CLINICAL REPORT

Prevention of Varicella: Recommendations for Use of Varicella Vaccines in Children, Including a Recommendation for a Routine 2-Dose Varicella Immunization Schedule

Guidance for the Clinician in Rendering Pediatric Care

Committee on Infectious Diseases

ABSTRACT

National varicella immunization coverage using the current 1-dose immunization strategy has increased among vaccine-eligible children 19 through 35 months of age from 27% in 1997 to 88% by 2005. These high immunization rates have resulted in a 71% to 84% decrease in the reported number of varicella cases, an 88% decrease in varicella-related hospitalizations, a 59% decrease in varicella-related ambulatory care visits, and a 92% decrease in varicella-related deaths in 1- to 4-year-old children when compared with data from the prevaccine era. Despite this significant decrease, the number of reported cases of varicella has remained relatively constant during the past 5 to 6 years. Since vaccine effectiveness for prevention of disease of any severity has been 80% to 85%, a large number of cases of varicella continue to occur among people who already have received the vaccine (breakthrough varicella), and outbreaks of varicella have been reported among highly immunized populations of schoolchildren. The peak age-specific incidence has shifted from 3- to 6-year-old children in the prevaccine era to 9- to 11-year-old children in the postvaccine era for cases in both immunized and unimmunized children during these outbreaks. Outbreaks of varicella are likely to continue with the current 1-dose immunization strategy.

After administration of 2 doses of varicella vaccine in children, the immune response is markedly enhanced, with >99% of children achieving an antibody concentration (determined by glycoprotein enzyme-linked immunosorbent assay) of ≥5 U/mL (an approximate correlate of protection) and a marked increase in geometric mean antibody titers after the second vaccine dose. The estimated vaccine efficacy over a 10-year observation period of 2 doses for prevention of any varicella disease is 98% (compared with 94% for 1 dose), with 100% efficacy for prevention of severe disease. Recipients of 2 doses of varicella vaccine are 3.3-fold less likely to have breakthrough varicella, compared with those who are given 1 dose, during the first 10 years after immunization.

To achieve greater levels of immunity with fewer serosusceptible people, greater protection against breakthrough varicella disease, and reduction in the number of outbreaks that occur nationwide among school-aged populations, a 2-dose varicella immunization strategy is now recommended for children ≥12 months of age.

- Children 12 months through 12 years of age should receive two 0.5-mL doses of varicella vaccine administered subcutaneously, separated by at least 3 months; if the second dose inadvertently is administered between 28 days and 3 months after the first dose, the second dose does not need to be repeated. All children routinely should receive the first dose of varicella-containing vaccine at 12 to 15 months of age. The second dose of varicella-containing vaccine is recommended routinely when children are 4 to 6 years of age (ie, before a child enters kindergarten or first grade) but can be administered at an earlier age.

- People ≥13 years of age without evidence of immunity, as defined in the "Recommendations" section of this report, should receive two 0.5-mL doses of varicella vaccine separated by at least 28 days. For people who previously received only 1 dose of varicella vaccine, a second dose is necessary to provide evidence of immunity.

Both a monovalent varicella vaccine (Varivax [Merck & Co Inc, Whitehouse Station, NJ]) and a combination quadrivalent varicella-containing vaccine (ProQuad [Merck & Co Inc] or measles-mumps-rubella-varicella) are licensed by the Food and Drug Administration for use in the United States. Monovalent varicella vaccine is approved for use in children ≥12 months of age (and, therefore, adolescents and adults as well), and measles-mumps-rubella-varicella is approved only for children 12 months through 12 years of age. Neither varicella-containing vaccine contains thimerosal or other preservatives. When all vaccine components are indicated, combination vaccines are preferred whenever possible to minimize the number of injections.

BACKGROUND AND RATIONALE FOR RECOMMENDATIONS

Before licensure of the monovalent varicella vaccine (Varivax [Merck & Co Inc, Whitehouse Station, NJ]) in March 1995, approximately 4 million cases of varicella, 10 500 to 13 500 hospitalizations attributable to complications of varicella, and 100 to 150 deaths occurred annually.[1–5] Beginning in 1996, routine varicella immunization was recommended for children between 12 and 18 months of age as well as for all susceptible people older than 19 months.[6,7] In 1999, the Centers for Disease Control and Prevention (CDC) recommended a varicella immunization requirement for children attending child care and at elementary school entry,[8] and in 2005 the CDC expanded this recommendation to include students from kindergarten through college.[9] By July 2006, the District of Columbia and all states except Idaho, Montana, Vermont, and Wyoming had implemented a varicella immunization school-entry requirement that covers all or some of the recommended cohorts[10] (see www.immunize.org/laws). Estimates of national varicella immunization coverage indicate an increase from 27% in 1997 to 88% by 2005 among vaccine-eligible children 19 to 35 months of age.[11]

These high immunization rates have had a dramatic effect on varicella disease burden, demonstrated by a 71% to 84% decrease in the reported number of varicella cases, an 88% decrease in varicella-related hospitalizations, a 59% decrease in varicella-related ambulatory care visits, and a 92% decrease in varicella-related deaths in 1- to 4-year-old children when comparing the prevaccine and postvaccine eras.[5,12,13] Recent data suggest that in areas with vaccine coverage of approximately 90%, the incidence of varicella has declined 90% (CDC, written communication, 2005). However, vaccine effectiveness for prevention of varicella disease of any severity has been 80% to 85%[14,15]; as a result, large numbers of individual breakthrough varicella cases (defined as wild-type chickenpox occurring >42 days after immunization) continue to occur. In addition, outbreaks among highly immunized populations of schoolchildren continue to be reported.[16–18] In these school outbreaks, varicella-vaccine coverage ranges from 96% to 100%, with vaccine effectiveness ranging from 72% to 85%. Immunized students with breakthrough varicella contributed to virus transmission, demonstrating that a 1-dose vaccine policy was not sufficient to control disease in these outbreaks. In addition, the peak age-specific incidence of varicella has shifted from 3- to 6-year-old children in the prevaccine era to 9- to 11-year-old children in the postvaccine era for both immunized and unimmunized children during these outbreaks.

Surveillance by the CDC and state health departments has demonstrated that the number of reported cases of varicella has been relatively constant during the past 5 to 6 years. Given this experience, it is likely that outbreaks will continue, given the effectiveness of a 1-dose immunization policy. As varicella immunization rates increase, most varicella cases occurring during outbreaks will be in people who have been immunized. However, this pattern does not indicate an increase in the rate of breakthrough disease or evidence of increasing vaccine failure.

When varicella develops in an immunized person (breakthrough varicella), the median number of skin lesions is generally <50, the duration of illness is shorter, and the incidence of fever is lower than that in an unimmunized person. Serious complications probably are reduced, although data are insufficient to establish whether a reduction in bacterial skin infections, pneumonia, or encephalitis is achieved. Approximately 25% of breakthrough cases result in an illness with >50 lesions, similar to that occurring in unimmunized children. The occurrence of breakthrough varicella raises a number of concerns:

- Approximately 15% of vaccine recipients (those with no or partial response to 1 dose of vaccine) remain at

increased risk of breakthrough disease. Despite local outbreaks, exposure to varicella-zoster virus (VZV) will become less common as vaccine uptake increases. Therefore, these susceptible children may be at risk of severe varicella associated with VZV infection in adolescence and adulthood.

- Although contagion may be reduced among children who experience breakthrough disease, results from carefully studied school outbreaks show that school-children with breakthrough disease can serve as the index case for an outbreak. School outbreaks that involve immunized children continue to occur regularly in the United States, particularly among elementary school students, even in states with high coverage rates. Students who experience breakthrough disease are excluded from school for 3 to 5 days, parents may miss employment while caring for their sick children, and exposed susceptible schoolteachers who may be pregnant or students with contraindications to immunization must be identified and considered for postexposure prophylaxis. These outbreaks place an increased workload on state health departments.

- Because most varicella cases occur in highly immunized populations, there may be concern regarding vaccine efficacy and a misunderstanding by physicians or parents who may conclude that vaccine efficacy is declining. This misperception can lead to frustration among both parents and physicians, with erosion of confidence in the varicella-vaccine program, especially among people who perceive varicella as a mild illness of childhood.

- Because immunized children who experience breakthrough disease are coinfected with 2 VZV strains (wild and vaccine types), they may be at increased risk of zoster from the reactivated wild-type strain later in life, compared with vaccine recipients who do not experience breakthrough disease.

EPIDEMIOLOGY OF THE DISEASE

VZV is a highly contagious pathogen, with 80% to 90% of susceptible people exposed in a household setting developing clinical infection.[19] Transmission occurs via direct contact, airborne droplets, or infected respiratory tract secretions. The virus initially enters a susceptible host through the upper respiratory tract or the conjunctivae. An infected host is contagious from 1 to 2 days before the onset of the rash until all skin lesions are crusted. Secondary cases in a family setting usually are more severe than the primary case, likely because of a higher viral inoculum resulting from a more intense exposure. VZV spreads less readily in tropical climates than in temperate climates,[20] and as such, a higher proportion of adults from tropical countries are serosusceptible to VZV compared with adults from countries with cooler climates.

During the 1980s, 33% of varicella cases occurred in 1- to 4-year-old children, and 44% occurred in 5- to 9-year-old children[21]; >90% of all cases of chickenpox occurred in children younger than 15 years of age. During the early and mid-1990s, the age-specific incidence of chickenpox shifted to younger ages, with 1- to 4-year-old children having the highest incidence of infection rather than 5- to 9-year-old children.[22,23] Data from the third National Health and Nutrition Examination surveys seroprevalence study from 1988 to 1994 indicate that, in the immediate prevaccine era, 95.5% of people 20 to 29 years old, 98.9% of people 30 to 39 years old, and >99.6% of people ≥40 years had immunity to VZV.[24]

In the prevaccine era, 97% to 99% of adults with a positive history of varicella were seropositive, and the majority of adults with negative or uncertain histories were seropositive (range: 71%–93%).[25–28] No published data were available on the predictive value of a positive history of varicella disease in children during that time period. History of varicella may be becoming less reliable in the vaccine era, with only 75% of unimmunized children 1 to 4 years of age who report a positive history of chickenpox actually being seropositive.[29] A second episode of chickenpox in a person is uncommon and occurs more frequently in immunocompromised hosts.[30]

After primary varicella infection (chickenpox), the virus establishes latency in neuronal ganglia. Reactivation of latent VZV causes herpes zoster (shingles). Approximately 20% to 30% of people over a lifetime develop herpes zoster, with disease incidence increasing markedly beginning at approximately 50 years of age.[31–33] This increase in incidence of herpes zoster is associated with a relative loss of cell-mediated immunity to VZV that occurs naturally with aging.[34–36] Herpes zoster in children is rare, although children who acquire chickenpox during the first year of life have an increased risk of shingles.[37] Herpes zoster occurs more frequently in immunocompromised patients.[38] Available data indicate that the risk of herpes zoster after immunization seems to be lower than the risk of zoster after wild-type varicella infection.[39]

CLINICAL MANIFESTATIONS OF THE DISEASE

After an average incubation period of 14 to 16 days (range: 10–21 days), clinically apparent disease ensues, with characteristic skin lesions in varying stages of development and resolution. Cutaneous lesions begin as macules and rapidly progress to papules, vesicles, pustules, and scabs. Fever and rash last approximately 5 days, with rash being more concentrated on the trunk and head than on the extremities. With wild-type disease, most children develop 250 to 500 skin lesions, and lesions frequently develop in the mouth, conjunctivae, or other mucosal sites. Bullous or hemorrhagic lesions

occur rarely. Elevations in hepatic transaminase levels occur relatively commonly during the acute illness.

Varicella in pregnant women may result in VZV transmission to the fetus or newborn. Intrauterine VZV infection may result in congenital varicella syndrome or clinical varicella in the newborn. Congenital varicella syndrome may consist of low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, chorioretinitis, and cataracts. It occurs at a rate of <1.5% among infants born to women who contract VZV in the first 28 weeks of gestation. Children infected by VZV in utero during the second half of gestation can experience inapparent varicella and then develop zoster early in life without having had extrauterine chickenpox. The onset of varicella in pregnant women 5 days before to 2 days after delivery may result in severe varicella in 17% to 30% of their newborn infants, which, if untreated, has a high mortality rate.[40]

Bacterial superinfection of skin lesions and bacterial pneumonia are among the most frequent complications of varicella in immunocompetent hosts. The viral skin lesions and associated pruritus predispose the infected person to *Staphylococcus aureus* superinfection, including methicillin-resistant *S aureus* (MRSA) infection. Varicella is an important risk factor for invasive group A streptococcal infections, including those that result in necrotizing fasciitis. The most common central nervous system complication of wild-type VZV infection is transient cerebellar ataxia, although encephalitis, viral meningitis, and transverse myelitis also can occur. Reye syndrome is associated with aspirin use in children with varicella and influenza but is rare now that aspirin is used infrequently in the pediatric population. Neutropenia and thrombocytopenia can occur 1 to 2 weeks after initial infection. In immunocompromised patients, disseminated varicella with severe and even fatal outcomes is possible; people with defects in cell-mediated immunity, such as organ transplant recipients and HIV-infected people, are at highest risk of complications.

VACCINE

Description

Two varicella-containing vaccines are licensed for use in children and adults in the United States for prevention of varicella, both of which contain the live-attenuated Oka strain of VZV.[41] Varivax is a monovalent vaccine that was licensed by the US Food and Drug Administration (FDA) in March 1995 for use in people 12 months and older.[42] ProQuad (MMRV; Merck & Co Inc) combines the varicella vaccine with attenuated measles-mumps-rubella (MMR) vaccine viruses and was licensed by the FDA in September 2005 for use in children 12 months through 12 years of age.[43] In addition to these 2 products, Zostavax (Merck & Co Inc) is a higher-concentration Oka/Merck strain vaccine that was licensed by the FDA in

May 2006 and reduces the risk of herpes zoster and postherpetic neuralgia in people 60 years and older.[33,44,45]

Monovalent varicella virus vaccine is lyophilized and should be stored frozen at an average temperature of −15°C or colder until it is reconstituted for injection. After reconstitution as directed in the package insert, it should be kept at room temperature for a maximum of 30 minutes. Reconstituted vaccine contains a minimum of 1350 plaque-forming units (PFU) of Oka/Merck VZV in each 0.5-mL dose. Each 0.5-mL dose also contains 12.5 mg of hydrolyzed gelatin, trace amounts of neomycin and fetal bovine serum, 25 mg of sucrose, and trace residual components of MRC-5 cells (including DNA and protein). More than 50 million doses have been distributed in the United States since licensure.

The MMR components of the combination MMRV vaccine are identical and of equal concentration to those in the trivalent M-M-R II vaccine (Merck & Co Inc). However, the amount of Oka/Merck VZV in MMRV is higher than in the monovalent varicella vaccine, with a minimum of 3.99 $\log_{10}$ PFU in each dose of MMRV, compared with a minimum of approximately 3.13 $\log_{10}$ PFU in each dose of monovalent varicella vaccine. The other constituents are similar between the 2 products. The lyophilized product should be stored frozen at an average temperature of −15°C or colder until it is reconstituted for injection. After reconstitution as directed in the package insert, it should be kept at room temperature for a maximum of 30 minutes. As with the monovalent vaccine, MMRV does not contain thimerosal or other preservatives. More than 2 million doses have been distributed in the United States since licensure.

Immunogenicity

Commercially available assays for detection of antibody to VZV include the enzyme immunoassay and latex agglutination test.[46,47] Two sensitive assays, gpELISA (glycoprotein enzyme-linked immunosorbent assay) and FAMA (sensitive fluorescent antibody to membrane antigen), have been used in clinical studies but are not commercially available.[48] Commercially available enzyme immunoassay and latex agglutination tests are less sensitive and, therefore, unreliable in detecting immunity among immunized people. In addition, the latex agglutination test can yield false-positive results.[49]

The concentration of varicella antibody as measured by gpELISA 6 weeks after immunization correlates with neutralizing antibody concentration, VZV-specific T-lymphocyte proliferative responses, and protection against breakthrough varicella after exposure to VZV.[50–54] Among children who have varicella antibody titers of ≥5 gpELISA units per mL 6 weeks after immunization, the vaccine efficacy rate is 95.5%, compared with an efficacy rate of 83.5% in children with <5 gpELISA units per mL.[51] Approximately 76% to 90% of children who are immunized with a single dose of varicella-containing

vaccine achieve varicella titers of ≥5 gpELISA units per mL.[52,53,55,56] Studies using the FAMA assay indicate that a titer of >1:4 at 16 weeks after immunization also correlates with protection against disease; fewer than 1% of healthy persons achieving a titer of >1:4 develop varicella after a household VZV exposure, compared with an attack rate of 55% among persons whose titers are <1:4.[57] After 1 dose of monovalent varicella vaccine, 76% of healthy children seroconvert, as measured by FAMA assay, suggesting that many breakthrough cases of varicella in children who have received 1 dose of varicella vaccine may be attributable to primary vaccine failure rather than waning immunity.[57]

Administration of 2 doses of monovalent varicella vaccine 3 months apart initially produces a higher geometric mean titer, compared with 1 dose of vaccine, and a larger percentage of patients who receive 2 doses have initial antibody concentrations of ≥5 gpELISA units per mL (99.6% vs 85.7%).[53] Recipients of a second varicella-vaccine dose have fewer cases of breakthrough varicella and increased vaccine efficacy.[53] When a second dose of varicella vaccine is administered 4 to 6 years after the first dose, a rise in VZV-specific antibody concentrations occurs rapidly and overall VZV antibody concentrations achieved are comparable with antibody concentrations achieved when 2 vaccine doses are administered 3 months apart.[58]

Varicella, measles, mumps, and rubella antibody concentrations after administration of a single dose of MMRV vaccine are comparable with concentrations after administration of MMR vaccine and monovalent varicella vaccine concomitantly at separate injection sites.[43] Among 5446 healthy children 12 to 23 months of age enrolled in 4 clinical trials, 91.2% achieved varicella antibody titers of ≥5 gpELISA units per mL (95% confidence interval: 90.3%–92%). Among a subset of 1035 healthy children who received a second dose of MMRV approximately 3 months after the first dose, 99.4% achieved varicella antibody titers of ≥5 gpELISA units per mL (95% confidence interval: 98.7%–99.8%). The varicella geometric mean titers increased approximately 41-fold after the second dose of MMRV vaccine.

Seroconversion rates for adolescents (≥13 years of age) and adults range from 75% to 94% after 1 dose of varicella vaccine but increase to 94% to 99% after a second dose of vaccine administered 4 to 8 weeks after the first.[42,59,60] No published data are available on the proportion of adolescents or adults who achieve a gpELISA concentration of ≥5 U/mL after either 1 or 2 doses of varicella vaccine. Persistence of antibody over the ensuing decade in this population varies, but studies using the FAMA assay have suggested that approximately 30% of adults lose detectable antibodies over this time period.[42,60,61] One study indicates that for adults who develop breakthrough disease after exposure to varicella, neither attack rates nor severity of illness increase over time.[62]

Humoral and cellular immunity are important for viral clearance and for protection against reinfection or reactivation of latent VZV.[34,35] Cellular immunity after 2 doses of varicella vaccine is more robust than that after 1 dose of vaccine. In children who received 1 dose of varicella vaccine, a VZV-specific T-lymphocyte response was maintained in 90% of 29 children 1 year after immunization and in 87% of 60 children 5 years after immunization. VZV-specific T-lymphocyte responses are significantly higher among recipients of 2 doses of vaccine, compared with recipients of 1 dose.[63]

Efficacy and Effectiveness

Before vaccine licensure, 1 placebo-controlled clinical trial that used an earlier formulation of the Oka/Merck vaccine than the currently licensed product was conducted in the United States.[64] This vaccine was 98% efficacious in preventing varicella after 2 years of follow-up and was 92% efficacious after household exposures. In open-label prelicensure studies in which efficacy was calculated by using historical attack rates for comparison, the efficacy of 1 dose of the varicella vaccine that ultimately was licensed most commonly ranged from 70% to 90% against infection and 95% against severe disease.[65–67] In general, postlicensure effectiveness studies have reported a similar range for prevention against infection,[16,68–73] with a few studies yielding lower[17,70] or higher[68] values. The vaccine is highly effective (≥97%) in preventing severe varicella in postlicensure evaluations.[14,15,72,74]

Fewer studies have evaluated efficacy and effectiveness of 2 doses of varicella vaccine. When 2 doses are administered 3 months apart, the estimated vaccine efficacy over a 10-year observation period for prevention of any varicella disease has been reported as 98.3%, with 100% efficacy for prevention of severe disease.[53] The efficacy of a 2-dose regimen is significantly higher than that of a 1-dose regimen (94.4%; $P < .001$).[53]

Recipients of 2 doses of varicella vaccine are 3.3-fold less likely to have breakthrough varicella, compared with recipients of 1 dose (2.2% vs 7.3%; $P < .001$) during the first 10 years after immunization.[53] Breakthrough cases developed annually in 0.0% to 0.8% of recipients of 2 vaccine doses, compared with 0.2% to 2.3% of recipients of 1 vaccine dose.

Safety

Studies conducted before and after licensure have confirmed that the varicella vaccine is safe and generally well tolerated. Pain and redness at the injection site were the only adverse events that occurred more frequently among vaccine recipients than among placebo recipients.[42] In a study that examined a 2-dose regimen of monovalent vaccine separated by 3 months, there were slightly more injection-site complaints after the second dose. After 1 dose, recipients of MMRV were more likely

than were recipients of monovalent varicella vaccine and MMR vaccine given at separate injection sites to have fever (21.5% vs 14.9%, respectively) and a measles-like rash (3% vs 2.1%, respectively).[43] Both fever and measles-like rash usually occurred within 5 to 12 days of immunization, were of short duration, and resolved without long-term sequelae. After the second dose, there were no differences in incidence of fever or rash among recipients of MMRV compared with recipients of simultaneous MMR and varicella vaccines.

The risk of transmission of vaccine virus from immunocompetent vaccine recipients in whom varicella-like rash develops after immunization is extremely low, having been documented in only 5 cases, all of which occurred after exposures in household and institutional settings.[75–77] No cases of transmission have occurred after immunization of health care professionals. Therefore, the benefits of immunizing susceptible health care professionals outweigh this negligible or extremely low potential risk. As a safeguard, institutions may wish to consider precautions for personnel in whom rash develops after immunization and for those immunized personnel who will have contact with susceptible people at high risk of serious complications.

Concomitant administration of MMRV with diphtheria-tetanus-acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines generates comparable seroconversion rates as does individual administration of these vaccines.[43] Data are absent or limited for concomitant use of MMRV with inactivated poliovirus, pneumococcal conjugate, influenza, and hepatitis A vaccines. Simultaneous administration of most widely used live-antigen and inactivated-antigen vaccines has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately. Therefore, monovalent varicella vaccine and MMRV vaccine may be administered simultaneously with other vaccines recommended for children 12 to 15 months and 4 to 6 years of age.

Cost/Benefit

Using current estimates of morbidity, mortality, direct costs, and indirect costs, analyses have found both 1-dose and 2-dose varicella immunization programs to be cost-saving at the societal level (F. Zhou, PhD, CDC, written communication, 2006). The incremental cost for the second dose is $96 000 per quality-adjusted life-year saved. When benefits from prevention of group A streptococcus infections and herpes zoster among immunized people are added to the model, incremental costs per quality-adjusted life-year saved are $91 000 and $17 000, respectively.

Vaccine Storage and Administration

Both monovalent varicella and MMRV vaccines must be stored frozen at an average temperature of −15°C (5°F) or colder. The diluent should be stored separately at room temperature or in a refrigerator. Both vaccines should be reconstituted according to directions in their respective package inserts. Both vaccines must be used within 30 minutes after reconstitution.

Monovalent varicella vaccine and MMRV vaccine should be administered subcutaneously.

RECOMMENDATIONS

Children 12 Months Through 12 Years of Age

Both monovalent varicella vaccine and MMRV vaccine have been licensed for use in healthy children 12 months through 12 years of age. Children in this age group should receive two 0.5-mL doses of varicella vaccine administered subcutaneously, separated by at least 3 months (evidence grade I [see Appendix 1]). The recommendation for at least a 3-month interval between doses is based on the design of the studies that evaluated 2 doses in this age group[53]; if the second dose is administered inadvertently between 28 days and 3 months after the first dose, the second dose does not need to be repeated (evidence grade III). The American Academy of Pediatrics recommends the use of combination vaccines when all vaccine components are indicated to minimize the number of injections children receive.[78]

All children routinely should receive the first dose of varicella-containing vaccine at 12 to 15 months of age (evidence grade I). The varicella vaccine should be administered to all children in this age range unless there is evidence of immunity to VZV (see "Documentation of Immunity") or a contraindication to administration of the vaccine (see "Contraindications"). The second dose of varicella-containing vaccine is recommended routinely when children are 4 to 6 years of age (ie, before a child enters kindergarten or first grade) but can be administered at an earlier age (evidence grade III). A routine health maintenance visit at 11 to 12 years of age is recommended for all adolescents to evaluate immunization status and administer necessary vaccines, including varicella vaccine.

People ≥13 Years of Age

People ≥13 years of age without evidence of immunity should receive two 0.5-mL doses of varicella vaccine separated by at least 28 days (evidence grade I). The recommendation for at least a 28-day interval between doses is based on the design of the studies that evaluated 2 doses in this age group. For people who previously received only 1 dose of varicella vaccine, a second dose is necessary to provide evidence of immunity. Monovalent varicella vaccine, but not MMRV vaccine, is licensed for use in this age group.

Documentation of Immunity

Only doses of vaccine for which written documentation of the date of administration is presented should be considered valid. Neither a self-reported dose nor a history of immunization of the child as provided by a parent is, by itself, considered adequate documentation of immunity. A health care professional should supply an immunization record for a patient if that health care professional has administered the vaccine or has seen a record that documents immunization. People who lack either adequate documentation of immunization or other evidence of immunity should be immunized.

Although parental self-reporting of varicella disease has historically been considered valid enough to count as evidence of immunity, recent data on self-reporting in the varicella-vaccine era have revealed it to be less reliable than in the prevaccine era,[29] probably because of the decrease in disease incidence and the proportion of mild cases among vaccine recipients, which are less readily recognized.

Serologic screening for VZV immunity generally is neither necessary nor recommended if a person has other acceptable evidence of immunity to the disease. With the exception of women who are known to be pregnant (see "Prenatal Screening and Postpartum Immunization"), people who lack acceptable evidence of immunity generally should be immunized without serologic testing. Postimmunization serologic testing to verify an immune response to varicella vaccine is not recommended, because available commercial assays are not sensitive enough and may give false-negative results.

Evidence of immunity to VZV in the pediatric population includes any of the following:

1. Documentation of 2 appropriately timed doses of varicella vaccine (evidence grade I)

2. Laboratory evidence of immunity or laboratory confirmation of disease (evidence grade I)

3. Varicella diagnosed by a health care professional or verification of history of varicella disease (evidence grade III)

   - For people reporting or presenting with typical disease, verification can be performed by any health care professional (eg, school or occupational clinic nurse, nurse practitioner, physician assistant, physician).

   - For people reporting or presenting with atypical and/or mild cases, assessment by a physician or physician's designee is recommended, and 1 of the following should be sought: (*a*) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case, or (*b*) evidence of laboratory confirmation, if it was performed at the time of acute disease. When such documentation is lacking, people should not be considered as having a valid history of disease, because other diseases may mimic mild atypical varicella.

4. History of herpes zoster diagnosed by a health care professional (evidence grade II-2)

Prenatal Screening and Postpartum Immunization

Prenatal screening of pregnant adolescent women for VZV immunity using the aforementioned criteria is recommended (evidence grade III). Varicella vaccine should not be administered to pregnant women, because the possible effects on fetal development are unknown, although no pattern of malformation has been identified after inadvertent immunization of pregnant women. After completion or termination of pregnancy, women who do not have evidence of VZV immunity should be immunized with the monovalent varicella vaccine before discharge from the hospital, birthing center, or abortion clinic; the second dose should be administered at least 28 days later (evidence grade III). Women should be counseled to avoid conception for 1 month after each dose of varicella vaccine.

A pregnant mother or other household member is not a contraindication for immunization of a child in the household (evidence grade III). Monovalent varicella vaccine should be administered to nursing mothers who lack evidence of immunity (evidence grade III).

Immunization of Immunocompromised Populations

General Recommendations

Varicella vaccine should not be administered routinely to children who have congenital or acquired T-lymphocyte immunodeficiency, including people with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems, as well as children receiving long-term immunosuppressive therapy. Certain children infected with HIV are an exception, as discussed later. Children with impaired humoral immunity may be immunized. 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.

When immunizing people with altered immunity against chickenpox (see "HIV Infection"), only monovalent varicella vaccine should be used. The Oka vaccine strain remains susceptible to acyclovir, and if a high-risk patient develops vaccine-related varicella, then acyclovir should be used as treatment.

Acute Lymphocytic Leukemia

Before routine immunization of heathy children against varicella was instituted in the United States in 1995, many young children with leukemia were susceptible to chickenpox. To protect them against serious and fatal

varicella, a research protocol for immunization against chickenpox was put in place, but this has since been terminated.[79] Considering the variability of chemotherapy regimens and the current decreasing incidence of varicella in the United States, however, these high-risk children should not be routinely immunized. Immunization of varicella-susceptible leukemic children in remission should be undertaken only with expert guidance and with the availability of antiviral therapy, should complications occur.

Live-virus vaccines usually are withheld for an interval of at least 3 months after immunosuppressive cancer chemotherapy has been discontinued.[80,81] The interval until immune reconstitution varies with the intensity and type of immunosuppressive therapy, radiation therapy, underlying disease, and other factors. Therefore, it often is not possible to make a definitive recommendation for an interval after cessation of immunosuppressive therapy when live-virus vaccines can be administered safely and effectively.[81]

HIV Infection
Screening for HIV infection is not indicated before routine VZV immunization. After weighing potential risks and benefits, varicella vaccine should be considered for HIV-infected children in CDC class 1 with a CD4$^+$ T-lymphocyte percentage of $\geq$15% (evidence grade II-1).[79] Eligible children should receive 2 doses of monovalent varicella vaccine with a 3-month interval between doses and return for evaluation if they experience a postimmunization varicella-like rash. With increased use of varicella vaccine and the resulting decrease in incidence of varicella in the community, exposure of immunocompromised hosts to VZV will decrease. As the risk of exposure decreases and more data are generated on the use of varicella vaccine in high-risk populations, the risk versus benefit of VZV immunization in HIV-infected children will need to be reassessed.

Children Who Receive Corticosteroids
Varicella vaccine should not be administered to people who are receiving high doses of systemic corticosteroids ($\geq$2 mg/kg per day of prednisone or its equivalent or 20 mg/day of prednisone or its equivalent) for $\geq$14 days (evidence grade III). The recommended interval between discontinuation of corticosteroid therapy and immunization with varicella vaccine is at least 1 month. Varicella vaccine may be administered to people on inhaled, nasal, and topical steroids.

Households With Potential Contact With Immunocompromised People
Transmission of vaccine-strain VZV from healthy people has been documented in 5 instances, resulting in 6 secondary cases. Even in families with immunocompromised people, including people with HIV infection, no precautions are needed after immunization of healthy children in whom a rash does not develop. Immunized people in whom a rash develops should avoid direct contact with immunocompromised susceptible hosts for the duration of the rash.

Contraindications
As generally with all vaccines, administration of varicella-containing vaccines is contraindicated in people with a history of severe (anaphylactic) reaction to the vaccine or its components (ie, neomycin or gelatin). Use of varicella-containing vaccines also is contraindicated in pregnant women and in people with known altered immunity (eg, HIV, hematologic and solid tumors, congenital immunodeficiency, and long-term immunosuppressive therapy) except as discussed previously. People with active untreated tuberculosis should not receive MMRV vaccine.

Of note, the monovalent varicella vaccine does not contain preservatives or egg protein, and although the measles and mumps vaccines included in MMRV are produced in chicken-embryo culture, the amounts of egg cross-reacting proteins are not significant. Therefore, children with egg allergy routinely may be given MMRV vaccine without previous skin testing.

Precautions
As with other vaccines, varicella-containing vaccines should not be administered to people who have moderate or severe illness, with or without fever. Recent receipt of blood products or immune globulin also is a precaution for administration of varicella-containing vaccines, as is a family history of immunodeficiency. Thrombocytopenia or a history of thrombocytopenic purpura are precautions for receipt of MMRV vaccine. For a detailed discussion of precautions, see the section on precautions and contraindications in the varicella chapter of the *Red Book*.[79]

Options for Postexposure Prophylaxis
Depending on a person's risk for serious varicella disease, options for postexposure prophylaxis include active immunoprophylaxis with a varicella-containing vaccine, passive immunoprophylaxis with VariZIG (the current formulation of varicella-zoster immune globulin, available under an investigational new drug application only) or immune globulin intravenous, or chemoprophylaxis with oral acyclovir. For a full consideration of these options, please refer to the *Red Book*.[79]

REPORTING ADVERSE EVENTS
Clinically significant adverse events, regardless of whether they are suspected to have been caused by varicella-containing vaccine, should be reported to the Vaccine Adverse Event Reporting System. Forms can be obtained and submitted electronically through a secure

Web site (http://vaers.hhs.gov) or obtained by telephone at 800-822-7967.

FUTURE NEEDS AND RESEARCH

As 2-dose immunization schedules are introduced into clinical care, diligent monitoring of breakthrough disease and disease outbreaks will be critical. A 2-dose schedule is anticipated to substantially decrease disease outbreaks and breakthrough disease. If this is the effect, then wild-type VZV will circulate to an even lesser extent than it does now, and whether decreased circulation of VZV will contribute to waning immunity over time after receipt of 2 doses of a varicella-containing vaccine will need to be monitored.

APPENDIX 1: US PREVENTIVE SERVICES TASK FORCE RATING SYSTEM OF QUALITY OF SCIENTIFIC EVIDENCE*

I. Evidence obtained from at least 1 properly designed, randomized, controlled trial.

II-1. Evidence obtained from well-designed controlled trials without randomization.

II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from >1 center or group.

II-3. Evidence obtained from multiple time series with or without the intervention or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s).

III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

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*Source: US Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Alexandria, VA: International Medical Publishing; 1996;861–865.

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