Varicella-Zoster Virus Vaccine

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Varicella-zoster virus (VZV) vaccine (VARIVAX; Merck Research Laboratories [MRL], Merck & Co. Inc., West Point, PA) was licensed in the United States in 1995, after 14 years of clinical research in this country. Following licensure, VARIVAX was recommended by the American Academy of Pediatrics [1] and the Advisory Committee for Immunization Practices [2] for universal use in children 12 months to 12 years of age and in susceptible adolescent and adult populations.

The VZV vaccine has been approved for use in certain immunosuppressed populations in several countries of the Far East and in Europe for >10 years. It has generally taken longer (Japan, Korea, Germany, Hong Kong, Singapore, the Philippines, and Indonesia) for acceptance as a pediatric vaccine, but several other countries have recommended its use in healthy children, adolescents, and adults.

This article summarizes the pathogenesis of VZV infection, the epidemiology of the diseases caused by VZV (chickenpox and herpes zoster [HZ]), the immune response to natural infections vs. to immunization, treatment of VZV infections, the development of the attenuated vaccine strain and related clinical trials, and future directions of vaccine-related research.

Pathogenesis of VZV Infection

VZV is a double-stranded DNA virus of the herpes family. It is classified as an alphaherpesvirus and is in the same subfamily as herpes simplex virus types 1 and 2. The virus is enclosed in a lipid envelope that is composed of host cell membranes and viral glycoproteins. These glycoproteins were originally termed gpI to gpVI but have recently been reclassified to correspond to their herpes simplex virus homologues: gE (gpI), gB (gpII), gH (gpIII), gI (gpIV), gC (gpV), and gL (gpVI). These glycoproteins are important in the host immune response to the virus, as they are expressed on the membranes of virus-infected cells.

The basic pathogenesis of chickenpox was outlined in 1981 [3] by Grose on the basis of the pathogenesis of mousepox, originally outlined by Fenner in 1948 [4]. The virus infects the host through the conjunctivae and/or mucosa of the upper respiratory tract. Over the next 2–3 days, the virus replicates in regional lymph nodes, and a primary viremia occurs on days 4–6 following infection. The virus replicates in the liver and spleen and possibly other organs, and a secondary viremia occurs about 10–14 days following infection.

This secondary viremia is coincident with the appearance of a vesicular rash characteristic of chickenpox. The lesions are pruritic and can scar if they become secondarily infected. New vesicular lesions occur over the next 5–6 days. Various stages of healing are noted on the infected subject over the course of the illness.

Although chickenpox was first proved to be an infectious disease in 1875, when Steiner [5] transmitted the virus from vesicles to susceptible volunteers, it was not until 1952 that the virus was isolated and propagated in vitro by Weller and Stoddard [6]. The virus can be propagated in primate cells, guinea pig embryo cells, and monkey kidney cells. Takahashi and colleagues were able to produce a live, attenuated strain for use as an appropriate VZV vaccine by several passages in human diploid cells, followed by guinea pig embryo cells, and then in human diploid cells again [7].

After the primary infection with VZV, the virus migrates to the dorsal root and trigeminal ganglia, where it remains latent for the lifetime of the individual. VZV DNA has been detected in the neurons of these ganglia and in the surrounding satellite cells [8]. It is thought that the waning of cellular immunity to VZV later in life or during immunosuppression from a variety of causes activates the virus, and a unilateral, dermatomal, usually painful vesicular rash ensues (HZ). More severe, widespread rashes occur in immunosuppressed individuals.

Epidemiology of Chickenpox and HZ

Chickenpox is a highly contagious disease associated with secondary attack rates in susceptible household contacts of >85% [9, 10]. It is estimated that there are 4 million cases each year in the United States. In temperate climates such as the United States, almost all individuals are infected by the time they reach adulthood; most acquire the disease in childhood. Seroprevalence studies done as part of the third National Health and Nutrition Examination Survey (1988–1994) demonstrated that 34% of children aged 4–5 years, 18% of children aged 6–10 years, 6% of individuals aged 11–19 years, and only 4% of adults aged 20–29 years are susceptible to varicella [11].
Age-specific incidence data derived from the National Health Interview Survey for the period 1980–1990 estimated that 33% of chickenpox cases occurred in preschool-age children, and 44% occurred in school-age children. In tropical climates the incidence of the disease is lower among children and much higher among older adolescents and adults [12]. In the United States most cases are reported during the winter and early spring.

The average course of chickenpox in children consists of a fever of 2–3 days’ duration, accompanied by a vesicular rash involving a median of 300 lesions. Otherwise healthy children and adolescents (i.e., persons <15 years of age) who contract chickenpox comprise the largest proportion (80%) of an estimated 9,300 annual chickenpox-related hospitalizations. The rate of complications is substantially higher for persons ≥15 years of age and for infants (i.e., children <1 year of age) [2].

Adults tend to have more severe disease with more prolonged fevers and a higher tendency to develop associated pneumonia. Women who contract varicella in the first 20 weeks of pregnancy have a 2% risk of their fetus developing congenital varicella syndrome [13]. In addition, pregnant women who contract natural varicella in the last trimester are at risk of severe pneumonia and death.

Infants are at risk of severe neonatal infection if the maternal infection appears from 5 days before delivery to 2 days afterward [14]. Approximately 60–100 previously healthy individuals die from complications of chickenpox each year in the United States [2].

The most common complication in children is secondary bacterial infection of the skin [15]. Staphylococci or group A β-hemolytic streptococci are the usual causative pathogens. The incidence of extracutaneous complications of varicella is low. The most common complication is acute cerebellar ataxia, which develops about 5–10 days after the rash, with truncal ataxia often the only neurological sign. Cerebellar ataxia in association with chickenpox is estimated to occur in 0.06% of cases among children <15 years of age and can result in hospitalization [16].

Varicella encephalitis is a more serious and less common complication than cerebellar ataxia and carries a more guarded prognosis. The risk of encephalitis in children ages 1–14 years of age is estimated to be 1.7 per 100,000 varicella cases [17]. Other complications include pneumonia, hepatitis, and Reye’s syndrome; the latter is rare since acetylsalicylic acid is now contraindicated for treatment of fevers in children.

HZ is the clinical picture resulting from reactivation of VZV that established latency after primary infection. The major risk factors for development of HZ are increasing age, immunosuppression, and VZV infection acquired in utero or during the first year of life (presumably because of a poor cell-mediated immune response to the virus at young ages) [18, 19].

It has been a well-observed phenomenon that the incidence rates of HZ increase sharply among persons >60 years of age.

Immune Responses to VZV

Both the humoral and cellular immune responses are necessary in eliminating infection and in the maintenance of persistent immunity. Serum antibodies to VZV are not usually detected until 1–3 days following the appearance of the vesicular rash. There is rapid induction of IgG, IgM, and IgA antibodies, generally directed at the viral glycoproteins and the nucleocapsid protein. The initial IgG antibodies to VZV are thought to be predominantly in the IgG3 subclass [21]. Neutralizing antibodies are predominantly IgM, but IgG antibodies have also been shown to neutralize the virus [22].

Since children with primary agammaglobulinemia usually have uncomplicated disease, whereas fatal infection is common in those with immunodeficiency disease affecting cell-mediated immunity, the latter is thought to play an important role in limiting the spread of disease and probably in eventual clearing of infection [23]. In the healthy host, chickenpox is associated with the rapid induction of T lymphocytes that recognize certain VZV proteins: gE, gH, and IE62 [24, 25]. These T cells release cytokines of the Th-1 type, including IL-2 and IFN-γ.

There is also nonspecific induction of IFN-α. Both IFN-α and IFN-γ have a direct antiviral effect on VZV replication. In vitro experiments indicate that the CD4+ T-cell response is predominantly of the Th-1 type, with little or known production of Th-2 cytokines [26]. Cytotoxic T-cell responses against IE62 and gE can be demonstrated in vitro.

Immunity appears to be lifelong in most instances after natural disease. There are few instances of second cases of chickenpox reported in the literature. When previously infected individuals are immunosuppressed, they typically develop HZ rather than chickenpox. Persistence of immunity may be related to periodic exogenous reexposure to the virus during epidemics of chickenpox, exposure to HZ, and/or subclinical reactivation of endogenous latent virus.

Similar humoral and cell-mediated responses have been noted in individuals vaccinated with the live, attenuated VZV vaccine [27–29]. Memory T-cell responses and cytotoxic T-cell responses are elicited by immunization with varicella vaccine. It has been noted that the immune response to vaccin-
lation in adults is somewhat less robust than that seen in children allowing one dose [30]. Better immune responses are seen in his older group following two doses of the vaccine given 8-8 weeks apart. Antibody and cell-mediated immune responses elicited by the vaccine are boosted by exposure to atural varicella.

The immune response to HZ is somewhat different than the response to primary infection with VZV. Although there is a rapid humoral response involving IgG, IgM, and IgA antibodies, analysis of the IgG subclasses indicates that IgG1 antibodies are predominant in HZ, whereas IgG3 antibodies are predominant in primary infection. However, the antibody response does not seem to be correlated with the severity of HZ. The administration of VZV immune globulin to immunocompromised individuals with HZ had no apparent effect on the course of disease [31].

A very robust VZV-specific T-cell proliferation coincides with the appearance of the cutaneous rash. Immunocompromised patients have a more sluggish and less robust cell-mediated immune response than do otherwise healthy patients with HZ. The resolution of HZ is accompanied by local production of FN-α [32]. The enhanced cell-mediated immune response to VZV persists for many years; perhaps this explains why secondary episodes of HZ are rare.

Treatment of VZV Infections

Acyclovir is currently the antiviral drug of choice for chickenpox in immunocompromised and some immunocompetent individuals. The use of oral acyclovir for immunocompetent persons with chickenpox has been controversial. The American Academy of Pediatrics does not recommend routine administration of acyclovir to immunocompetent pediatric patients. The efficacy of the drug was not impressive in this population in double-blind, placebo-controlled clinical trials [33, 34]. In addition, widespread use of acyclovir among children with chickenpox may increase the number of acyclovir-resistant strains circulating in the United States.

The effects of acyclovir were more pronounced in a double-blind, placebo-controlled study of adults with chickenpox [35]. Most physicians use oral acyclovir for treatment of chickenpox in older adolescents and adults. Postexposure prophylaxis with oral acyclovir for chickenpox in family contacts has been reported to be effective, but it is not recommended since this practice would increase selection for resistant viruses [36]. VZV immune globulin can be given to prevent chickenpox after exposure, but it must be given within 72 hours after exposure, and the protection is short-lived (≤3 months).

Acyclovir is also recommended for the treatment of HZ. Studies have indicated that early treatment with acyclovir limits the rash and decreases the pain associated with the rash [37]. Recently, famciclovir and valacyclovir also have been licensed for the treatment of HZ. Famciclovir and valacyclovir have spectrums of antiviral activity and mechanisms of action similar to those of acyclovir but have enhanced bioavailability and longer half-lives.

Additional clinical trials have investigated the efficacy of alternative antiviral agents that may be useful to treat VZV resistant to acyclovir and its analogues, such as foscarin and bromovinyl arabinosyl uracil. However, these drugs are associated with higher incidences of side effects and are reserved for special at-risk populations, such as patients with AIDS and other immunosuppressed persons.

Despite the availability of well-tolerated antivirals, their effect on the course of VZV disease is minimal. The best scenario is prevention of the disease with a safe and effective vaccine.

Unique Problems Associated with the Clinical Trials and Licensing of a Live, Attenuated VZV Vaccine

Development and licensure of an appropriate live, attenuated vaccine were slower than those of other live, attenuated vaccines for childhood diseases, i.e., measles, mumps, and rubella. Several reasons made the development and licensure of a VZV vaccine more difficult: (1) technical difficulties with cultivation and attenuation of the virus; (2) consideration of varicella as a mild disease, until studies by Preblud and others at the Centers for Disease Control and Prevention (CDC) reported significant morbidity and some mortality, even among otherwise healthy individuals [15, 17]; (3) concerns about the impact of vaccination on HZ; and (4) concerns about persistence of immunity following vaccination.

Initiation of Clinical Studies in Japan

Clinical trials with a live, attenuated VZV vaccine were initiated in Japan by Takahashi in 1974. He obtained wild-type VZV from the vesicular fluid of a 3-year-old boy with chickenpox, whose family name was Oka. Classical methods of attenuation were used, i.e., passage at lower temperature and attenuation of the virus; (2) consideration of varicella as a mild disease, until studies by Preblud and others at the Centers for Disease Control and Prevention (CDC) reported significant morbidity and some mortality, even among otherwise healthy individuals [15, 17]; (3) concerns about the impact of vaccination on HZ; and (4) concerns about persistence of immunity following vaccination.
Development of the VZV Vaccine in Other Countries

Takahashi licensed out the Oka strain to various manufacturers worldwide, and clinical studies were initiated in Europe and the United States. Over the past 15 years, multiple pharmaceutical companies have investigated the safety, immunogenicity, and efficacy of various formulations of the Oka-strain live, attenuated VZV vaccine. Vaccines produced by different manufacturers vary in the number of passages of VZV in human diploid cells, the pfu levels of the final product, and stabilizers included in the vaccine.

Antibody responses to the vaccines have been measured by various assays, including cellular immune adherence hemagglutination assay, fluorescent antibody to membrane antigen (FAMA) assay, ELISA, glycoprotein-based ELISA (gpELISA), and in vitro neutralization assays. The ELISA is commercially available but is not as sensitive as the gpELISA. The FAMA assay is less sensitive but more specific than either ELISA but is more difficult and expensive to perform.

The in vitro neutralization tests are performed only in research laboratories. Cellular immune responses were measured during clinical trials in subsets of subjects by in vitro methodologies or delayed hypersensitivity skin testing. Immune responses were typically measured 30–56 days postvaccination.

SmithKline Beecham Biologicals (Rixensart, Belgium) initiated studies in immunosuppressed children and adults in Europe with the Oka-strain VZV vaccine in the late 1970s. Studies in the United States were initiated with the Oka strain in 1981 by MRL and involved healthy children and adolescents. Early studies involving immunocompromised subjects and adults in the United States were done by MRL in collaboration with the National Institutes of Allergy and Infectious Diseases (NIAID).

Later, in the 1980s, Pasteur Merieux Serums & Vaccins S.A. (Lyon, France) initiated clinical studies in France involving immunosuppressed persons, which were followed by studies of healthy children. Since the majority of recently reported studies used the MRL VZV vaccine (VARIVAX), the results of clinical trials with this vaccine are emphasized herein.

Clinical Trials in Healthy Children

The primary goal of the VZV vaccine development program by MRL in the United States was to obtain data to support universal immunization of children. Since 1981, >10,000 children have received varying formulations of the VZV vaccine during clinical studies in the United States [28, 29, 39–46]. Several dose levels of vaccine were used in clinical studies and various formulations were tested over the 14-year span prior to licensure. Since VZV is a very temperature-labile virus, it proved challenging to make consistent large-scale manufacturing lots of a potency high enough to ensure adequate immunogenicity. Each time improvements were made to the process, several thousand children were tested for safety and immunogenicity.

Efficacy Studies

A double-blind, placebo-controlled efficacy study was conducted in children in the early 1980s in the suburbs of Philadelphia [41]. In this study, 468 children were immunized with one dose of varicella vaccine and 446 were given placebo. Over a period of 9 months, there were 39 cases of chickenpox, all in placebo recipients, resulting in a vaccine efficacy of 100%. During the second year of follow-up, one vaccinated child developed a mild varicella-like syndrome (MVLS), consisting of 17 lesions, after exposure to natural chickenpox; thus, the efficacy rate was 98%. During a 7-year follow-up, 95% of these vaccinees remained free of chickenpox [45].

A second double-blind, placebo-controlled efficacy study was done with SmithKline Beecham’s VZV vaccine (Varilrix) in Finland in the late 1980s [47]. The children in this study received one dose of a vaccine containing ~10,000 pfu, a vaccine containing ~1,000 pfu, or placebo. The efficacy over 1 year of follow-up was 88% in children receiving the higher-potency vaccine and 55% in those receiving the 1,000-pfu vaccine. Most of those who were not totally protected had only a mild rash, usually consisting of <50 lesions, and were afebrile.

Most published studies have indicated that each year postvaccination, anywhere from <1% to 3% of vaccinated children have developed MVLS after significant exposure to wild-type varicella [44, 45, 47–50]. Most cases of MVLS consist of a rash with <50 lesions but no fever, and the rates and severity of MVLS do not increase over time following vaccination.

According to the CDC, the attack rate of natural varicella in unvaccinated children of similar ages in the United States is 8.3%–9.1% each year. Thus, the vaccine decreases the incidence of varicella by ~65%–90%, depending on the potency of the vaccine they received. The higher protection rates were noted in children who received the higher-potency lots, which are representative of the vaccine now marketed in the United States by Merck & Co., Inc.

Safety Studies

The VZV vaccine has been well tolerated in children. The most common complaints in the 4–8 weeks postvaccination are mild tenderness and redness at the injection site (19.3%), mild rash (3.8%), and fever, defined as an oral temperature of ≥102°F (14.7%). In one double-blind, placebo-controlled clinical trial, the only complaint that occurred more often in vaccinated children was pain and redness at the injection site (P < .05) [41].

Approximately 4% of vaccinees report a generalized maculopapular rash consisting of 10 or fewer lesions, occurring from 7 to 21 days postvaccination. A similar percentage of children report a rash at the injection site, usually consisting of 2–4 lesions. It is difficult to isolate vaccine-type virus from a vaccine-associated rash, but it has been reported rarely [51]. Vaccini-
nated healthy children who develop >10 lesions postvaccination would be suspect for intercurrent infection with wild-type strain.

Transmission of the vaccine strain was studied in two clinical studies in healthy children [41, 52]. In one study, children in a household were randomized to receive either vaccine or placebo [41]. In that study, there were no reports of transmission of clinical disease (rash); however, three of 439 initially seronegative placebo recipients exposed to vaccinees seroconverted for VZV, but no rash was reported in either the placebo recipients who seroconverted or the vaccine recipients. In the second study, siblings of susceptible immunocompromised children were vaccinated [52]. There was no evidence of clinical or serological transmission of infection following vaccination in the families studied.

Since marketing of the vaccine began in the United States, there has been one reported case of transmission of Oka-strain virus from a vaccinated child to his susceptible mother. However, this case is suspect since the vaccinee developed >10 lesions postvaccination and may have had intercurrent wild-type infection with a strain that resembled the Oka strain. When evaluated by restriction endonuclease analysis, the Oka vaccine strain resembles many of the other wild-type strains circulating in Japan, but it can be differentiated from most indigenous strains in the United States.

The case occurred in a West Coast city with a large Asian population whose frequent travel to the Far East may have introduced wild-type Japanese strains of varicella into the community. If transmission does occur from healthy vaccinees, studies in leukemic children (see below) indicate that when the vaccine virus is transmitted from the vaccinee it remains attenuated in the second host. Results to date indicate that the likelihood of transmission of vaccine virus from a healthy individual is low and may be more likely to occur if the vaccinee develops a rash postvaccination.

There have been eight reported cases of HZ in healthy children who previously received the vaccine, which is less than what would be expected in a pediatric population experiencing natural chickenpox [53]. No vaccine virus was cultured in any of these cases. The HZ was mild in all individuals. At present, there seems to be no increased risk and perhaps a decreased risk of HZ in vaccinated children.

Immune Response

Over 95% of vaccinated children develop humoral and cell-mediated immune responses to VZV following vaccination. Although cytotoxic lymphocyte responses to VZV in vaccinated children have not been reported because of the difficulties in obtaining target cells for the assay, adults who have received varicella vaccine have cytotoxic lymphocyte responses similar to those seen following natural infection [54]. A detectable immune response has been shown to persist from 6 to 10 years postvaccination [43, 45, 46, 53, 55, 56].

Because the varicella vaccine is a live, attenuated vaccine, it is anticipated that most vaccinees will have lifelong immunity, similar to what is observed in recipients of live, attenuated measles-mumps-rubella vaccine. The longest experience has been reported in Japan, where 20-year follow-up studies revealed persistent evidence of immunity [57]. Studies sponsored by MRL are ongoing at a health-maintenance organization in northern California that is following 7,000 vaccinees for 15 years postvaccination to determine the need and optimal timing for a second dose of vaccine.

Clinical Trials in Healthy Adolescents and Adults

Clinical trials have been conducted in adolescents and adults in the United States, Europe, Singapore, and Japan [58–61]. The vaccine has been licensed for use for adults in high-risk situations, i.e., health-care personnel and VZV-susceptible parents of immunosuppressed children, in Europe and Japan since the 1980s. Outbreaks in the military and in hospital settings in the United States promoted interest in licensure of the vaccine for susceptible adults in the United States [62, 63]. In the early 1980s, studies in the United States were sponsored by the NIAID in collaboration with MRL.

In the trials reported by Gershon et al., 37 vaccinees with household exposure to natural chickenpox were documented [59, 60]. Eleven of the vaccinees, all of whom had lost detectable antibody before exposure, developed MVLS. Most of these vaccinees had received only one dose of vaccine. It was also reported by Gershon’s group that adults had a less robust antibody and cell-mediated immune response to vaccination than did healthy children, and their response was more similar to that of immunosuppressed leukemic children [59].

Later studies by MRL indicated that two doses 4–8 weeks apart were necessary to yield seroconversion rates and antibody levels as high as those in healthy children in whom efficacy had been demonstrated in a double-blind, placebo-controlled study [61]. Persistence of immunity following this regimen has been studied for only 2–3 years. However, earlier studies by Hardy and Gershon with use of other regimens, some involving one dose, did not indicate loss of protection during 6 years of follow-up postvaccination [64].

Since the vaccine contains a live, attenuated virus, it is contraindicated to give the vaccine to any woman who is pregnant or planning to get pregnant within the next 3 months. To collect information on whether the vaccine can result in teratogenic effects, a registry has been established by MRL and the CDC to report the outcome of pregnancy for any woman who is inadvertently given the vaccine during pregnancy. The telephone number is 1-800-986-8999. Most experts would not recommend routine therapeutic abortion if a woman is vaccinated during pregnancy but advocate serial ultrasounds early in the pregnancy to determine if fetal abnormalities characteristic of the congenital varicella syndrome (e.g., short limbs or microcephaly) are present.
The safety and tolerability of the vaccine in adolescents and adults are similar to those observed in healthy children, with the most common complaints being mild injection-site reactions. In clinical studies conducted by MRL, non-injection site varicella-like rashes occurred in 5.5% of vaccinees following the first dose (median number of lesions, 5.0) and in 0.9% of vaccinees following the second dose (median number of lesions, 5.5).

Fever (oral temperatures of $\geq 100\,^\circ F$) were reported in 10.2% and 9.5% of vaccinees after dose 1 and dose 2, respectively, but occurred in a random fashion over the 42-day follow-up period and were usually associated with other intercurrent respiratory infections. Only one case of HZ in an adult vaccinee has been reported. In that case, the vaccinee lost detectable antibodies and developed MVLS and subsequently HZ, which was culture-positive for wild-type VZV [65].

Clinical Trials in Immunocompromised Children and Adolescents

Results of clinical studies in Japan, Europe, and the United States indicate that immunocompromised children and adolescents could be safely vaccinated if they were 1 year away from induction chemotherapy, if they had lymphocyte counts of $\geq 700/mm^3$, and if chemotherapy was suspended around the time of vaccination [66–72]. Most of these studies were conducted in children and adolescents with acute lymphocytic leukemia (ALL), but a few studies were conducted in children with solid tumors.

The immune response is somewhat lower in immunocompromised individuals, and administration of two doses 3 months apart is recommended. Results of long-term follow-up of these high-risk subjects indicate that if a person has seroconverted at any time postvaccination, VZV immune globulin is no longer needed following an exposure, even if the vaccinee has become seronegative around the time of exposure. Immunocompromised individuals report more frequent and severe rashes following vaccination than do healthy individuals.

In the NIAID collaborative study using the MRL vaccine, rash developed in 5% of leukemic children no longer receiving chemotherapy and in 50% of those receiving maintenance chemotherapy, about 1 month following the first dose of vaccine. Vaccinees were routinely treated with acyclovir if they developed >50 skin lesions or had rashes lasting >7 days. Disseminated VZV infection has not been noted in vaccinated immunosuppressed individuals when chemotherapy has been suspended for 1 week before and 1–2 weeks after vaccination.

Transmission of VZV from leukemic vaccinees has been observed, but only when the leukemic child has had a vaccine-associated rash, and the likelihood of spread was found to be proportional to the number of skin lesions in the vaccinee [73]. The chance of spread of vaccine virus in a household setting was 20%–25%, about one-fourth of the usual rate of transmission of the wild-type virus [10]. Siblings who developed MVLS following household exposure to a vaccinee with rash had an average of 38 lesions, much fewer than the quantity seen in natural infection, a finding suggesting that the vaccine virus remains attenuated through at least one human passage.

This sentinel group of vaccinees, many of whom are now adults, has provided much information about the persistence of immunity and the occurrence of HZ postvaccination. Studies by Gershon indicate that protection persists for at least 11 years after immunization, even though many vaccinees become seronegative [74]. The incidence and severity of MVLS do not increase over time postvaccination.

Hardy et al. reported that the attenuated Oka strain could establish latency and that the incidence of HZ was significantly lower in vaccinated children with ALL than in children with ALL who had experienced natural chickenpox [75]. Although the vaccine is licensed for administration to immunosuppressed individuals in several countries in Europe and the Far East, in the United States it is available only under a compassionate-use program sponsored by MRL for children and adolescents with ALL.

Cost-Benefit Analysis of a Universal VZV Vaccination Program in the United States

Before the Advisory Committee for Immunization Practices recommended universal immunization of children, the CDC sponsored a cost-benefit analysis of vaccination in the United States. Results of the study, conducted by Lieu et al., indicated that a routine varicella vaccination program for healthy children would result in net savings from the societal perspective, which included work-loss costs as well as medical costs [76]. The authors concluded that in comparison with other prevention programs, it would also be relatively cost-effective from the health-care payers’ perspective.

The study assumed that a routine VZV vaccination program for healthy children would prevent 94% of all potential cases of chickenpox, provided the vaccination coverage rate was 97% at school entry. On the basis of a vaccine cost of $35/dose, the program would save more than $5 for every dollar invested in vaccination, if work-loss costs as well as medical costs are considered. However, from the health-care payers’ perspective (medical costs only), the program would cost ~$2 per chickenpox case prevented.

An additional program for catch-up vaccination of 12-year-olds would have high incremental costs if the vaccination coverage rate of children of preschool age was 97%, but it would result in net savings at a coverage rate of 50%. On the basis of these estimates, the CDC recommended routine immunization of all susceptible children in the United States, preferably at 12 months to 12 years of age, and vaccination of susceptible adolescents and adults, with priority given to health-care workers and family contacts of immunocompromised persons [2].
Epidemiological Impact of Universal VZV Vaccination in the United States

In addition to the cost-benefit analysis, the CDC also sponsored a study to evaluate the impact of various vaccination approaches on the natural history of varicella. Halloran et al. utilized various assumptions regarding coverage and efficacy of the vaccine to produce a mathematical model to predict the epidemiological and morbidity effects of routine varicella immunization of preschool-age children in the United States [77]. The authors concluded that although implementation of a vaccination program resulted in a shift in the age distribution of remaining varicella cases toward older ages with higher complication rates, the overall reduction in cases resulted in decreased morbidity, as measured by overall number of hospitalizations and number of primary cases.

Routine immunization with a live, attenuated varicella vaccine would result in a substantial reduction in the number of uncomplicated primary cases of chickenpox, as well as a decrease in the number of complicated cases requiring hospitalization. An effective catch-up program for susceptible adolescents and adults and high vaccine coverage rates resulted in the best estimates for overall reduction in morbidity from a vaccination program.

Indications for VZV Vaccine Use and Future Directions

Since the licensure of varicella vaccine in the United States in March 1995, >4.5 million doses have been administered to children, adolescents, and adults. Since the recommendations by the CDC were not published until the summer of 1996, it is expected that over the next few years many more children will receive the vaccine under government-funded programs.

One dose is recommended for children 12 months to 12 years of age, and two doses given 4–8 weeks apart are recommended for individuals ≥13 years of age who are susceptible to chickenpox. The vaccine may be given with the measles-mumps-rubella vaccine MMRII (Merck & Co., Inc.), since clinical studies have shown no clinically relevant interaction with any of the viral components contained in either vaccine if given simultaneously at separate anatomic sites.

Studies have been conducted involving administration of VZV vaccine, MMRII vaccine, Tetramune (diphtheria-tetanus-pertussis vaccine + Haemophilus influenzae type b vaccine; Wyeth-Lederle Laboratories, Pearl River, NY), and Orovax (trivalent oral polio vaccine), Wyeth-Lederle Laboratories [78]. The only effect noted between the group given all the vaccines simultaneously at separate sites and those given the vaccines on separate visits was a lower level of antibodies to VZV. The clinical significance of this finding is unknown since the study showed similar levels of antibody to VZV at 1 year after vaccination. To achieve more universal immunization, it is prudent to administer the varicella vaccine at the same visits as other pediatric vaccines.

An investigational combination MMRII + VZV vaccine has been tested in several thousand children. Although seroconversion rates for all of the viral components was satisfactory when compared with those for MMR and VZV vaccines given separately, the titer of antibodies to the varicella component with use of the combination vaccine was about half that with use of the separate vaccines [79]. Further evaluations of different formulations are expected in the near future.

Additional large postmarketing studies sponsored by MRL are underway in the United States to evaluate use of the VZV vaccine for boosting the immune response to VZV in the elderly, in hopes of preventing or attenuating HZ. In vitro studies have indicated that the vaccine will boost cellular immunity to VZV in individuals >60 years of age [80, 81]. Whether this will result in clinical efficacy can be determined only by a large double-blind, placebo-controlled trial in which vaccinees will be observed for incidence and severity of HZ for several years after vaccination.

Other groups are evaluating the use of subunit vaccines to circumvent any safety issues that may be related to a live, attenuated vaccine as well as to facilitate the use of potent adjuvants that may be useful in the program to prevent/attenuate HZ in the elderly [82].

Finally, the CDC will play an integral part in determining the effects of a large-scale vaccination program on the impact of both chickenpox and HZ following initiation of universal vaccination of children and whether any modifications will need to be made in the future. Since VZV establishes latency and can later appear as HZ, it is not expected that a universal immunization program with a live, attenuated VZV vaccine will eliminate circulation of the virus.

Nevertheless, the addition of this generally safe, effective vaccine will improve the health of many children, adolescents, and adults who will no longer have to suffer with chickenpox.

Acknowledgments

The author thanks Tara D'Lutz for technical assistance with the manuscript and Dr. Sandra Holmes for editorial assistance.

Suggested Additional Reading


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To earn credit, read the State-of-the-Art Clinical Article carefully and answer the following questions. Mark your answers by circling the correct responses on the answer card (usually found toward the front of the issue), and mail this card after affixing first-class postage. To earn credit, a minimum score of 80% must be obtained.

Certificates of CME credit will be awarded on a per-volume (biannual) basis. Each answer card must be submitted within 3 months of the date of the issue.

This program is made possible by an educational grant from Roche Laboratories.

1. VZV is
   A. an alphaherpesvirus containing a double-stranded DNA core surrounded by a glycoprotein envelope.
   B. a betaherpesvirus with a double-stranded DNA core surrounded by a glycoprotein envelope.
   C. an alphaherpesvirus with an RNA core surrounded by a glycoprotein envelope.
   D. none of the above.

2. Chickenpox
   A. occurs at an incidence of ~4 million cases/year in the United States.
   B. is more common in adolescents and adults than in children, in tropical areas.
   C. has a case-fatality rate of 1:100.
   D. A and B only
   E. A, B, and C

3. Herpes zoster
   A. becomes more common in individuals >60 years of age.
   B. occurs more often in children who had chickenpox at <1 year of age.
   C. should be treated with an oral antiviral drug when it occurs in otherwise healthy adults.
   D. A and C only
   E. A, B, and C

4. The VZV used in the marketed vaccine
   A. was passaged through human diploid cells and then guinea pig embryonic cells for attenuation.
   B. is a heat-stable virus.
   C. has been shown in clinical trials in immunocompromised children to remain attenuated through at least one human passage.
   D. A and C only
   E. A, B, and C

5. VZV vaccine has been shown in clinical trials to be safe and effective in
   A. preventing chickenpox in children in remission from acute lymphocytic leukemia.
   B. preventing herpes zoster in the elderly.
   C. preventing chickenpox in healthy children.
   D. A and C only
   E. A, B, and C

6. The most common complaint following vaccination with VZV vaccine in children is
   A. fever.
   B. rash.
   C. injection site redness and tenderness.
   D. fatigue.

7. Persistence of protection from chickenpox has been demonstrated
   A. in children in the United States, for up to 9 years following vaccination.
   B. in immunosuppressed individuals in the United States, for up to 11 years following vaccination.
   C. in individuals in Japan, for up to 20 years following vaccination.
   D. A and B only
   E. A, B, and C

8. Mild varicella-like syndrome
   A. occurs at a rate of <1% to 3%/year in children following vaccination, depending on the level of pfu contained in the VZV vaccine.
B. usually consists of <50 lesions.
C. usually is not accompanied by fever.
D. A and B only
E. A, B, and C
9. VZV vaccine is recommended for use in the United States for universal immunization of
A. elderly individuals, to prevent herpes zoster.
B. children 12 months to 12 years of age (one dose administered subcutaneously).
C. susceptible adolescents and adults (two doses subcutaneously, 1–2 months apart).
D. B and C only
E. A, B, and C
10. The United States is the only country that has licensed a VZV vaccine for use in healthy individuals.
A. True
B. False