VARICELLA (CHICKENPOX) HERPES ZOSTER

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Varicella (chickenpox) is the primary infection caused by the varicella-zoster virus (VZV).

VZV is a DNA virus and a member of the herpes virus group. Like other herpes viruses, 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.

Epidemiology

Humans are the only source of infection for this virus.

Varicella is highly infectious with secondary infection rates in susceptible household contacts approaching 90%.

Transmission occurs from person-to-person by direct contact with patients with either varicella or zoster lesions, or by airborne spread from respiratory secretions.

Prior to the availability of varicella vaccine, almost everyone developed varicella during their lifetime. Thus, the number of cases approximated the birth cohort over time, resulting in an estimated four million cases of varicella in the United States annually. Varicella affects mainly children, with approximately 90% of cases occurring before the age of ten years. The highest rates of disease are among children five to nine years of age followed closely by children one to four years of age. Some recent studies have reported the highest rate of disease in the pre-school age group. This may be associated with a trend towards earlier attendance at day care and/or pre-school. Although more than six million doses of vaccine having been administered since licensure of the live attenuated varicella vaccine in the U.S. during 1995, the impact of vaccination on disease incidence has yet to be documented at the national or state level. Currently, varicella continues to occur with millions of cases per year. In addition, there are an estimated 4,000 to 9,000 hospitalizations each year for varicella and its complications, with 100 to 125 deaths annually having varicella as an underlying cause.

The incubation period is from 14 to 16 days from exposure, with a range of ten to 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 VZIG.

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 four to six days after infection, which 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 five days before to one or two days following the appearance of the rash.
Clinical Description

A mild prodrome may precede the onset of a rash. Adults may have one to two 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, pruritic and rapidly progresses from macules to papules to vesicular lesions before crusting. The rash usually appears first on the scalp, followed by 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 1mm to 4 mm in diameter. The vesicles are superficial and delicate and contain clear fluid on an erythematous base. Vesicles may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in 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 to 500 lesions in two to four successive crops. The clinical course in healthy children is generally mild, with malaise, pruritus (itching), and fever up to 102°F for two to three 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 uncommon, but may occur, 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.

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 varicella at a young age (<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 or extra-medullary 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. Post-herpetic 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. Post-herpetic 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.

Acute varicella is generally mild and self-limited, but may be associated with complications. The most common complications of varicella include secondary bacterial infections of skin lesions, dehydration, pneumonia and central nervous system 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 one 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 clinical hepatitis. In the prevaccine era, approximately 11,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately two to three per 1,000 cases among healthy children and eight per 1,000 cases among adults. Death occurred in approximately one in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella was reported each year. Most deaths occur in immunologically normal children and adults.

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They are much higher in persons older than 15 years of age and infants younger than one year of age. For instance, among children one to 14 years of age, the fatality rate of varicella is approximately one per 100,000 cases. Among persons 15 to 19 years of age, the fatality rate is 2.7 per 100,000 cases; among adults 30 to 49 years of age, 25.2 per 100,000 cases. Adults account for only 5% of reported cases of varicella, but account for approximately 35% of mortality.

**Immunocompromised persons** have a high risk of 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 five days before to two 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 five days or more prior to delivery usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

**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 (<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.

Although immunity following varicella infection is generally long lasting, second cases of varicella do occur rarely among immunologically normal persons.

**Mortality**

Before varicella vaccination was included in routine childhood immunization, approximately 11,000 varicella-related hospitalizations and 100 to 150 deaths were reported annually in the United States; in Louisiana the estimate would be 200 hospitalizations and two to three deaths. Implementation of the varicella
vaccination program in the U.S. has led to declines of greater than 95% in varicella-related illnesses, hospitalizations and deaths in populations that received routine vaccination. However, of 24,488 varicella-related hospitalizations in the U.S. during the years 2000 to 2006, a total of 17,142 (70%) were among healthy persons with no contraindications for vaccination. Among 112 varicella-related deaths during 2002 to 2007, a total of 100 (89%) were among persons with no high-risk preexisting conditions, such as cancer, immunodeficiency, or pregnancy.

**Laboratory Tests**

Laboratory testing has become more necessary since the introduction of the vaccine, as the incidence of varicella disease has declined. Breakthrough infections can be atypical in appearance, with fewer lesions and no characteristic vesicles. Diagnostic tests used to confirm recent varicella infection include serologic tests and viral identification, culture and typing/strain identification. DNA detection methods for virus identification are the preferred diagnostic tests to confirm varicella infection.

Skin lesions are the preferred specimen for laboratory confirmation. Specimens should be collected by unroofing a fresh fluid-filled vesicle, then rubbing the base of the skin lesion with a polyester swab. Scabs from skin lesions are also useful, especially for PCR detection of DNA. Collecting specimen from lesions of breakthrough cases may be challenging because these rashes are often maculopapular, with few vesicles. Other specimen sources, including nasopharyngeal secretions, blood, saliva, bronchial washings, and cerebrospinal fluid are not as likely to produce positive results. Blood can be used to test for varicella immunity.

**Rapid VZV identification**

The preferred method of rapid clinical diagnosis is VZV identification by PCR. It is sensitive, specific, and widely available. Results can be obtained within hours. It allows for the rapid amplification of specific sequences of viral DNA. The direct fluorescent antibody (DFA) test may be used if PCR is not available. This test is also specific and rapid, but not as sensitive as PCR. It also requires meticulous collection and handling of the specimen. A vesicle should be unroofed and scrubbed vigorously enough to collect cellular matter at the base. Serum antibodies in blood can generate false-negative results, so extreme caution must be taken to avoid contaminating the lesion sample with blood. Crusts may not be used for this test. Because infected-cell viral proteins persist after cessation of viral replication, immunologic assays to detect infected cells or viral antigen (DFA) may be positive when viral cultures are negative.

**Viral culture**

The diagnosis of VZV infection may be confirmed by isolation of VZV. Newer, more sensitive and rapid culture techniques using the shell vial method may provide results within two to three days. They are not as sensitive as PCR, however. The best results are obtained from vesicular fluid, with lower yield from other sites (e.g., nasopharyngeal secretions, blood, urine, bronchial washings, cerebrospinal fluid). Infectious VZV is usually recoverable from varicella lesions for two to three days and from zoster lesions for seven days or longer. In immunocompromised patients, it may also be cultured from blood or cerebrospinal fluid. It cannot be recovered from crusted lesions.

**Viral strain identification**

The purpose of strain identification is to distinguish wild VZ virus from the vaccine (Oka/Merck) strain. This can be done by strain differential real-time PCR or PCR combined with restriction fragment length polymorphism analysis. It is most often used in situations such as: 1) rash with greater than 50 lesions; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster; or 4) any serious adverse event. Merck and Co., Inc., offers a free viral identification service. Details of this service and the proto-
col for specimen collection for VZV PCR analysis can be obtained by calling Merck and Co., Inc., at 1-800-672-6372.

Serologic testing

Serological tests are available for IgG and IgM antibodies to VZV. Testing for IgM antibody is not indicated since available methods lack sensitivity and specificity. Experience with IgM antibody tests is extremely limited for both vaccinated and unvaccinated persons. False negatives can occur, and therefore these tests should not be used to rule out diagnosis. False positive IgM results are common in the presence of high IgG levels. Single serological IgG tests may be used to identify the immune status of individuals whose history of varicella is negative or uncertain, and who may be candidates for VZIG or vaccination. Paired acute and convalescent antibody tests are used in situations of mild, unusual presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important.

A variety of methods have been used to detect IgG antibody to varicella zoster virus, both wild and vaccine strains. None of the tests listed below are as sensitive as the glycoprotein (gp) ELISA test used in pre-licensure clinical trials to study immune response post-vaccination; however, this test is not commercially available. Currently available tests may not be sensitive enough to detect low levels of antibody post vaccination; however, the following tests may be useful:

- Enzyme-linked immunosorbent assays (ELISA). The ELISA tests are widely used for screening of varicella immune status, especially when large numbers of specimens are tested. The ELISA tests range in sensitivity from 86% to 97% and range in specificity from 82% to 99% for detecting antibody after natural infection. Commercial ELISA are highly specific but less sensitive than the fluorescent antibody to membrane antigen test (FAMA) with the result that 10% to 15% of individuals who are immune may be identified as susceptible.

- Latex agglutination (LA). The LA test is useful for screening for varicella immunity. LA is rapid, simple-to-perform (15 minutes) assay to detect antibodies to VZV; dilutions of sera are added to latex particles coated with VZV glycoprotein antigen. It requires no specialized equipment, is as sensitive as the FAMA and is more sensitive that the enzyme-linked immunosorbent assay (ELISA). It is however, less sensitive than FAMA in detecting antibody response following vaccination. False-positive results may occur, which could mistakenly categorize a susceptible person as immune.

- Fluorescent antibody to membrane antigen (FAMA) test. The FAMA test is highly sensitive and is the "gold standard" for screening for immune status for VZV, but is not widely available. In convalescent-phase serum specimens, up to 100% are positive by FAMA and 96% by LA. After vaccination of persons who were previously VZV antibody negative, 77% are positive by FAMA, 61% by LA and 47% by ELISA.

Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

Treatment

Children with varicella should not be given aspirin because administration of salicylates to children with varicella increases the risk of Reye syndrome.

Surveillance

Varicella is a condition reportable within five business days of diagnosis.

Surveillance is needed to:
1) document and monitor the vaccination impact on disease incidence, morbidity and mortality
2) evaluate the effectiveness of prevention strategies
3) evaluate vaccine efficacy under conditions of routine use.

Surveillance data are also useful for evaluating vaccine effectiveness under conditions of routine use. Clinical trials indicate vaccine efficacy of 70% to 90% for all disease and greater than 95% for severe disease; however, field efficacy may be lower due to improper storage and handling of vaccine at any stage of the cold chain from the manufacturer to the end user (e.g., the clinic or physician's office). Because mild "breakthrough" varicella may be expected to occur in 10% to 20% of vaccinated children, it is important to evaluate whether varicella among vaccinated children, mild or severe, is occurring at a rate higher than expected.

**Case Definition**

**Clinical case definition:** An illness with acute onset of diffuse (generalized) papulovesicular rash without other apparent cause.

**Laboratory criteria for diagnosis**

- Isolation of varicella-zoster virus or demonstration of VZV DNA by direct fluorescent antibody (DFA) or polymerase chain reaction (PCR) tests from a clinical specimen, ideally scabs, vesicular fluid, or cells from the base of a lesion. These tests are useful in diagnosing breakthrough disease.

- Significant rise in serum varicella immunoglobulin G (IgG) antibody levels by any standard serological assay, or positive serologic test for varicella-zoster IgM antibody using a capture assay, are sometimes used but are not very reliable to confirm diagnosis.

**Case classification:**

- **Probable.** A case that meets the clinical case definition, is not laboratory-confirmed, and is not epidemiologically linked to another probable or confirmed case.
- **Confirmed.** A case that is laboratory-confirmed, or that meets the clinical case definition, and is epidemiologically linked to a confirmed or probable case.

Comment: Two probable cases that are epidemiologically linked would be considered confirmed cases, even in the absence of laboratory confirmation. However, in an outbreak, it is recommended that at least three to five cases be laboratory-confirmed.

**Vaccine rash.** A varicella rash in a child recently vaccinated for varicella is defined as a vaccine rash. Approximately 4% of children receiving varicella vaccination develop a generalized rash, with a median of five lesions, five to 26 days post-vaccination; 4% develop a localized rash, with a median of two lesions, eight to 19 days post-vaccination. The rash may be atypical in appearance (maculo-papular with no vesicles).

**Breakthrough disease.** Breakthrough disease is defined as a case of wild-type varicella infection occurring more than 42 days post-vaccination in a person who has a documented history of varicella vaccination. Such disease is almost always mild with shorter duration of illness and fewer than 50 skin lesions.

**Secondary transmission.** Secondary transmission is defined as a case of varicella occurring between one to three incubation periods (10 to 63 days) after exposure to either wild or vaccine virus. However, one case of vaccine rash that occurred five days post-vaccination has been reported; thus secondary transmission from the vaccine virus may also be possible as early as five days post exposure.
Investigation

Rapid case identification and prompt reporting is not warranted routinely for suspected cases of varicella. However, in certain high-risk settings (e.g., hospitals and other health care settings), rapid case identification and public health action are important to prevent infection of susceptible persons at high risk for serious complications of varicella, such as immunocompromised persons and pregnant women.

Because no public health interventions are routinely undertaken in response to varicella, case investigation of individual cases is generally not recommended. However, investigation is warranted under some circumstances including: for all varicella related deaths; as part of an outbreak investigation; potentially susceptible persons at high risk of serious complications of varicella are exposed; or severe complications such as invasive group A streptococcal infections are documented. Because of the stringent cold-chain requirements of this vaccine, an investigation should be considered when an outbreak occurs in a vaccinated population.

Information to collect

For routine surveillance of varicella, only aggregate case counts by age group are collected in most areas. For information on reporting requirements in your state, contact the state health department.

In special circumstances, collection of additional information on individual cases is warranted. Such circumstances include outbreak investigations or exposure of potentially susceptible persons at high risk of serious complications of varicella such as might occur in a hospital setting. Epidemiologically important information in these circumstances includes previous history of varicella, history of varicella vaccination, and underlying medical conditions. For more information or for assistance with case investigation, contact the state health department.

Outbreak investigation

Investigation of unusual outbreaks of varicella is recommended, especially those associated with death, severe disease and/or a high rate of complications, or those involving infants younger than one year of age, older children or adults. The investigation of outbreaks provides an opportunity to study vaccine effectiveness in the field and to more accurately describe morbidity from this disease that is now vaccine-preventable. If vaccine effectiveness is found to be lower than expected, vaccine storage and handling practices should be reviewed.

Outbreak control

Because varicella vaccine has not been available for a long period of time and coverage is not yet high, outbreaks of varicella are frequent and undertaking aggressive public health action for all outbreaks is not feasible. Priority should be given to outbreaks in which disease is severe or associated with complications, such as invasive group A streptococcal infection. In such outbreaks, vaccination of susceptible children one year of age and older, adolescents and adults should be carried out to prevent additional cases of severe varicella.

Even if aggressive outbreak control using varicella immunization clinics is not feasible, efforts should be made to inform the affected population (e.g., students and staff at the child care center or school) that varicella is a potentially serious and even life-threatening disease which may be prevented by vaccination. Written materials on varicella and varicella vaccine should be provided recommending that susceptible persons (or their parents/care givers) contact their health care provider to receive the varicella vaccine. For guidance on outbreak control, contact the state health department.

Exclusion

Exclusion of individuals with varicella until all of their lesions have crusted is routinely recommended for outbreak control. Because substantial transmission of chickenpox occurs before rash onset, exclusion
probably has limited value as an outbreak control measure.

Exclusion is also recommended for exposed susceptible individuals who may be in contact with persons at high risk of serious complications (e.g. health care workers and family members of immunocompromised persons). Exclusion is required for the duration of the period of communicability (i.e. from the 10th until the 21st day post-exposure).

Vaccine for control

Several studies indicate that varicella vaccine given within three (3) to five (5) days of exposure is effective in preventing secondary cases of varicella among susceptible contacts in the household or hospital setting. The efficacy of post exposure vaccination in controlling outbreaks in larger closed settings such as child care centers and schools, where the potential exists for multiple sources of exposure, is now undergoing study; although the effectiveness of vaccination in outbreak control is not yet established, persons who have been exposed but not yet infected will be protected when subsequently exposed. For this reason, vaccination of susceptible persons should be recommended in these settings.

Varicella vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) in order to prevent outbreaks among patients and staff in health care settings. These outbreaks pose a special problem because varicella may be transmitted between patients and staff. For this reason, many health care institutions have existing employee screening programs to determine if employees have had varicella in the past. If employees do not have a history of varicella based on serologic testing, many hospitals will provide varicella vaccine.

Workers with active varicella or susceptible workers with a history of exposure to a patient or staff with active varicella should be relieved from direct patient contact. This exclusion should take place from the 10th day after the first exposure through the 21st day after last exposure. Staff with zoster should cover lesions and should not care for high-risk patients until their skin lesions have become dry and crusted.

Health care workers who are susceptible to varicella and exposed to an individual with active zoster should be relieved from direct patient contact for the same duration as workers exposed to persons with varicella.

Newborns

Newborn with maternal rash onset five 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 the age of ten days, they should be kept in strict isolation for the entire incubation period (until day 28 or longer).

Immunization

Although vaccine use is expected to result in an overall reduction in the burden of varicella disease, universal vaccination of infants in the absence of catch-up vaccination of older susceptible children and adults may shift peak disease incidence to adolescents and adults among whom the disease is more severe. Surveillance data may be used to characterize groups or areas at highest risk of disease so that additional intervention efforts can be focused to more effectively reduce the burden of disease.

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 a healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988 and licensed in the U.S. 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, 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.

**Immunogenicity And Vaccine Efficacy**

After one dose of vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titers. Over 90% of vaccine responders maintain antibodies for at least six years. In Japanese studies, 97% of children had antibodies seven to ten years after vaccination. Vaccine efficacy is estimated to be 80% to 90% against infection and 85% to 95% against moderate or severe disease. Among healthy adolescents and adults, an average of 78% develop antibodies after one dose and 99% develop antibodies after a second dose given four to eight weeks later. Antibodies have persisted for at least over a year in 97% of vaccinees after the second dose was given four to eight weeks after the first dose. Studies on the persistence of antibodies and clinical efficacy in both children and adults are ongoing.

Immunity appears to be long lasting and is probably permanent in the majority of vaccinees. However, approximately 1% of vaccinees per year have developed breakthrough infections (i.e., developed varicella disease even though they had responded to the vaccine). 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 the 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 also identified the presence of asthma and/or use of steroids and earlier age (i.e., <15 months) as a risk factor for breakthrough varicella. However, because of the inconsistency of these data, ACIP has not changed the recommendations for use of varicella vaccine.

Breakthrough varicella infection could be a result of several factors, including interference of vaccine virus replication by circulating antibodies, impotent vaccine due to 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 varicella compared with those who received varicella vaccine before, simultaneous 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.

**Vaccination Schedule And Use: Varicella virus vaccine is recommended for all children without contraindications at 12 to 18 months of age.** The vaccine may be given to all children at this age regardless of prior history of chickenpox. Varicella vaccine is also recommended for all susceptible children 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 assure 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. 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 measles-mumps-rubella (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) as all other childhood vaccines. The ACIP strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 to 18 months of age.
Children with a reliable history of chickenpox can be assumed to be immune to varicella. A parental history is acceptable and physician documentation is not necessary. Children without a reliable history or with an uncertain history of chickenpox should be considered susceptible. 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 susceptible. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella vaccine should be administered to all susceptible adolescents and adults. 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 four to eight weeks. If there is a lapse of more than eight weeks after the first dose, the second dose may be administered at any time without repeating the first dose.

Adolescents and adults with reliable parental or personal histories of chickenpox can be assumed to be immune. Those without a reliable history can be considered to be susceptible, or may be tested to determine varicella immunity. Epidemiologic and serologic studies indicate that up to 90% of adults are immune to varicella, including those who do not recall having had chickenpox. As a result, serologic testing prior to vaccination is likely to be cost effective for adults. As with children, a prior history of chickenpox is not a contraindication to varicella vaccination.

Assessment of varicella immunity of all adolescents and adults and vaccination of those who are susceptible, is 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.

Varicella vaccination should be considered for susceptible adolescents and adults who are at high risk of exposure to varicella. This group includes: persons who live or work in environments in which there is a high likelihood of transmission of varicella, such as teachers of young children, daycare workers and residents and staff in institutional settings; persons who live or work in environments in which varicella transmission may occur (e.g. college students, inmates and staff of correctional institutions and military personnel); non-pregnant women of childbearing age, in order to reduce the risk of VZV transmission to the fetus if the susceptible woman should develop varicella during pregnancy; international travelers.

Varicella vaccination is also recommended for susceptible adolescents and adults who will have close contact with persons at high risk for serious complications of acquired varicella. This group would include healthcare workers and susceptible family contacts of immunocompromised individuals.

The ACIP recommends that all healthcare workers be immune to varicella, either from a reliable history of varicella disease or 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. Seroconversion may not always result in full protection against disease. If a vaccinated healthcare worker is exposed to varicella, the exposed person should be tested for varicella antibody as soon as possible following the exposure. Persons with detectable antibody are unlikely to develop varicella. Persons without antibody can be retested five to six days later to determine if an anamnestic response is present (i.e., antibodies appear quickly after exposure). If antibodies are present less than seven days after exposure it is unlikely that the exposed person will develop disease. Persons who remain susceptible (i.e., antibody negative) seven days following exposure should be furloughed, or monitored very closely and then furloughed at the onset of symptoms suggestive of varicella. The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact appears to be very low 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 susceptible immunosuppressed persons).

**Evidence of Immunity to Varicella:** Evidence of immunity to varicella includes any of the following:

**Documentation of age-appropriate vaccination with a varicella vaccine:**

- Preschool-aged children (i.e., aged >12 months): one dose
- School-aged children, adolescents and adults: two doses
- Laboratory evidence of immunity or laboratory confirmation of disease
- Birth in the United States before 1980
- Diagnosis or verification of a history of varicella disease by a health-care provider
- Diagnosis or verification of a history of herpes zoster by a health-care provider.
- For children who received their first dose at age younger than 13 years and for whom the interval between the two doses was greater than 28 days, the second dose is considered valid.
- For health-care personnel, pregnant women and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.
- Verification of history or diagnosis of typical disease can be provided by any health-care provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or their designee is recommended and one of the following should be sought: 1) an epidemiologic link to atypical varicella case or to a laboratory-confirmed case or 2) 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 might mimic mild atypical varicella.

**Post-exposure 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 three days, and possibly up to five days, of exposure. The ACIP recommends the vaccine for use in susceptible persons following exposure to varicella. If exposure to varicella does not cause infection, post-exposure 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, pre-exposure vaccination of all susceptible healthcare workers 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 six months. Varicella vaccine has been used successfully to control these outbreaks. Varicella vaccine should be used for outbreak control by advising exposed susceptible persons to contact their healthcare providers for vaccination.

**Adverse Reactions Following Vaccination**

The most common adverse reactions following varicella vaccine are injection site complaints 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 3% of children and by 1% of adolescents and adults following the second dose. In both circumstances, there has been a median of two lesions.

These lesions generally occur within two weeks, and are most commonly maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4% to 6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with a median of five lesions. Most of these generalized rashes occur within three 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 has been mild and has not been associated with complications, including post-herpetic neuralgia.

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.

Persons with immunosuppression due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low dose (<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 stopped for one month (three months for chemotherapy) may be vaccinated. Varicella vaccine is available from the manufacturer through a research protocol for special use in certain patients with acute lymphoblastic leukemia in remission.

Varicella vaccine should not be administered to persons with cellular immunodeficiency. However, in 1999, the 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 immune deficiency syndrome (AIDS), should not receive varicella vaccine. However, vaccination should be considered for children with asymptomatic or mildly symptomatic HIV infection (Centers for Disease Control and Prevention [CDC] class N1 or A1, age-specific CD4+ T-lymphocyte percentage greater than 25%). These children should receive two doses of varicella vaccine with a three-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 post-vaccination varicella-like rash.

Women known to be pregnant or attempting to become pregnant should not receive varicella vaccine. The effects of varicella vaccine on a developing fetus are unknown. Since infection with wild varicella virus poses only a small risk to the fetus and the vaccine virus is attenuated, the risk to the fetus, if any, should be even lower. Although the manufacturer’s package insert states otherwise, the ACIP and the American Academy of Pediatrics (AAP) recommend that pregnancy be avoided for one month following receipt of varicella vaccine.

The manufacturer, in collaboration with the 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 illnesses, 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, intravenous immune globulin, 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 three to 11 months after antibody-containing blood products. The ACIP recommends applying the same intervals used to separate antibody-containing products and MMR to varicella vaccine.

Immune globulin or VZIG should not be given for three weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, the vaccinees should either be revaccinated or tested for immunity greater than three 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 should avoid the use of salicylates for six 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 the secondary clinical illness has 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 susceptible persons 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 within the last five to ten years, are designed to maintain temperatures as low as -4°F (-20°C), and are acceptable for storage of the 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, 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 storing the vaccine, 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 assure that the appropriate storage temperature is maintained. The vaccine may be kept at refrigerator
temperature for up to 72 hours, but must then be discarded if not used. The vaccine should not be refrozen.

Varicella Zoster Immune Globulin (VZIG)
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 is susceptible 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 to $500 for the maximum dose in an adult), and provides only temporary protection.

VZIG is indicated for use in susceptible individuals at high risk for complications who have had a significant exposure (continuous household contact; playmate contact of more than an hour; hospital contact in the same two to four bedroom area; prolonged direct contact), to a person with varicella. It is most commonly used for postexposure prophylaxis of immunocompromised children (immune deficiencies, neoplastic disease, or on immunosuppressive therapy), and newborns of mothers with varicella onset five 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 less than 1,000 gram birth weight (who may not have received adequate maternal antibodies 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 individuals are susceptible. 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 ten 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 post-exposure.

Antiviral Therapy
Several antiviral drugs are active against varicella zoster virus, including acyclovir, valacyclovir, famciclovir and foscarnet. Famciclovir and valacyclovir 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, resulting 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. The ACIP has not made recommendations regarding the use of antiviral therapy for varicella. The AAP does not recommend routine antiviral therapy for otherwise healthy infants or children with varicella. Oral acyclovir can be considered in otherwise healthy adolescents and adults or 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 disorder, persons receiving long-term salicylate therapy and for 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 post-exposure prophylaxis. Oral acyclovir is not routine-ly 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.

**Hospital precaution and isolation:** Airborne precautions.

Sample Exclusion from School letter follows:
To: Parent/Guardian of Select Students at ____________________________

From: ____________________________________________

**Re: Exclusion of Students from Attendance at School**

Dear Parent,

I am writing this letter to inform you that one or more students at ______________ have been diagnosed with Chickenpox. Chickenpox, as you may know, is caused by the Varicella Zoster Virus. It is a highly contagious illness that can be spread easily through coughs, sneezes, or through direct contact with secretions from the rash of affected individuals.

For the protection of your child and to prevent further transmission of this illness in the school, the Louisiana Office of Public Health requires that children who are unvaccinated or who do not meet the sufficient criteria for vaccination against the Varicella Zoster Virus to be excluded from school for at least 21 days following the identification of the last case in school. As of the last identified case to date, the earliest return date to school for those who do not obtain the varicella vaccines as recommended shall be ____________________________.

Students may be allowed to return to school before this date if immediate vaccination is received. This is based on the fact that it takes on average 10 to 21 days for an individual to develop chickenpox symptoms after being exposed. Thus, if a child is vaccinated before the tenth day of exposure and before they show any signs or symptoms of the disease, they may be considered immune for our purposes. Accordingly, students obtaining the required Varicella vaccination and showing proof of such immunization by or before ____________________________ may immediately return to school.

We realize that this may pose an inconvenience for you and your child, but in the interest of protecting the health of other students and our community, I am requesting your full cooperation with these measures. If you have any questions, you may contact ____________________________

Thank you,

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