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Preventing Varicella-Zoster Disease

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INTRODUCTION

That one virus causes both varicella and zoster was recognized about 100 years ago in early attempts to develop a vaccine, when mild varicella occurred in susceptible children who were inoculated with vesicular fluid from patients with zoster (137, 138). The virus is therefore called varicella-zoster virus (VZV), and it is now recognized as one of the eight herpesviruses that infect humans. Varicella (chickenpox) represents primary infection with VZV, and zoster (shingles) is the result of reactivation of latent virus, acquired during the attack of varicella (137, 138). The severity of natural varicella in immunocompetent individuals has been the subject of controversy for a number of years. However, it is recognized as causing significant complications such as those involving the central nervous system, as well as serious bacterial superinfections (23). It was partly the hope of reducing such complications that drove attempts to develop a safe and effective VZV vaccine. A further inducement was the possibility that such a vaccine might protect against zoster, a cause of serious morbidity in the immunosuppressed and elderly.

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VIROLOGY

VZV is an alphaherpesvirus that is closely related to herpes simplex virus (HSV) types 1 and 2. However, it has become clear that VZV is quite distinct from HSV both in its biology, including the pathogenesis of latency, and in its clinical behavior (122). The genome of VZV, the smallest among human herpesviruses, is composed of at least 70 unique genes (32). All of these genes are thought to be expressed in lytic infection (30). The genes are divided into three classes, immediate early (IE), early (E), and late (L); gene expression proceeds in a regulated cascade. In general, L genes encode structural proteins whereas E and IE encode nonstructural proteins such as enzymes, although there are some notable exceptions. Among the structural proteins is an important group of at least eight glycoproteins (gps) that stimulate immune responses and are crucial in spread of the virus from one cell to another. It is thought that VZV can spread in two ways, (i) by release of enveloped virions into the extracellular space, which occurs mainly in the vesicular skin lesions that develop in disease, and (ii) by cell-to-cell spread of infection, which does not require enveloped virions. This latter type of spread is seen in cell cultures, from which infectious VZV is not released into supernatant media. Cell-associated spread is also thought to be important during natural infection, for example in dissemination of varicella to the skin (through leukocyte-associated viremia).

During latent infection, in contrast to lytic infection, limited gene expression leads to the formation of only a small subset of

TABLE 1. Methods used to measure antibodies to VZV

Test	Comments
ELISA	Uses extract from cells infected with VZV as antigen. Many commercial tests available. Lacks good sensitivity and specificity, particularly for measuring antibody titers following vaccination. Can be automated, so is useful to test large numbers of sera.
gpELISA	Uses glycoproteins of VZV as antigen. Not commercially available. Used to evaluate VZV antibodies in many vaccine studies. Many experts consider this test oversensitive. Six-week postvaccination titer inversely correlated with risk of breakthrough varicella; arbitrary cutoff at 5 gpELISA units suggested as correlate of protection.
FAMA	Uses live, unfixed cells infected with VZV as antigen. Not commercially available. High correlation of titers of 1:4 or greater to protection from varicella following close exposure to virus. Used successfully to evaluate immunity in small vaccine studies in healthy and immunocompromised populations.
LA	Uses latex particles coated with VZV glycoproteins as antigen. High correlation between the results of FAMA and LA assays. Requires experience in reading agglutination to interpret the test. Not automated.

viral proteins. Studies of animal models and human sensory ganglia at autopsy indicate that at least 7 VZV open reading frames, 4, 21, 29, 40, 62, 63, and 66, may be transcribed (26, 79, 80, 101–104). Presumably during latent infection there is a block in gene expression, which is overcome on reactivation (26). Lytic infection then develops, resulting in zoster. This scenario contrasts with HSV latency, in which only the latency-associated transcripts are transcribed and no viral proteins are expressed (106). It is presumed, based on autopsy studies, that latent VZV infection develops in the sensory ganglia of the majority of individuals following natural varicella (80, 101); however, only about 15% ever develop zoster (34).

CLINICAL FEATURES OF VARICELLA AND ZOSTER

VZV is though to gain entry to the body as airborne virus reaching the respiratory mucosa. The disease is preceded by a rather long incubation period of about 2 to 3 weeks, probably accounting in part for the success of passive and active immunization. During this period, at least two phases of viremia occur, culminating in the delivery of virus to the epidermis along with the appearance of constitutional symptoms such as fever, malaise, and anorexia. VZV infection of epidermal keratinocytes produces the typical vesicular lesions of chickenpox (4, 51, 68). It is from these intensely pruritic vesicles that infectious enveloped viral particles are shed into the air. The crusting over of the last crop of vesicles therefore marks the end of contagion. The possible infectiousness of individuals with varicella before the vesicles develop suggests an alternative site of viral shedding at this stage, such as the respiratory tract, but this has been more difficult to identify (62, 128).

Significant complications of varicella include cerebellar ataxia, encephalitis, and bacterial superinfection (particularly of the skin and lungs). Reye's syndrome was at one time a dreaded complication of varicella, but it disappeared with the cessation of the use of aspirin as a childhood antipyretic agent. Varicella is 25 times more likely to be serious in adults than in children. Immunocompromised individuals and the newborn are also at high risk of developing severe or fatal varicella. A disabling but rare congenital varicella syndrome (consisting of skin scarring, limb abnormalities, brain damage, and ocular malformations) affects up to 2% of offspring born to women who contract chickenpox in the first or second trimester of pregnancy (37, 51, 70).

Zoster is manifested by a localized, unilateral, and painful vesicular rash. In itself, this represents considerable morbidity. Zoster may also be complicated some weeks later by postherpetic neuralgia, an extremely painful condition for which there is little effective treatment. Immunocompromised hosts may experience disseminated cutaneous and/or visceral zoster, occasionally with a fatal outcome (67, 121). A forme fruste termed zoster sine herpete (without rash) has been described. In this illness, otherwise unexplained pain occurs in a dermatomal distribution in association with VZV reactivation (61).

IMMUNITY TO VARICELLA-ZOSTER VIRUS

Immunity to VZV is complex and not yet fully understood. Antibodies develop following the rash of varicella and persist for many years. Based on experience with passive immunization (see below), it appears that antibodies may play a role in immunity to varicella, and neutralizing antibodies can be demonstrated in vitro.

Antibodies are directed against the gps of VZV as well as against the nucleocapsid and tegument. The relative importance of these antibodies in prevention of reinfection is not known (51). Antibodies can be demonstrated by a variety of practical methods including enzyme-linked immunosorbent assay (ELISA) immunofluorescence, and latex agglutination (LA). ELISA is now the most commonly used method, but it is often insufficiently sensitive to demonstrate an antibody response following immunization (89). In addition, some ELISAs are associated with a certain degree of nonspecificity (49). The absence of a sensitive and specific measure of immunity to VZV has posed a problem in evaluating the success of varicella vaccine. Over long-term follow-up, the magnitude of the initial postvaccination antibody response, as measured by gpELISA, is correlated with protection against varicella (25, 96, 143). A 6-week antibody titer of at least 5 gpELISA units/ml has been proposed as a "reasonable correlate of protection" following vaccination, since it defines a low-responding group with a 3.5-fold excess risk of breakthrough varicella (96). This appears a somewhat arbitrary figure, but it may prove to be a useful standard for comparison between studies. What is sorely needed is a robust and convenient measure of protection of the individual against VZV rather than "seroconversion" per se. The only antibody test that is known to correlate protection from infection with a specific titer of antibodies is the fluorescent antibody to membrane antigen (FAMA), a research test that is not widely available (47, 147). In some laboratories, the LA assay has proven useful to determine VZV antibody titers after immunization, and there is an

TABLE 2. Diagnostic tests for VZV infections

Test	Comments
Culture	The "gold standard" for diagnosis. May take up to a week to demonstrate cytopathic effect. Vesicular fluid positive only in the first few days of rash. Requires experience in reliable isolation of virus.
Direct immunofluorescence	Commercial kits available with monoclonal antibody to VZV glycoprotein E (the most abundant) conjugated to fluorescein. Results available within a few hours. Possible to distinguish between HSV, VZV, and poxviruses easily with this assay.
PCR	Becoming more readily available and performed by commercial laboratories. Useful for diagnosis with scabs and skin lesions several days old after culture is no longer positive. Most sensitive of the diagnostic assays. Can be used on cerebrospinal fluid; culture of cerebrospinal fluid is rarely positive in disease. In specialized laboratories, PCR can be used to differentiate between wild-type and vaccine VZV strains.
Serology	The rapid diagnostic utility of immunoglobulin M and G measurements has not been demonstrated.

excellent correlation between this assay and FAMA (53, 120). An overview of the various antibody tests and their advantages and disadvantages is presented in Table 1.

Humoral immunity is thought to be less important in host defense than cell-mediated immunity (CMI), possibly because the majority of VZV in active infection is cell associated. Thus, children with hereditary deficits in CMI are at risk of developing severe varicella while those with agammaglobulinemia are not. CMI toward VZV can be demonstrated by a variety of assays including lymphocyte proliferation in response to VZV antigen, cytotoxicity assay, and enzyme-linked immunosorbent spot-forming cell assay (ELISPOT) (94). At present these remain research tools, but measurable correlates of clinical immunity, particularly in patients at high risk of developing zoster, are being sought.

LABORATORY DIAGNOSIS

Laboratory diagnosis of VZV infections is well established and generally available in the United States. VZV can be isolated from the vesicular skin lesions of varicella and zoster, especially in the first 1 to 2 days after onset of rash. Other successful diagnostic approaches are direct immunofluorescence (DFA) and PCR (49). Although somewhat nonspecific, electron microscopy can be extremely useful in rapidly distinguishing between herpesvirus and poxvirus infections. Wild-type and vaccine strain VZV may be distinguished by molecular methods; this has been helpful in evaluating patients who have been vaccinated and develop a vesicular rash. Table 2 summarizes information regarding diagnostic tests for VZV.

ANTIVIRAL THERAPY

Both varicella and zoster may be treated with acyclovir (ACV) that is administered either by the oral route or intravenously, depending on the severity of the illness. Zoster can also be treated successfully with the oral medications famciclovir and valacyclovir. There is a high correlation between early treatment and a successful outcome. Antiviral therapy for varicella does not prevent latent VZV infection (146). For further information, the reader is directed to recent reviews (3, 38).

EPIDEMIOLOGY

Varicella in the prevaccine era was mainly a disease of children under the age of 10 years, while zoster remains an illness mainly of individuals over the age of 50 years. In nonvaccinated populations in temperate climates, a trend toward younger (preschool) age at primary infection has been seen over recent years (54). In contrast, varicella tends to be less of a childhood infection in the tropics, with correspondingly higher rates of susceptibility among adults. Varicella shows seasonal variation in incidence, being commoner in winter and spring (114).

Varicella is a highly contagious disease, with a clinical attack rate of 65 to 86% following household exposure of susceptible individuals (72, 112). Nearly every adult in the United States today has experienced varicella, although this will change over time following the introduction of vaccination in 1995. Although the complication rate in healthy children is low, the previous high rate of disease accounted for significant varicella-related mortality and morbidity. In the prevaccine era there were about 4 million cases of varicella annually in the United States, with 100 deaths (mostly in otherwise healthy individuals and despite the availability of antiviral therapy) and 11,000 hospitalizations (42, 107, 139). Most VZV infection results in a clinical illness, but about 5% of primary infections are subclinical. Second attacks of varicella are unusual in otherwise healthy individuals, although they are recognized to occur (56, 77, 78, 137). One estimate is that 1 in 500 history-positive persons with a household exposure to varicella will experience a second attack (49).

Zoster is mainly a disease of individuals over the age of 50 years and immunocompromised persons. Among the latter, bone marrow transplant recipients and children with human immunodeficiency virus (HIV) are at particular risk. Postherpetic neuralgia is most likely to afflict the elderly and highly immunocompromised patients (51, 66). It is thought that waning CMI is a major factor in the increased rates of zoster in the elderly, particularly since antibody titers remain intact or may even increase with age (5, 11, 20, 52, 69). Recently a link with local trauma was postulated (127), but, other than the factors mentioned, surprisingly little is known about the epidemiology of zoster (126).

PREVENTION OF VARICELLA

Postexposure Prophylaxis in Immunocompromised Individuals

The success of passive immunization could be said to offer a "proof of concept" that active immunization would also be successful. Administered in the form of varicella-zoster immune globulin (VZIG), passive immunization is useful in preventing or ameliorating clinical varicella in VZV-exposed persons at high risk of severe chickenpox (whereas prompt administration of live attenuated vaccine is appropriate post-

exposure prophylaxis in susceptible immunocompetent individuals). The main use of VZIG, therefore, has been in immunocompromised children (23). VZIG has a number of drawbacks, including the need for administration within 96 h of exposure, the fact that it is a blood product, and its expense. These factors, together with well-documented failures of protection by VZIG (149), have prompted attempts to use ACV as postexposure prophylaxis either alone (10, 82, 98) or as an adjunct to VZIG (63, 74). Published series are too small to make valid comparisons, but there is undoubtedly a place for ACV at 7 to 14 days postexposure in vulnerable patients who have missed the time window for VZIG. Happily, the indication for postexposure prophylaxis is in decline in the United States, since individual patients are more likely to be VZV immune (due to prior vaccination) and are less likely to be exposed to varicella. In effect, they are protected by both personal and herd immunity. However, the availability of alternative approaches remains important for certain susceptible individuals when VZIG is either not available or no longer likely to be effective.

Active Immunization

History. The development of the live attenuated varicella vaccine was a landmark in vaccine research (123). It remains the only vaccination in use today against any of the herpesviruses. The concept of immunization against an agent that causes latent infection was entirely novel and at first provoked a great deal of controversy. In part, this may account for the long interval, a period of over 10 years, between the demonstration of efficacy and licensure in the United States. In addition, it was the first live vaccine to be administered successfully to immunocompromised children. Indeed, early studies of efficacy were conducted in the 1980s with children with underlying leukemia who were at high risk of death from varicella had they not been immunized (49).

Development of the Oka vaccine strain. The virus used to develop the vaccine was isolated from an otherwise healthy 3-year-old Japanese boy with varicella (123). Attenuation of the virus was accomplished as follows. It was passaged 11 times at 34°C in human embryonic fibroblasts, 12 times at 37°C in guinea pig fibroblasts, and 5 times at 37°C in human diploid fibroblasts (WI-38 and MRC-5 cells) (123). Additional passages were carried out by the manufacturers to prepare the vaccine for large-scale production. Because VZV is so strongly cell associated, the final product is sonicated and centrifuged to produce live cell-free virus. Current commercial sources are Merck and Co., Glaxo SmithKline (GSK), Biken Institute, and Green Cross Vaccine Corp. in South Korea. Only the Merck vaccine is licensed in the United States. Not enough is known about these individual products to be able to judge whether one has advantages over another, despite claims to the contrary (90).

It is now well accepted that the Oka vaccine strain is attenuated. It replicates less efficiently in human skin than does wild-type VZV, as studied in the SCID-hu mouse model (108). A number of mutations are present in the vaccine strain that are absent from the parental Oka virus (64, 65, 99, 100). Most of these mutations are in open reading frame 62, although exactly which are responsible for attenuation remains under study.

There is also overwhelming clinical evidence of attenuation. Both the incidence and severity of rash following vaccination (either by injection or by inhalation) are decreased by a factor of about 20, in comparison to natural infection (13, 55). The vaccine strain is far less transmissible to others than is the wild-type virus, and transmission has been demonstrated to occur only when an individual has a vaccine-associated rash. Despite its use in over 40 million individuals in the United States, only 4 instances of transmission from healthy vaccinees have been reported (87, 113, 117). (In contrast, children vaccinated during remission from leukemia were more likely to transmit vaccine strain VZV to others, probably reflecting defective CMI and greater incidence of rash.) Contact cases are extremely mild or subclinical (117, 128). There are no reports of reversion of the vaccine strain to clinical virulence in these rare transmission events. There is only one report of tertiary spread of the vaccine virus (128).

Safety in healthy individuals. Safety is the major concern in evaluating any preventive agent that is to be used on a routine basis, particularly in children. In extensive pre- and postmarketing studies in the United States, the live varicella vaccine was found to be extremely safe in susceptible children and adults. In prelicensure clinical trials, more than 11,000 healthy adults and children were immunized without even moderate toxicity (47, 141). Adverse effects, such as irritation at the injection site and rash, were minor and transient.

Since the advent of clinical research trials, it has been possible to distinguish between the wild-type virus and the Oka vaccine strain (105). This has been important in order to separate natural disease from possible complications of vaccination. At first, it was necessary to propagate VZV from a rash or other specimen before it could be ascertained whether the vaccine type virus was truly implicated (45). More recently, distinction has been possible by using PCR (64, 65, 86, 99, 100).

Following licensure in 1995, an extensive collaborative postmarketing safety study of the vaccine was carried out (117, 148). Medical providers and consumers were invited to submit their observations on suspected adverse reactions. Clinical information was collated by individuals at Merck and Co., while samples such as vesicular fluid or tissues were analyzed by PCR at Columbia University. Testing was done first for VZV, and then typing was performed if VZV was identified (86). Although these data were collected passively, important information emerged. These findings are echoed by the Food and Drug Administration, which receives notifications through the Vaccine Adverse Events Reporting System including all of those reported through the Merck surveillance scheme (148).

Between 1995 and 1999, over 16 million doses of varicella vaccine were distributed in the United States. Rash was the adverse event most frequently reported. The vast majority of rashes consisting of more than 50 skin lesions were found to be caused by wild-type VZV, particularly in the first 2 weeks after immunization. Only three patients with rash caused by the Oka vaccine strain had more than 200 skin lesions, which is below even the average number (about 300) in children experiencing natural varicella. There were 19 reports of encephalitis and 24 reports of ataxia in the year following vaccination. The Oka vaccine strain, however, was not implicated in these illnesses, although wild-type VZV was identified in one patient with ataxia and one with encephalitis. There were no reports of fatal

TABLE 3. Immunogenicity of VZV vaccine in immunocompetent, varicella-susceptible subjects

Study (yr) (reference)	No. of doses	Sample size[a]	Age group	Test used	Timing of test (wk)	Seroconversion rate (%)
Weibel et al. (1984) (136)	1	468	Children	IAHA/FAMA	8	94
Gershon et al. (1988) (58)	1	184[b]	Adults	FAMA	4, 8, and 12	82
	2	150[b]				94
LaRussa et al. (1990) (89)	1	33	Children	FAMA	6	91
White et al. (1991) (142)	1	3,303	Children and adolescents	gpELISA	6	96[c]
Clements et al. (1995) (28)	1	426	Children	ELISA/gpELISA	6	95
Kuter et al. (1995) (84)	1	490	Adolescents and adults	gpELISA	4	75
	2					99
Asano (1996) (6)	1	2,330	Children	IAHA	4	92
Ngai et al. (1996) (109)	1	1,731	Children	gpELISA	6	98[d]
	2	718				100
Varis and Vesikari (1996) (130)	1	325	Children	FAMA	5–9	99
Johnson et al. (1997) (76)	1	292	Children	FAMA	6	96

[a] Excluding seropositive individuals.
[b] Subjects were tested after each dose of vaccine in a two-dose protocol (i.e., the sample populations overlap).
[c] 79% in the 13- to 17-year age group.
[d] Only 86% of "seroconverters" to a single dose of vaccine achieved titers of 5 gpELISA units/ml or above (83).

VZV infection caused by the Oka vaccine strain in this study (117) or in any other investigation regarding varicella vaccine, although fatalities due to wild-type VZV are well known.

Five children with serious and/or disseminated infections due to the Oka vaccine strain have been reported. In every case there was significant underlying immunodeficiency, although this was not suspected at the time of vaccination. There were various underlying pathologies: HIV infection and almost no CD4 lymphocytes (81), asthma and high-dose steroids (117), adenosine deaminase deficiency (60), neuroblastoma identified and treated immediately after vaccination (92), and deficiency in natural killer cells (95). Each child received antiviral therapy for VZV with recovery.

In one study, a vaccinee who became immunocompromised after immunization developed chronic zoster caused by an ACV-resistant Oka virus (92). However, in general, zoster has been reported infrequently after vaccination; indeed, the incidence of zoster was significantly reduced in leukemic children receiving VZV vaccine compared with those experiencing natural infection (2, 69). It is hypothesized that vaccination will also be protective against zoster in healthy vaccinees, and information obtained since 1995 strongly suggests that this is the case. Between 1995 and 1999, the vaccine strain was identified in 22 zoster patients while wild-type VZV was found in 10 (117). Fewer than 50 proven cases of zoster due to the Oka vaccine strain were reported via postmarketing surveillance after distribution of over 30 million doses from 1995 to 2002 (41). However, this figure is likely to reflect significant underascertainment of zoster. The long-term (30 to 40-year) risk of vaccine strain zoster remains unknown pending the accrual of prospective follow-up data over time.

Immunogenicity of varicella vaccine in healthy children and adolescents. Live attenuated varicella vaccine is highly immunogenic, as judged by a variety of serological tests (Table 3). In studies carried out prior to licensure, children younger than 12 years showed a seroconversion rate of 97% after one dose of vaccine, as determined by gpELISA 6 weeks after immunization (110, 142). Using the FAMA test, 184 adolescents and adults showed seroconversion rates of 82% after one dose of vaccine; this rose to 94% after two doses were given (47). In studies of roughly 500 leukemic children, the FAMA assay indicated a seroconversion rate of 82% after one dose of vaccine and 95% after two doses (48). A seroconversion rate of 91.5% was determined using immune adherence hemagglutination, a test rarely used today, to examine the rate in 2,565 children who received a single dose of vaccine between 1987 and 1993 in Japan (6). A number of apparent failures of seroconversion in the Merck-Columbia postlicensure study may have been attributable to the insensitivity of commercially available ELISAs (117, 148).

Efficacy of varicella vaccine. Early studies of leukemic children who received VZV vaccine during remission from their illness indicated that this was both safe and highly protective against varicella (57). Two doses of vaccine were usually given, 3 months apart. About 85% of these children were completely protected against disease following household exposure to varicella, and those who developed breakthrough infection had mild disease that required no antiviral therapy. The calculation of vaccine efficacy was based on the observation that in varicella-susceptible individuals, 86% become clinically ill following this type of exposure (112). Early studies indicated that healthy children gained a similar degree of protection against household exposure after a single dose of vaccine, with breakthrough disease occurring in about 15% (140). The results of a number of pre- and postlicensure studies, addressing vaccine efficacy and effectiveness, respectively, are outlined in Table 4.

Two double-blind placebo-controlled studies of varicella vaccine (one with Merck vaccine, and one with vaccine prepared by GSK) together involved about 1,500 children. They showed that high-titer vaccine (10,000 to 17,000 PFU) was between 88 and 98% protective against varicella (130, 135,136). Lower doses (<1,000 PFU) gave reduced rates of protection (130, 135, 136). Many different doses of varicella vaccine have been studied in various clinical trials. The currently licensed Merck vaccine contains about 3,000 PFU per dose, and the GSK vaccine contains about 10,000 PFU at the time of release, which, prior to the expiration date, falls to about 3,000 PFU. The Merck vaccine is lyophilized and frozen, while the GSK product is lyophilized and refrigerated (54).

TABLE 4. Studies of varicella vaccine efficacy and effectiveness in children

Study design	Study (yr) (reference)	No. of vaccinees studied[a]	No. of unvaccinated susceptible children studied	No. of doses of vaccine	Duration of follow-up (yr)	% Efficacy/effectiveness (range) against:	
						All forms of varicella	Severe varicella
Double blind, placebo-controlled trial	Weibel et al. (1984) (136); Kuter et al. (1991) (85)	468	446	1	2	98[b]	100
	Varis and Vesikari (1996) (130)	325[c]	155	1	2.4	72[c]	
Uncontrolled clinical trial	White et al. (1991) (142)	82[d]	HPC[i]	1	1	86	
	Johnson et al. (1997) (76)	281	HPC	1	6–10	66–81	
	Takayama et al. (1997) (124)	64–159[e]	HPC	1	6–8	43	
	Kuter et al. (2004) (83)	618–1104[e]	HPC	1	10	94[f] (93–96)	100
		607–1,017[e]	HPC	2	10	98[g] (97–99)	100
Case control	Vazquez et al. (2001 and 2004) (131, 132)	592	416	1	0–8	87[h] (81–91)	98 (93–99)
Dynamic cohort	Clements et al. (1999) (27)	(4,658 person-months)	(10,274 person-months)	1		83 (69–91)	100
Retrospective	Izurieta et al. (1997) (75)	66	82	1		86 (73–92)	100 (96–100)
Cohort outbreak investigations	Buchholz et al. (1999) (19)	40	19	1		76	
	Dworkin et al. (2002) (35)	146	63	1		88	
	Galil et al. (2002) (44)	25	18	1		44 (7–66)	86 (39–97)
	Galil et al. (2002) (43)	80	20	1		79 (66–88)	95 (84–98)
	Tugwell et al. (2004) (129)	152	7	1		72 (3–87)	

[a] Only those seronegative at the time of vaccination are considered.
[b] 100% in the first year, and 96% in the second year.
[c] Two different titers of vaccine were compared, the lower (630 to 1,260 PFU) being approximately 55% effective and the higher (10,000 to 15,850 PFU) being about 88% effective in protecting from varicella.
[d] Efficacy was measured against varicella following household exposure.
[e] Subjects were monitored for 10 years, with a gradual reduction in sample size.
[f] 90% (84% to 98%) effective against household exposure.
[g] 96% (92% to 100%) effective against household exposure.
[h] When analyzed by time since vaccination, population efficacy was 97% in the first year, falling to 84% thereafter.
[i] HPC, historical population controls.

Effectiveness of Varicella Vaccine and Its Impact in the United States

Prospective studies of the vaccine in clinical practice are especially significant because of the likelihood that results will differ in this setting compared to research settings. A postlicensure case-control study involving otherwise healthy children is being carried out in the offices of pediatricians in New Haven, Conn. The "cases" are PCR-proven cases of varicella, and the "controls" are demographically matched children without varicella. This study, which is under way, has indicated that the vaccine as used in the United States is highly effective in preventing varicella (131). In the initial report, there were 202 children with varicella and 389 matched controls. Of these, 23% with varicella and 61% of controls had been immunized, indicating a vaccine effectiveness of 85%. Of 56 vaccinated children with varicella, 86% had only mild disease; in contrast, 48% of the 187 unvaccinated children had mild varicella. A follow-up of this study published in 2004 indicated that between 2 and 8 years after vaccination, the vaccine was 84% effective (132).

The best indication of the effectiveness of varicella vaccine, however, is the reported dramatic decline in the disease in the United States since the introduction of routine childhood vaccination in 1995. This has been demonstrated by investigators at the Centers for Disease Control and Prevention (CDC), who coordinated active surveillance of varicella in three sentinel counties in Texas, California, and Pennsylvania (115). Vaccination coverage by the year 2000 in these counties ranged from 73.6 to 83.8% among children 19 to 35 months old. During the study, the number of varicella cases decreased by between 71 and 84% in these counties. Annual hospitalizations for varicella per 100,000 persons decreased from 2.7–4.2 in 1995 to 1998 to 0.6 in 1999 and 1.5 in 2000. Varicella incidence also declined in nonvaccinated groups such as adults and infants too young to be immunized, indicating that herd immunity had occurred (115).

These data are supported by a further prospective study of varicella in 11 day care centers in North Carolina (23, 25). Between 1995 and 1999, the rate of vaccine coverage increased from 4.4 to 63.1% while the incidence of varicella fell markedly among both vaccinated and unvaccinated groups. The rate per 1,000 person-months fell from 5.35 to 1.01 cases for vaccinees and from 16.74 to 1.53 cases for unvaccinated children. This was again interpreted as indicative of herd immunity (29). Vaccine effectiveness during a 19-month period within the study was estimated to be 83% (27).

The vaccine has been shown to be cost-effective in a number of studies in the developed world (12, 14,21, 31, 33, 97). In general, VZV vaccine is geared for use in developed countries, where chickenpox has a significant economic impact due to parental absence from work. There is essentially no information about the use of this vaccine in developing countries,

where attention appropriately focuses on more pressing threats to public health.

Recommended Vaccine Use in the United States

Contraindications to varicella vaccine include pregnancy, allergy to vaccine components, and immunodeficiency. It is currently recommended that healthy children be immunized between 12 and 18 months of age. Vaccination is also recommended for susceptible older children, adolescents, and adults. Children receiving over 2 mg of prednisone per kg per day or an equivalent steroid dose should not be immunized until steroid use has been discontinued for at least 3 months. The CDC recommends immunization of asymptomatic children infected with HIV, provided that their CD4 percentage is more than 25%. Two doses of vaccine are given to HIV-infected children, 3 months apart (22, 93). Children undergoing renal transplantation in France have been safely immunized, with excellent protection against varicella and a decreased incidence of zoster (16–18). There are, however, no official recommendations to immunize such children in the United States. Rather, North American advice is to protect VZV-susceptible immunocompromised patients, including those being treated for leukemia, by immunizing their healthy susceptible contacts. These include healthy children whose pregnant mothers are susceptible to varicella and children whose VZV-susceptible siblings have malignant diseases for which they are being treated. This recommendation has been made because transmission of the vaccine virus to others is rare whereas natural varicella is highly contagious.

Varicella vaccine can provide protection to susceptible individuals who have already been exposed, as demonstrated in studies in Japan in the 1970s and 1980s (7, 8). Susceptible family members of index patients with varicella were immunized within 3 days, and their disease was largely prevented. Vaccination was also used successfully to terminate an epidemic of varicella in a shelter for homeless families (134).

Controversies Regarding Varicella Vaccine

Does immunity to varicella wane with time after immunization? Breakthrough cases of chickenpox have consistently been reported following administration of varicella vaccine, even in the early clinical trials involving leukemic children (57). Breakthrough varicella may occur months to years after immunization, and it is caused by wild-type VZV (88). It may be so mild that it is misdiagnosed clinically. However, the occurrence of breakthrough varicella represents loss of protection from potential wild-type zoster for the affected individual and a transmission risk within the community. Different rates of breakthrough varicella have been reported, with the highest figures, not surprisingly, being generated during chickenpox outbreaks. It should be remembered that wild-type varicella does not induce complete immunity in every individual; it seems unrealistic to expect a vaccine to provide better protection than the natural illness. However, it is clearly important that the many possible causes of breakthrough varicella are carefully considered so that public health policy may be shaped accordingly.

Vaccine failure is divided into two types, primary and secondary. Primary vaccine failure occurs when there is no measurable immune response following vaccination and the person remains susceptible to the disease. A priori, this may reflect improper preparation or storage of vaccine or inability of the individual to mount an immune response. In the Merck-Columbia postmarketing study, there were 11 reports of severe varicella despite immunization (117), but how often primary vaccine failure occurs with varicella vaccine is unknown. As a surrogate, at least 3% of healthy children fail to seroconvert after a single dose of VZV vaccine, even when assessed using the perhaps excessively sensitive gpELISA antibody test. By this yardstick, of the 4 million children immunized annually in the United States, over 100,000 may experience primary vaccine failure. However, the relationship between seroconversion and protection is imprecise, with some level of protection being achieved even in individuals with negligible antibody responses (96). It is certainly the case that VZV vaccine is heat labile and therefore vulnerable to cold-chain disruption. On the host side, children with asthma may respond less than optimally to the vaccine, possibly as a result of steroid medication (75, 116, 133). A CDC-sponsored study to examine the rate of seroconversion in VZV-vaccinated asthmatic children, as determined by FAMA, is currently under way in the United States. A number of completed studies show higher rates of breakthrough varicella in children vaccinated before 15 months of age, possibly reflecting a higher risk of primary vaccine failure in this age group (35, 43). When varicella vaccine is administered less than 1 month after another live vaccine, the incidence of breakthrough varicella may also increase (24).

Secondary vaccine failure occurs when the immune response decreases over time, leaving the vaccinee with a degree of susceptibility to the disease. Modified or typical illness may result on exposure. An extremely high degree of persistence of antibodies and cellular immunity to VZV, approaching 100%, has been reported for as long as 20 years after vaccination in Japanese and American studies (1, 2, 9). In agreement, a study of over 400 vaccinated adults (most of whom received two doses) indicated no obvious increase in the incidence or severity of breakthrough varicella with time, with up to 20 years of follow-up (1). However, the situation with mass childhood vaccination may prove somewhat different, due to the huge change in epidemiology this represents. In particular, the withdrawal of VZV from circulation is likely to reduce natural boosting of immunity, with consequences for both vaccinated and varicella-experienced individuals (for a discussion of zoster risk, see below). The breakthrough rate of varicella in children monitored prospectively for as long as 10 years after immunization has been variously reported between 2 and 34% (27, 28, 76, 124). Since 1995, outbreaks of varicella in vaccinated young children in the United States have been reported (19, 35, 43, 44, 46, 75, 129). In all probability, outbreaks have resulted from a combination of primary and secondary vaccine failure.

The report of an outbreak of chickenpox at a day care center in New Hampshire, in which the rate of vaccination in attendees was high (72%) and vaccine efficacy was very low (44%), is especially compelling with regard to the possibility of waning immunity or secondary vaccine failure (44). In the outbreak described, 25 (28.4%) of 88 children developed varicella over a 6-week period. Of these 25 children, 17 (68%) had been

immunized. The index patient developed full-blown varicella after exposure to his sister with zoster and may have had primary vaccine failure. An interval of more than 3 years since vaccination was associated with vaccine failure in the outbreak. A follow up of the Yale-Columbia study also indicates that vaccine efficacy decreased with time, from 97% in the first year after vaccination to 86% in the following year (132).

Continued investigations are necessary to elucidate the causes of breakthrough varicella following immunization. However, it seems likely that, whatever the underlying causes, a second dose of varicella vaccine given routinely might alleviate potential problems of primary and secondary vaccine failure (46, 132). One recently published study showed that, over 10 years of follow-up, children who had been randomized to receive two doses of vaccine were three times less likely to develop breakthrough varicella than were those in the single-dose group (83). A practical way to achieve compliance with such a strategy would be to administer routinely two doses of vaccine as measles, mumps, rubella, varicella (MMRV). Developing an immunogenic formulation of the varicella component of MMRV has been difficult (119) but is not considered insurmountable. Varicella vaccine and MMR may currently be administered safely together at different sites of injection (140). Varicella-susceptible adolescents and adults, who respond less well to vaccination than children, are routinely given two doses of varicella vaccine, 4 to 8 weeks apart (1, 58, 59). Of note, administration of vaccine to persons with immunity to varicella is not associated with adverse events (54).

Could wild-type zoster increase in the vaccine era? Realistic expectations of protection against zoster in vaccinated individuals have been discussed above (2, 69, 117). In contrast, an increase in wild-type zoster might result from mass childhood vaccination, in persons who have had natural varicella. It would be important to determine the magnitude of any such increase and in whom it is occurring. Several recent studies have suggested that exposure to varicella may be protective against zoster, presumably because of boosting of the CMI response to VZV. In vaccinated leukemic children, both household exposure and additional doses of varicella vaccine were correlated with greater protection against zoster (50). A case-control study showed that in a healthy population, exposure to children with natural varicella was protective with respect to zoster (125). Similar conclusions were reached by Brisson et al. (15), who compared zoster incidence among adults living with or without children in the United Kingdom. These authors constructed a mathematical model to describe the protection afforded by varicella exposure and used it to examine the impact of mass varicella vaccination. This model projected a delayed "epidemic" of zoster, with accompanying significant mortality, among individuals aged 5 to 44 years at the introduction of vaccination (15). However, their figures suggested that the incidence of zoster would peak at about 50% above its prevaccination level. By current estimates of zoster incidence, we might therefore expect up to 8 cases per 1,000 person-years (perhaps 16 per 1,000 in the over-54-year age group) (34, 73). The rate of zoster in immunocompromised groups is 4 to 20 times higher and has not been considered "epidemic" (50). Moreover, studies of immunocompromised individuals show lower mortality from zoster than that from varicella (39, 40, 118, 144, 145); the prediction that overall deaths from zoster would balance lives saved from varicella, albeit based on limited epidemiologic data (36), is therefore questionable.

Observation of the incidence of zoster in countries where varicella vaccine is being used routinely will be necessary to provide an answer to this question. In the United States, the CDC is monitoring the incidence of zoster in sentinel populations. Should an increase in zoster be recognized, however, it might be approached by a new immunization strategy, as described below.

Can vaccination prevent zoster in the elderly? In attempts to explore whether vaccination may be used to boost immunity to VZV and possibly to prevent zoster, at least eight clinical trials, mostly open-label studies, have been performed by investigators in the United States and Europe. These trials have demonstrated a boost of CMI to VZV safely in most elderly subjects when live attenuated vaccines, with higher potency than in varicella prevention, were used. While no firm conclusions can be drawn, there were encouraging suggestions of reduced occurrence and severity of zoster (91).

Consequently, a large double-blind placebo-controlled study of immunization of healthy individuals older than 60 years has been undertaken, involving approximately 30,000 subjects with an average of 3 years of follow-up. Information regarding this study is expected to become available by 2005. Thus, in the future, herpes zoster may also be preventable by vaccination.

Can an inactivated vaccine prevent zoster? The advantage of an inactivated vaccine would be that it could safely be given to highly immunocompromised patients in order to try to reduce their risk of wild- type zoster. In an early controlled study, the administration of three doses of heat-inactivated vaccine to immunocompromised patients appeared to modify but not prevent zoster (111). In a second, more successful clinical trial, four doses of the same vaccine were employed, including one given a month before transplantation. The subject population was homogeneous and included patients with lymphoma who had undergone autologous stem cell transplantation (71). Induration, erythema, or pain was reported after 10% of the doses, but the vaccine was generally well tolerated. Importantly, zoster was only half as common in vaccinees than in controls, affecting 17 (30%) of the 56 unvaccinated patients and 7 (13%) of the 53 vaccinees. Protection correlated with reconstitution of CMI to VZV. Because all the patients who developed zoster received antiviral therapy for their illness, it was not possible to evaluate the effect of vaccination on the severity of zoster. This experimental vaccine holds promise for future prevention of zoster in immunocompromised patients.

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