does not contain egg, ovalbumin, or preservative.

On September 6, 2005, the Food and Drug Administration licensed a combined live attenuated measles-mumps-rubella and varicella (MMRV) vaccine (ProQuad) 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 3.99 $\log_{10}$ plaque-forming units (PFU) versus 1,350 PFU (~3.13 $\log_{10}$), respectively.

Immunogenicity and Vaccine Efficacy

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 85%–95% against moderate or severe disease. In field conditions, varicella vaccine is 80%–85% effective against infection and more than 95% effective against severe disease.

Among healthy adolescents and adults, an average of 78% develop antibody after one dose, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody has persisted for at least 1 year in 97% of vaccinees after the second dose given 4 to 8 weeks after the first dose. Studies on the persistence of antibody and clinical efficacy in both children and adults are ongoing.

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.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. Breakthrough infection (i.e., varicella disease in a vaccinated person) 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 younger age (i.e., younger than 15 months) risk factors for breakthrough varicella. However, because of the inconsistency of these data, ACIP has not changed its recommendations for use of varicella vaccine.

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 in two health maintenance organizations found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of

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

Breakthrough Infection

- Retrospective cohort study of 115,000 children vaccinated in 2 HMOs during 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

breakthrough varicella compared with those who received varicella vaccine before, simultaneously with, or more than 30 days after MMR. Inactivated vaccines (DTaP, Hib, IPV, and hepatitis B) and OPV did not increase the risk of breakthrough varicella if administered less than 30 days prior to varicella vaccine.

Varicella Vaccine Recommendations Children

- Routine vaccination at 12-18 months of age
- Recommended for all children without evidence of varicella immunity by the 13th birthday

Vaccination Schedule and Use

Varicella virus vaccine is recommended for all children without contraindications at 12–18 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella. However, vaccination is not necessary for children with reliable histories of chickenpox.

Varicella vaccine is also recommended for all children without evidence of varicella immunity (see below) by the 13th birthday. Children who have not been vaccinated previously and who do not have a reliable history of chickenpox are considered susceptible. Efforts should be made to ensure varicella immunity by this age, because after 13 years of age varicella disease is more severe, complications are more frequent, and two doses of vaccine are required.

MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in children 12 months through 12 years of age; persons outside of this age group should not receive this vaccine. MMRV vaccine can reduce the number of injections when administered to children 12 months through 12 years of age for whom a) the first dose of MMR and varicella vaccines are indicated, and b) the second dose of MMR and either the first or the second dose (i.e., during varicella outbreaks) of varicella vaccines are indicated. Use of licensed combination vaccines, such as MMRV vaccine, is preferred to separate injection of their equivalent component vaccines. When used, MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination.

Varicella vaccine should be administered subcutaneously. It 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 12–18 months of age.

Children with a reliable 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 who do not have evidence of varicella immunity**. Approximately 80% of adolescents and adults respond to a single dose of varicella vaccine. In contrast, at least 97% of healthy children will develop detectable antibody after a single dose. As a result, persons 13 years of age and older should receive **two doses** of varicella vaccine separated by 4–8 weeks. If there is a lapse of more than 8 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 health-care 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.

Vaccination of Persons 13 Years of Age and Older

Varicella vaccine was previously recommended for persons 13 years of age and older without evidence of immunity who have close contact with persons at high risk for severe disease (e.g., healthcare workers and family contacts of immunocompromised persons) or who are at high risk for exposure or transmission. The ACIP now recommends that all other persons in this age group without evidence of immunity be vaccinated with two doses of varicella vaccine administered 4–8 weeks apart. The vaccine may be offered during routine healthcare visits.

The ACIP recommends that **all healthcare workers** be immune to varicella, either from a reliable history of varicella disease or from vaccination. 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.

Varicella Vaccine Recommendations Adolescents and Adults

- All persons ≥13 years of age without evidence of varicella immunity
- Two doses separated by 4-8 weeks
- Do not repeat first dose because of extended interval between doses

Vaccination of Healthcare Workers

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

Seroconversion does not always result in full protection against disease, although no data regarding correlates of protection are available for adults. If a vaccinated health-care worker is exposed to VZV, the employee should be monitored daily from day 10 to day 21 after exposure through the employee health program or infection control nurse to determine clinical status (screen for fever, skin lesions, and systemic symptoms). Of note, 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. Healthcare institutions may establish protocols and recommendations for screening and vaccinating healthcare workers and for management of healthcare workers following exposures in the workplace.

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, below), and the benefits of vaccinating susceptible healthcare workers 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 precautions 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).

Varicella Immunity

- Written documentation of age-appropriate vaccination
- Born in the U.S. before 1966
- History of typical varicella disease among:
  - —non-U.S. born persons born before 1966
  - —all persons born during 1966-1997
- History of herpes zoster based on healthcare provider diagnosis
- Laboratory evidence of immunity or laboratory confirmation of disease

Varicella Immunity

In 2005 the ACIP approved a revised definition for evidence of immunity to varicella. Evidence of immunity to varicella includes any of the following:

1) Written documentation of age-appropriate vaccination;
2) Born in the United States before 1966;
3) History of varicella disease based on healthcare provider diagnosis or self or parental report of typical varicella disease for non-U.S.-born persons born before 1966, and all persons born during 1966–1997. For persons reporting a history of atypical mild disease, healthcare providers should seek either a) an epidemiologic link to a typical varicella case (e.g., case occurred in the context of an outbreak or patient had household exposure in the previous 3 weeks), or b) evidence of laboratory confirmation, if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease because other diseases may mimic mild atypical varicella.

For persons born during or after 1998, history of disease is no longer considered as evidence of immunity, unless the illness was laboratory confirmed.

4) History of herpes zoster based on healthcare provider diagnosis; or
5) Laboratory evidence of immunity or laboratory confirmation of disease.

Postexposure Prophylaxis

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 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 post-exposure 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 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 >5 days but will produce immunity if not infected

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. Varicella vaccine should be used for outbreak control by advising exposed persons without evidence of varicella immunity to contact their healthcare providers for vaccination or by offering vaccination through the health department. The ACIP now recommends a second dose of varicella vaccine for outbreak control. During a varicella outbreak, persons who have received one dose of varicella vaccine should, resources permitting, 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).

Adverse Reactions Following Vaccination

The most common adverse reactions following varicella vaccine are those at the **injection site**, such as pain, soreness, redness, 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

Varicella Vaccine Adverse Reactions

- Injection site complaints
  19% (children)
  24% (adolescents and adults)
- Rash – 3%-4%
  - —may be maculopapular rather than vesicular
  - —average 5 lesions
- Systemic reactions not common

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 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 a median of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

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 intercurrent 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.

Zoster Following Vaccination

- Most cases in children
- Risk from vaccine virus less than from wild virus
- Usually a mild illness without complications

Contraindications and Precautions to Vaccination

Contraindications and precautions to varicella vaccine are similar to those for other live attenuated vaccines. Persons with a **severe allergic reaction to a vaccine component or following a prior dose of vaccine** should not receive varicella vaccine. Varicella vaccine contains minute amounts of neomycin and gelatin but does not contain egg protein or preservatives.

Varicella Vaccine Contraindications and Precautions

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

Persons with **immunosuppression** due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to varicella vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

Varicella Vaccine Use in Immunocompromised Persons

- Most immunocompromised persons should not be vaccinated
- Vaccinate persons with isolated humoral immunodeficiency
- Consider varicella vaccination for asymptomatic HIV-infected children with CD4% $\geq$15% (CDC class A1 and N1)

Varicella vaccine should not be administered to persons with cellular immunodeficiency. However, in 1999, ACIP recommended that persons with isolated humoral immunodeficiency (e.g., hypogammaglobulinemia and agammaglobulinemia) should be vaccinated.

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. However, vaccination should be considered for children with asymptomatic or mildly symptomatic HIV infection (CDC class N1 or A1, age-specific CD4+ T-lymphocyte percentage of 15% or higher). These children should receive two doses of varicella vaccine with a 3-month interval between doses. Because persons with impaired cellular immunity are potentially at greater risk for complications after vaccination with a live vaccine, these vaccinees should be encouraged to return for evaluation if they experience a postvaccination varicella-like rash.

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

The ACIP now recommends **prenatal assessment and postpartum vaccination** for varicella. Women should be assessed during a prenatal healthcare visit for evidence of varicella immunity. 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 4–8 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.

Transmission of Varicella Vaccine Virus

- Transmission of vaccine virus not common
- Asymptomatic seroconversion may occur in contacts without evidence of varicella immunity
- Risk of transmission increased if vaccinee develops rash

Varicella Vaccination in Pregnancy Registry

800.986.8999

The effect of the administration of **antibody-containing blood products** (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin, or varicella zoster immune globulin [VZIG]) 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 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, for additional details). Immune globulin or VZIG 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.

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 vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Transmission of Varicella Vaccine Virus

Available data suggest that transmission of vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported. However, 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. However, 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.

Vaccine Storage and Handling

Varicella vaccine is very fragile and must be handled with extreme care. To maintain potency, the lyophilized vaccine 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 designed to maintain temperatures as low as -4°F (-20°C) and are acceptable for storage of the

Vaccine Storage and Handling
Varicella Vaccine

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

vaccine. 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, the vaccine must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

If varicella vaccine is inadvertently placed in the refrigerator, or if unreconstituted vaccine is left at room temperature for a short time, it may still be potent enough to use. Mishandled vaccine should be clearly marked and replaced in the freezer separate from properly handled vaccine. After the vaccine is stored this way, the manufacturer must be contacted for recommendations before any of the mishandled vaccine is used. The Merck Vaccine Division varicella information telephone number is 800-9VARIVAX (800-982-7482). If the vaccine has been kept cold or has been exposed to room temperature for a very short time, the manufacturer may recommend that the expiration date be shortened and that the vaccine be used as quickly as possible. Mishandled vaccine should never be destroyed until the manufacturer has been consulted.

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 high-quality 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. The vaccine may be kept at refrigerator temperature for up to 72 hours, but it must then be discarded if not used. The vaccine should not be refrozen.

MMRV must be shipped to maintain a temperature of -4°F (-20°C) or colder at all times. It must be stored at an average temperature of 5°F (-15°C) or colder at all times. MMRV may not be stored at refrigerator temperature at any time. MMRV must be administered within 30 minutes of reconstitution.

Varicella Vaccine Information

800-9VARIVAX

Vaccine Storage and Handling MMRV

- Must be shipped to maintain a temperature of ≤- 4°F (-20°C) at all times
- Must be stored at an average temperature of ≤5°F (-15°C) at all times
- May NOT be stored at refrigerator temperature at any time
- Must be administered within 30 minutes of reconstitution

Varicella Zoster Immune Globulin (VZIG)

- May modify or prevent disease if given within 96 hours after exposure
- Indications
  - —immunocompromised persons
  - —newborn of mothers with onset 5 days before to 48 hours after delivery
  - —premature infants with postnatal exposure
  - —susceptible adults and pregnant women
- Supply of VZIG limited – may use IVIG or acyclovir (see NIP website for details)

Varicella Zoster Immune Globulin

VZIG is a human blood product that contains high titers of varicella zoster virus antibody. It was licensed in 1981 and is **available from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477.** If administered within 96 hours of exposure, VZIG can modify or prevent clinical varicella and prevent complications or death, especially in susceptible immunocompromised individuals.

The decision to administer VZIG should be based on whether the patient does not have evidence of varicella immunity, either by having a negative history of chickenpox or by lacking documentation of vaccination; whether the exposure is likely to result in infection; and, most importantly, whether the patient is at greater risk of complications than the general population. VZIG is expensive ($400–$500 for the maximum dose for an adult) and provides only temporary protection.

VZIG is indicated for use in persons without evidence of varicella immunity who are at high risk for complications and who have had a significant exposure (continuous household contact; playmate contact of more than an hour; hospital contact in the same 2- to 4-bed room; or prolonged direct contact) to a person with varicella. It is most commonly used for postexposure prophylaxis of immunocompromised children (immune deficiencies, neoplastic disease, or receiving immunosuppressive therapy), and newborns of mothers with varicella onset 5 days before to 48 hours after delivery. It is also recommended for premature infants with postnatal exposure, including those born at less than 28 weeks' gestation or who are less than 1,000 gram birth weight (who may not have received adequate maternal antibody regardless of whether the mother is immune), or premature infants whose mother is not immune to varicella.

Healthy and immunocompromised adults and pregnant women are at increased risk of complications of varicella. VZIG should be considered if such persons do not have evidence of varicella immunity. There is no evidence that VZIG will prevent congenital varicella if given as postexposure prophylaxis to a pregnant woman.

VZIG is supplied in vials containing 125 or 625 units. The recommended dose considered likely to prevent or modify varicella is 125 units per 10 kilograms of body weight, up to a maximum of 625 units, or five vials. Higher doses can be considered for immunosuppressed persons. VZIG is given intramuscularly and must never be given intravenously. It should be given within 96 hours of exposure, preferably as soon as possible. The administration of VZIG may prolong the incubation period of varicella to 28 days or longer postexposure.

More detailed information on the evaluation of a person exposed to varicella and the use of VZIG can be found in the varicella ACIP statement (available at http://www.cdc.gov/nip/publications/acip-list.htm).

As of December 2005, because of discontinuation of the product by the manufacturer, the distributor has limited supplies of VZIG (625-unit vials only) that are expected to last until only until early 2006. In light of the VZIG shortage, the ACIP approved recommendations for postexposure prophylaxis of severe varicella during a VZIG shortage.

For postexposure prophylaxis of varicella of patients without evidence of immunity who are at high risk for severe disease and complications, VZIG is the preferred method. If VZIG is not available, intravenous immune globulin (IGIV) can be used. The recommendation for the use of IGIV is based on "best judgment of experts" and is supported by reports comparing VZV IgG antibody titers measured in both IGIV and VZIG preparations and patients given IGIV and VZIG. Licensed IGIV preparations contain anti-varicella antibodies at varying levels. No clinical data demonstrating effectiveness of IGIV for postexposure prophylaxis of varicella are available.

Indications for the use of IGIV include 1) immunocompromised patients; 2) neonates whose mothers develop signs and symptoms of varicella around the time of delivery (5 days before to 2 days after); 3) premature infants exposed during the neonatal period whose mothers do not have evidence of immunity; 4) premature infants who are less than 28 weeks' gestation or who weigh less than 1,000 grams at birth and who are exposed during the neonatal period, regardless of maternal history of varicella; or 5) pregnant women. Clinicians may choose either to administer IGIV or closely monitor the pregnant woman for signs and symptoms of varicella and institute treatment with acyclovir if illness develops.

Based on experience with VZIG, IGIV could be expected to provide maximum benefit when administered as soon as possible after the exposure and may be effective if administered as late as 96 hours after exposure. IGIV should be administered intravenously as directed by the manufacturer. The recommended IGIV dose for postexposure prophylaxis of varicella is 400 mg/kg. This dose is estimated to yield VZV antibody titers in the recipients comparable to those produced by the recommended VZIG dose (22.5 mg/kg).

The antiviral drug acyclovir is also recommended by some experts for postexposure prophylaxis in a dosage of 40–80 mg/kg/day for children and 800 mg five times/day for adults. The recommendation is for administration beginning from day 7 to day 10 after exposure and for a total of 7 days of therapy.

Special Varicella Exposure Situations

Hospital Personnel

Healthcare workers who do not have evidence of varicella immunity and have significant exposure to varicella should be furloughed from day 10 after first exposure to day 21 after last exposure. If workers develop chickenpox, varicella lesions must be crusted before they return to direct patient contact. Receipt of VZIG can prolong the incubation period by one week; the period of furlough should be lengthened to 28 days after last exposure if VZIG is administered.

Newborns

Newborn whose mothers experience rash onset 5 days before to 48 hours after delivery should receive VZIG. Since about 50% of infants who receive VZIG will develop varicella, if these infants remain hospitalized beyond age 10 days, they should be kept in strict isolation for the entire incubation period (until day 28 or longer).

Varicella Antiviral Therapy

- Not recommended for routine use among otherwise healthy infants and children with varicella
- Consider for persons age >13 years
- Consider for persons with chronic cutaneous or pulmonary disorders, long-term salicylate therapy, or steroid therapy
- IV in immunocompromised children and adults with viral-mediated complications
- Not recommended for postexposure prophylaxis

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Antiviral Therapy

Several antiviral drugs are active against varicella zoster virus, including acyclovir, valacyclovir, famciclovir, and foscarnet. Valacyclovir and famciclovir are approved for use only in adults. Clinical studies indicate that these drugs may be beneficial if given within 24 hours of onset of rash; they have resulted in a reduction in the number of days new lesions appeared, in the duration of fever, and in the severity of cutaneous and systemic signs and symptoms. Antiviral drugs have not been shown to decrease transmission of varicella, reduce the duration of absence from school, or reduce complications.

The decision to use antiviral therapy, and the duration and route of therapy should be determined by specific host factors, the extent of infection, and the initial response to therapy. ACIP has not made recommendations regarding the use of antiviral therapy for varicella. The American Academy of Pediatrics does not recommend routine antiviral therapy for otherwise healthy infants or children with varicella. Oral acyclovir can be considered for otherwise healthy adolescents and adults or persons with secondary cases in the household because of the increased risk of severe illness in these groups. Antiviral therapy may also be considered for persons with a chronic cutaneous or pulmonary disorders, persons receiving long-term salicylate therapy, and children receiving short, intermittent or aerosolized courses of corticosteroids. If the child is immunocompromised, intravenous administration is indicated. Corticosteroids should be discontinued, if possible, after exposure. Antiviral drugs are not recommended for routine postexposure prophylaxis.

Oral acyclovir is not routinely recommended for pregnant adolescents or adults with uncomplicated varicella because the risks and benefits to the fetus and mother are not known. However, some experts recommend oral acyclovir for pregnant women with varicella, particularly during the second and third trimesters.

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