Recommendations for the Use of Live Attenuated Varicella Vaccine

Committee on Infectious Diseases

Live attenuated varicella vaccine was licensed by the Food and Drug Administration on March 17, 1995, for use in individuals 12 months of age or older who have not had varicella. The American Academy of Pediatrics provides the following recommendations for varicella vaccine use in pediatric practice.

**VARICELLA AND ZOSTER**

Varicella-zoster virus (VZV) is the cause of two diseases, varicella (chickenpox), which is a primary infection, and zoster (shingles), a secondary infection caused by reactivation of latent VZV.

In the United States, varicella is typically an illness of children under the age of 10 years; 5% to 10% of adults remain susceptible. Varicella is a systemic infection that stimulates development of antibodies and cell-mediated immunity (CMI); second episodes in healthy persons are unusual. Varicella in otherwise healthy children is usually a self-limited disease characterized by fever, malaise, and a generalized vesicular pruritic rash of approximately 250 to 500 vesicles that usually lasts about 5 days.

Varicella is a characteristic disease that is easily recognized. A history of varicella infection is associated with positive serologic findings for VZV antibodies in >95% of individuals. Serologic tests include enzyme immunoassay (EIA), latex agglutination (LA), indirect fluorescent antibody, and fluorescent antibody membrane antigen assays. These tests are reliable in determining immune status in healthy persons but may not be as reliable in determining the immune status of immunocompromised persons in whom a positive but low titer may not correlate with protection. The complement fixation test is not sensitive enough to be reliable in determining susceptibility in any child. In children and adults with a history of varicella, antibody testing generally is not necessary to establish immune status. Those under the age of 18 years without a history of varicella are probably susceptible to infection. In persons over 18 years of age, even with no history or an unknown history of varicella infection, >70% have been infected, resulting in positive serologic findings. Therefore, in these older individuals, determination of immune status before considering VZV immunization may be cost-effective.

During varicella the VZV gains access to sensory nerve ganglia, where it establishes a latent infection. It is estimated that VZV causes no further disease in 85% of the affected population. The remaining 15% of the US population experiences clinical reactivation of latent VZV, with the rate increasing with advancing age. Zoster is characterized by a unilateral vesicular rash generally limited to one to three dermatomes and in adults is often accompanied by pain. Factors influencing the development of zoster are not fully understood, but most important is low VZV-specific CMI. This factor may account for the more frequent occurrence of zoster in children who contracted varicella in utero or early in life, in immunocompromised persons, and in the elderly.

VZV is transmitted person-to-person through direct contact with skin lesions and by airborne respiratory droplet infection. Skin vesicles in varicella and zoster contain high titers of infectious virus, and patients with zoster can transmit varicella to susceptible contacts. Varicella is one of the most contagious diseases, resembling pertussis and measles. Within households, 80% to 90% of exposed susceptible contacts will develop varicella.

About 3.9 million cases of varicella are estimated to occur annually in the United States. Most cases that occur in otherwise healthy children are self-limited and free of complications. Complications of varicella are unusual and include bacterial superinfection of the skin, lungs, and bones; Reye syndrome (often in association with salicylate administration); pneumonitis, encephalitis (cerebellar ataxia and a cerebral form); glomerulonephritis; and arthritis. Infrequent complications of this common disease result in significant morbidity. About 90 fatal cases are reported annually to the Centers for Disease Control and Prevention, mostly in otherwise healthy persons <20 years of age. Much of the morbidity and mortality caused by varicella, however, is not reported.

In addition to medical complications, varicella has economic and social costs. In a study published in 1985, the annual health care costs including home care for chickenpox were $399 million. At that time, the estimated reduction in cost by a vaccine program was 50%. A cost-benefit analysis published in 1994 has indicated that routine use of varicella vaccine at 1 year of age would result in a savings of $384 million per year in the United States. This cost savings estimate includes the price of the vaccine as well as the savings in potential hospitalization costs and parental time lost from work. The majority of savings are in the latter category. In the average household, a child with varicella loses 8.7 days of...
school and adult caretakers lose 0.5 to 1.8 days of work outside the home.\textsuperscript{12,13}

Varicella is potentially severe in adults and in specific groups of children—children with cancer who are receiving chemotherapy and/or radiotherapy, children receiving high doses of systemic corticosteroids (2 mg/kg/d or more of prednisone, or its equivalent) for any reason (including asthma), children with human immunodeficiency virus (HIV) infection, and children with congenital immunodeficiency. Although rare, a congenital varicella syndrome occurs in about 2% of infants born to women who contract varicella in the first or second trimester of pregnancy. Congenital varicella syndrome is associated with profound abnormalities of the skin, limbs, eyes, and central nervous system.\textsuperscript{14} Although current recommendations for VZV immunization do not include most of these high-risk groups, many of these individuals would be vaccinated before entering a high-risk group later in life and may be protected from natural varicella infection.

With the recent influx of young adults from tropical countries into the United States, the incidence of varicella-susceptible adults appears to be increasing.\textsuperscript{15,16} It appears that the heat-sensitive varicella virus does not spread as successfully among children in tropical countries, resulting in a large number of immigrant adults from these areas who are susceptible.

**DEVELOPMENT AND STABILITY OF VARICELLA VACCINE**

A live attenuated varicella vaccine was developed in Japan in the 1970s.\textsuperscript{17} A similar vaccine is produced and marketed in the United States by Merck and Company Inc (West Point, PA). The vaccine is a cell-free preparation of OKA strain VZV. The original virus was obtained from an otherwise healthy Japanese boy with natural varicella and was propagated in human embryonic lung fibroblasts, guinea pig embryonic cells, and finally in two different cell strains of human diploid cell cultures (WI-38 and MRC-5). A varicella vaccine is licensed for routine use in Japan and Korea, where over 2 million doses have been given. It is also licensed in several European nations for use in immunocompromised children. It has been tested in the United States in clinical trials in which >9000 children and 1600 adults have been enrolled.\textsuperscript{18}

The recommended dose of the vaccine, 0.5 mL, contains not <1500 plaque-forming units of VZV, as well as trace amounts of neomycin. This lyophilized preparation must be stored frozen. Storage in a freezer with a temperature of −15°C (+5°F) or colder is required and results in a storage life of up to 18 months. Once the vaccine has been reconstituted, it should be used immediately to maintain viral potency. If it is not used within 30 minutes of reconstitution it must be discarded. The vaccine is licensed for subcutaneous injection, and although intramuscular administration results in similar seroconversion rates,\textsuperscript{19} the intramuscular route is not routinely recommended.

**Immunogenicity**

In healthy children 12 months to 12 years of age, using a sensitive glycoprotein EIA, a single dose of vaccine results in a seroconversion rate of >95%.\textsuperscript{20} Preexisting (presumably transplacental) antibody, if present at 12 months, does not appear to interfere with antibody response. As with other viral vaccines, the antibody response after vaccination is lower than that seen after natural disease.

A study of immunized adults has indicated age-related decreases in the ability of the immune system to mount and maintain a primary response to VZV.\textsuperscript{21} Seroconversion rates of 79% to 82% after one dose and 94% after two doses have been reported in adolescents older than 12 years and in adults.\textsuperscript{20,21} The cause of this diminished response is not known, but susceptible adults and children older than 12 years should receive two doses of vaccine. In ongoing studies in Japan and the United States at a time in which wild VZV continues to circulate, antibodies to VZV were detected for as long as 10 years after immunization in >95% of those immunized.\textsuperscript{22,23}

**Efficacy**

Children. In a double-blind, placebo-controlled trial of children 1 to 14 years of age, using a high titer experimental vaccine, the efficacy was 100% in the first year after vaccination.\textsuperscript{24} According to unpublished data from the manufacturer, the protection against any disease in vaccinees after household exposure was approximately 70%, but was >95% against more severe disease. Most importantly, all studies demonstrate high rates of protection against severe disease. Varicella in vaccinees has been much milder than that occurring in unvaccinated children, with fewer skin lesions (median of 15 to 32), lower rate of fever (10% of cases with temperatures ≥102°F), and more rapid recovery.\textsuperscript{22,25} At times, the disease is so mild that it is not easily recognizable as varicella because the skin lesions may resemble insect bites. Nevertheless, vaccinated children with mild disease may be potentially infectious to susceptible persons.

The rate of varicella after immunization during 8 years of study has averaged from <1% to 3% per year after exposure to wild virus compared with an annual varicella rate of 7% to 8% in unvaccinated children and has not increased with time after immunization.\textsuperscript{23,25} Waning immunity in this age group, thus, has not been demonstrated at a time when wild VZV continues to circulate.

Adults. Approximately 70% of adults whose antibodies initially seroconverted after immunization are completely protected against varicella after household exposure. The remaining 30% of these adults most often develop attenuated disease after close exposure and have <100 skin lesions, many of which are not vesicular, and with little or no systemic toxicity.\textsuperscript{21}

**Adverse Events**

Adverse events after vaccination are minimal. Within 1 month of immunization, about 7% of chil-
Children and 8% of susceptible adolescents and adults develop a mild vaccine-associated maculopapular or varicelliform rash, with a median of two to five lesions,20,21 which may occur at the vaccine injection site or elsewhere. Vaccine virus very rarely has been recovered from these skin lesions. Approximately 20% of children and 25% to 35% of adolescents and adults who have been vaccinated complain of transient pain, tenderness, or redness at the injection site after each dose of vaccine. Although a temperature above 102°F has been observed from 1 to 42 days after immunization in 15% of healthy vaccinated children, fever also occurs in a similar percentage of children receiving placebo and thus is not considered to be a significant adverse event of immunization.20 A temperature above 100°F has been reported in 10% of adolescents and adults who are immunized with the vaccine. Other unusual side effects, reported in <1% of healthy vaccinees, include upper respiratory tract symptoms, headache, and fatigue. Immunization of 985 individuals immune to varicella from natural disease or vaccine has not resulted in a significant increase in adverse effects compared with nonimmune individuals (C.J. White, written communication, October 1993, Merck data).

The spread of vaccine virus from healthy vaccinees to other persons is theoretically possible because virus has been recovered from vaccine recipients with skin lesions. No clinical cases of varicella from contact with healthy vaccinees have been reported, but in one study 3 of 446 contacts of vaccinees seroconverted.24 The spread of vaccine virus to others from vaccinees with leukemia who had a vaccine-associated rash has been observed.25 Contact cases have been subclinical or have developed extremely mild illness, indicating that the vaccine virus remains attenuated when transmitted.

A zoster-like illness, marked by rash and minimal or absent systemic symptoms, has been reported in 8 of 9000 healthy children who were immunized with varicella vaccine.18 No case was severe. This incidence was no higher than that which occurs after natural varicella. Zoster is unusual in childhood, and is estimated to occur with a frequency of 77 cases per 100 000 person-years.27 To date, the frequency in vaccinated children after 7 years of follow-up is 18 cases per 100 000 person-years. Moreover, in children with leukemia, zoster is less common after vaccination than after natural varicella.828 In the United States, >1500 adults have been immunized in clinical trials, with 11 to 13 years of follow-up, and the only case of zoster was caused by wild virus.29

Possible Risks

The long-term changes in VZV epidemiology that may result from widespread use of varicella vaccine are not fully known. The incidence of zoster may be decreased when immunized children reach middle age because the attenuated vaccine virus may result in fewer latent infections in comparison with natural infection. Although the incidence of zoster is unlikely to be increased following immunization of healthy children, long-term follow-up of vaccinees is necessary to determine the true incidence.

Long-term immunity to varicella may wane after vaccination, but no evidence of loss of immunity has been noted in 6 to 10 years of follow-up in healthy children immunized at a time when wild VZV continues to circulate. As a result of widespread but not universal use of vaccine, an increased rate of clinical cases of varicella could occur in adults who were not vaccinated as children. This theoretical risk is inherent in the use of any live virus vaccine. If waning immunity is identified in postlicensure studies, booster doses of vaccine may be required.

The importance of immunologic boosting due to exogenous reexposure to VZV in maintaining long-term immunity to varicella is not known. Because some cases of zoster as well as mild varicella will continue to occur in vaccinees, opportunities for immunologic boosting will likely continue, although at a markedly decreased frequency. The extent to which these exposures and possible transmission of VZV contribute to immunity in large population groups will need to be studied.

RECOMMENDATIONS FOR VACCINE USE

Vaccine for universal use in early childhood and immunization in susceptible older children and adolescents is recommended based on the frequency of serious complications and deaths after infection with mild varicella, the excess cost to the family and society incurred by varicella infection, and the efficacy and safety of the live attenuated varicella vaccine.

Indications

1. Age 12 months to the 13th birthday
   a. Age 12 to 18 months. One dose of varicella vaccine is recommended for universal immunization for all healthy children who lack a reliable history of varicella.
   b. Age 18 months to the 13th birthday. One dose of varicella vaccine is recommended for immunization of all children from age 18 months to the 13th birthday who have not been immunized previously and who lack a reliable history of varicella infection. Vaccination may be given any time during childhood but before the 13th birthday because after this age natural varicella is more severe, complications are more frequent, and two doses of vaccine are needed.
   c. Simultaneous administration of other vaccines. Varicella vaccine may be given simultaneously with measles-mumps-rubella (MMR) vaccine, but separate syringes and injection sites must be used.30 If not given simultaneously, the interval between administration of varicella vaccine and MMR should be at least 1 month. Although further immunogenicity studies are needed on the use of varicella vaccine administered simultaneously with diphtheria, tetanus, pertussis (DTP) vaccine, live or inactivated polio virus vaccine, hepatitis B vaccine, and Haemophilus influenzae type b vaccines, no reason exists to suspect that varicella vaccine will affect the immune response to these vaccines. When necessary, varicella vaccine may be given simulta-
neously or at any interval after or before these vaccines.

2. Healthy adolescents and young adults. Healthy adolescents past their 13th birthday who have not been immunized previously and have no history of varicella infection should be immunized against varicella by administration of two doses of vaccine 4 to 8 weeks apart. Longer intervals between doses do not necessitate a third dose, but may leave the individual unprotected for the intervening months.

Performing serologic tests, using a sensitive assay such as LA or EIA, before vaccination in healthy individuals older than 18 years who have no history of varicella is optional. If the initial test is positive, the vaccine does not need to be given. In some individuals immunized with VZV vaccine, such as health care workers or others exposed to immunocompromised individuals, postexposure testing to document seropositive status will help in management of personal placement in high-risk areas after varicella exposure or outbreaks.

3. Adults. Recommendations regarding varicella vaccine use in adults is beyond the scope of this statement. This issue has been addressed by the Centers for Disease Control Advisory Committee on Immunization Practices.

Contraindications and Cautions

1. Immunocompromised patients

a. General recommendation. Varicella vaccine should not be given routinely to immunocompromised individuals, such as those with congenital immunodeficiency, blood dyscrasias, leukemia, lymphoma, symptomatic HIV infection, and malignancy for which they are receiving immunosuppressive therapy. The exceptions include children with acute lymphocytic leukemia under study conditions (see below). Asymptomatic HIV infection also is a contraindication for immunization, but since the risk in these persons is currently only theoretical, routine screening for HIV is not indicated. Immunodeficiency should be excluded before immunization in children with a family history of hereditary immunodeficiency. The presence of an immunodeficient or HIV-seropositive family member does not contraindicate vaccine use in other family members.

b. Households with potential immunocompromised contacts. Transmission of vaccine-type VZV from healthy individuals has been infrequently if at all documented. Thus, even in families with immunocompromised individuals, including those with HIV infection, no precautions need to be taken after vaccination of healthy children who do not develop a rash. Vaccinees who develop a rash should avoid contact with immunocompromised susceptible hosts for the duration of the rash. If contact inadvertently occurs, the use of varicella zoster immune globulin is not recommended currently because transmission is rare and disease, if it develops, is mild.

c. Children receiving steroids. The potential risks of vaccination with the attenuated virus must always be weighed against the potential risks of becoming infected with wild type VZV infection, which has an increased risk of severe disease.

Varicella vaccine should not be administered to individuals who are receiving high doses of systemic corticosteroids (2 mg/kg/d or more of prednisone, or its equivalent or 20 mg/d of prednisone if their weight is >10 kg) for >1 month. After steroid use at this dosage has been discontinued for 3 months, according to generic recommendations for the use of live-virus vaccines, a child may be immunized. Most experts agree, however, that with varicella vaccine an interval of 1 month or more after discontinuation of steroid use is probably sufficient to safely administer the vaccine.

Children with no history of varicella who are receiving systemic steroids for conditions such as nephrosis and asthma may be immunized if not otherwise immunosuppressed, assuming that they are receiving <2 mg/kg/d of prednisone or its equivalent (or <20 mg/d if their weight is >10 kg). Some experts, however, suggest discontinuing steroid use for 2 to 3 weeks after immunization if possible. In studies in Japan, children with nephrosis receiving these doses of systemic steroids were immunized safely when steroid use was also suspended for 1 to 2 weeks before immunization.32 Most experts agree that immunization of children receiving only inhaled steroid would not increase the risk of disease from varicella vaccine, although no studies in such children have been performed.

d. Acute lymphocytic leukemia (ALL). The current vaccine is not licensed for routine use in children with malignancies. Immunization should be considered when a child with ALL has been in continuous remission for at least 1 year and has a lymphocyte count over 700/μL and platelet count over 100,000/μL 24 hours before vaccination. Immunization has been shown to be safe, immunogenic, and effective in these children, and the vaccine may be obtained free for use in a research protocol. (To immunize a child with ALL, the following organization should be consulted: The Varivax Coordinating Center, Bio-Pharm Clinical Services, Inc, 4 Valley Square, Blue Bell, PA 19422; telephone, 215-283-0897). This protocol monitors and evaluates safety and requires approval by the appropriate institutional investigative review board.

2. Pregnancy and lactation. Varicella vaccine should not be administered to pregnant women, because the possible effects on fetal development are unknown. When postpubertal females are immunized, pregnancy should be avoided for 1 month after immunization. A pregnant mother or other
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3. Postexposure vaccination. No data indicate that currently formulated varicella vaccine prevents the occurrence of varicella when administered to susceptible individuals who have been exposed to varicella or zoster in the previous 21 days.

4. Allergy to neomycin. Varicella vaccine should not be administered to individuals who have had an anaphylactoid reaction to neomycin, because trace amounts of neomycin are included in the vaccine. Most individuals with allergy to neomycin have contact dermatitis, which is not a contraindication to vaccination.

5. Intercurrent illness. As with other vaccines, varicella vaccine should not be administered to individuals who have moderate or severe illnesses, because no data indicate whether such illnesses interfere with the development of immunity.

6. Immune globulin. Whether immune globulin can interfere with varicella vaccine-induced immunity is unknown, although immune globulin can interfere with immunity induced by other live viral vaccines. As with other live viral vaccines, varicella vaccine should not be administered within at least 5 months after receipt of any form of immune globulin or other blood product. Transplacental antibodies to VZV do not interfere with the immunogenicity of varicella vaccine at 12 months of age or older.

7. Salicylates. It is unknown whether Reye syndrome results from the administration of salicylates after vaccination for varicella in children. No cases have been reported. The vaccine manufacturer, however, recommends that salicylates not be administered for 6 weeks after the varicella vaccine has been given because an association between Reye syndrome, natural varicella, and salicylates is well established. Physicians need to weigh the theoretical risks associated with varicella vaccine against the known risks of the wild-type virus in children receiving long-term salicylate therapy.

8. Storage and administration. The vaccine must be stored in a freezer with a temperature of −15°C (+5°F) or colder. Once reconstituted, the vaccine must be used immediately. If the vaccine is not used within 30 minutes, it must be discarded.

**FUTURE DEVELOPMENTS**

**Booster Immunization**

Currently, routine booster immunization is not recommended, but the need for revaccination will be reassessed with time.

**Combined Vaccines**

In the future, it is anticipated that varicella vaccine will be combined with MMR as MMRV. Studies to date have shown that all four viral vaccines can be combined, resulting in the development of immune responses to each virus and no increase in adverse reactions. The currently licensed vaccines should not be mixed in the same syringe because their effectiveness can be altered under these conditions.

**REFERENCES**


