Zoster Vaccine: Current Status and Future Prospects

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Live, attenuated Oka/Merck varicella-zoster virus (VZV) vaccine (zoster vaccine) protects immunocompetent adults from herpes zoster and its complications. Success of zoster vaccine in preventing the clinical manifestations of latent VZV reactivation contrasts with the failure to achieve similar results with vaccination to prevent recurrent herpes simplex. This reflects major differences in the pathophysiology of latency and reactivation of these 2 alphaherpesviruses. The Shingles Prevention Study and many others have demonstrated that VZV-specific cell-mediated immunity, but not VZV antibody, plays a critical role in limiting reactivation and replication of latent VZV and, thus, in preventing herpes zoster and its complications. Consequently, induction of VZV-specific cell-mediated immunity and not antibody should be used as a proxy for the clinical efficacy of new formulations and uses of zoster vaccine. Prospects for improved zoster vaccines and their use in immunocompromised patients are discussed, and questions related to zoster vaccine use are addressed.

BACKGROUND

Natural history and epidemiology. Varicella-zoster virus (VZV) causes 2 distinct diseases [1–4].

Primary VZV infection causes varicella (ie, chickenpox), a highly contagious febrile illness characterized by a generalized pruritic vesicular rash. In the United States (before widespread varicella vaccination), varicella occurred predominantly in children, with annual epidemics in winter and spring. Consequently, >99% of US adults aged ⩾40 years are now immune to VZV [5]. One episode of varicella results in lifelong immunity to the disease, and second episodes are rare, even among immunocompromised patients [6–10].

Herpes zoster (ie, shingles) is a disease of the sensory ganglion, nerves, and skin caused by reactivation and replication of VZV that has remained latent in sensory neurons after varicella. Herpes zoster is characterized by unilateral radicular pain and a vesicular rash generally limited to a single dermatome, corresponding to the sensory ganglion in which latent VZV reactivated [11]. Segmental neuralgia, with pain and paresthesia in the involved dermatome, often precedes the herpes zoster rash by several days and occasionally by ⩾1 week. This presents a diagnostic dilemma, because herpes zoster cannot be clinically diagnosed until the characteristic rash appears [11]. Pain usually accompanies the rash, and neuropathic pain and discomfort (eg, allodynia and severe pruritus) may persist for weeks, months, or even years after the rash has healed, a debilitating complication known as postherpetic neuralgia (PHN). Herpes zoster is sporadic without seasonal prevalence, but its frequency and severity increase with age [12–17]. In the United States, the incidence of herpes zoster exceeds 1% per year among persons ⩾60 years of age. More than 1 million new cases occur each year, and one-third of the current US population will experience herpes zoster during their lifetime—figures destined to increase with the increasing age of the population [16–19].

VZV. VZV, like herpes simplex virus (HSV), is an alphaherpesvirus [20]. The VZV genome is smaller than that of HSV, but most VZV genes have HSV homologs. Nevertheless, the 2 viruses differ markedly in their biology and the pathophysiology of latency and reactivation [21–23], resulting in significant clinical and epidemiological differences with important implications for disease control and prevention.

The genomes of many wild-type strains of VZV, the attenuated Oka vaccine strain, and its wild-type Oka parent have been sequenced [22, 24–28]. Although there is only 1 VZV serotype, there are multiple genotypes that display geographic segregation, as well as recombination [25–29].

The live, attenuated Oka VZV vaccine. The Oka strain of VZV was isolated from a healthy Japanese child with varicella and attenuated by serial passage in cell culture (Table 1). Clinical studies in Japan and the United States demonstrated the safety, immunogenicity, and clinical efficacy of Oka vaccine in

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The observations and conclusions in this review are those of the author and do not necessarily reflect the views of his colleagues or the Department of Veterans Affairs.

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Table 1. Live, Attenuated Oka Varicella-Zoster Virus (VZV) Vaccines

Characteristic	Description	References
History	The Oka strain of VZV was isolated from a healthy Japanese child with varicella and attenuated by serial passage at 34°C in human and guinea pig cells	[30–32]
Properties	Mixture of genotypically distinct VZV strains	[24, 33–40]
	Forty-two SNPs distinguish the Oka vaccine from the wild-type Oka parent strain of VZV	
	Twenty of the 42 SNPs specify amino acid changes	
	Although each is genotypically unique, all strains of VZV in the Oka vaccine share a subset of the 42 SNPs	
	Three SNPs (at positions 106262, 107252 and 108111 in open reading frame 62, which encodes a transactivator of viral genes required for VZV replication) distinguish the Oka vaccine from all wild-type strains of VZV	
	Differences in strain content are observed among Oka vaccines produced by different manufacturers and even between different batches from the same manufacturer	
Varicella vaccine	Clinical studies in Japan demonstrated the safety, immunogenicity and clinical efficacy of Oka vaccine, which protected susceptible immunocompetent and immunocompromised children against varicella, even when administered shortly after exposure	[41–62]
	Vaccine virus establishes latency and reactivates to cause HZ, but at a lower frequency than wild-type VZV	
	Oka vaccine also boosted VZV-specific cell-mediated immunity in immunocompetent and immunocompromised adults	
	In the United States, the safety and efficacy of Oka vaccine was documented in healthy children and adults and in several groups of immunocompromised children and adolescents	
	Varicella vaccine (Varivax; Merck) was licensed by the FDA in 1995	
	Routine childhood vaccination has markedly reduced the incidence of varicella in the United States	
Zoster vaccine	Same preparation of live, attenuated Oka/Merck VZV as used in varicella vaccine	[18, 63]
	Minimum potency at least 14 times greater than that of varicella vaccine (higher potency is necessary to induce a significant increase in VZV-specific cell-mediated immunity in older adults, who are already immune to varicella)	
Zoster vaccine safety and efficacy	The Shingles Prevention Study demonstrated the safety and efficacy of zoster vaccine in immunocompetent adults ⩾60 years of age: reduced the burden of illness caused by HZ by 61% (Table 3); reduced the incidence of HZ by 51% (Table 3); reduced the incidence of clinically significant postherpetic neuralgia by 67% (Table 4); and neither caused nor induced HZ	[18, 19, 63–66] (Merck, personal communication)
	Zoster vaccine (Zostavax; Merck) was licensed by the FDA in 2005	
	Recommended for routine use in immunocompetent adults aged ⩾60 years	
	As of March 2010, ~6 million doses have been distributed in the United States, sufficient to immunize ~12% of the population of ⩾60 year-old persons for whom it is recommended	
Recent developments	Genetic analysis of VZV Oka strains isolated from vaccine-associated rashes and cases of HZ may help identify specific SNPs that differentiate Oka vaccine from wild-type strains of VZV, and which contribute to the attenuation of the vaccine and the pathogenicity of wild-type VZV	[62, 67–78]

NOTE. FDA, US Food and Drug Administration; HZ, herpes zoster; SNP, single nucleotide polymorphism.

immunocompetent and immunocompromised children and adults (Table 1). Oka vaccine also boosted VZV-specific cell-mediated immunity (VZV-CMI) in immunocompetent and immunocompromised adults (Table 1). Routine childhood immunization has markedly reduced the incidence of varicella in the United States [59–62].

Live, attenuated Oka vaccines consist of a mixture of distinct VZV genotypes, which share several nucleotide substitutions that distinguish them from all wild-type strains of VZV (Table 1). Differences in strain content are observed among Oka vaccines produced by different manufacturers, and even among different batches from the same manufacturer (Table 1). This underlines the importance of genotyping VZV strains from vaccine-associated illnesses, including herpes zoster.

Pathogenesis. During primary infection, VZV, like HSV, establishes lifelong latent infections in sensory neurons without ganglionic pathology, likely by centripetal axonal transport from mucocutaneous sites of virus replication. In varicella, infection at the oropharyngeal portal of entry is silent; VZV infects tonsillar T cells, which transport virus to the skin, where innate immune responses delay VZV replication and rash formation (Table 2). Latent infection of sensory neurons is established by retrograde axonal transport from lesions in the skin or by infected T cells that reach the sensory ganglia hematogenously (Table 2). There are also major differences between VZV and HSV in the nature and control of latency and reactivation that have important implications for the development of effective preventive measures (Table 2).

During VZV latency, a restricted set of immediate early and early VZV genes are transcribed and the corresponding proteins are synthesized in latently infected neurons (Table 2). During HSV latency, transcription is restricted to latency-associated transcripts (LATs); no HSV proteins are synthesized (Table 2).

In VZV latency, symptomatic reactivation is infrequent, and there is no evidence that asymptomatic virus shedding contributes to VZV transmission. VZV reactivation results in a productive lytic infection that spreads within the ganglion, infecting and destroying many neurons (Figure 1 and Table 2). Consequently, the herpes zoster rash usually involves a large portion of the dermatome, and ganglionic pathology results in severe prodromal pain, sensory abnormalities, and PHN. It is not known whether VZV-CMI can prevent reactivation of latent VZV. However, subsequent replication and spread of VZV within the ganglion provides ample opportunity for VZV-CMI to inhibit the process before the development of herpes zoster (Table 2 and Figure 1).

HSV reactivation is frequent, with frequent virus shedding from sensory nerve endings at the dermal-epidermal junction. The small area of epithelium involved, usually limited to the sensory field of a single neuron, indicates that reactivation is restricted to individual neurons (Figure 1). The high frequency of recurrences without sensory loss or PHN indicates that HSV reactivates repeatedly without permanently damaging or destroying the latently infected neuron, or causing ganglionic pathology (Table 2 and Figure 1). In contrast to VZV, multiple symptomatic HSV recurrences occur in immunocompetent persons, and asymptomatic shedding is frequent, playing a major role in HSV transmission (Table 2).

RATIONALE FOR A VACCINE AGAINST HERPES ZOSTER

On the basis of his observation that the frequency and severity of herpes zoster and PHN increase with advancing age, Hope-Simpson [12] hypothesized that immunity to VZV, induced by varicella, prevents the development of herpes zoster. He further hypothesized that this immunity gradually decreases over time, but is periodically boosted by exogenous exposure to varicella and by subclinical reactivations of endogenous latent VZV that are contained by host immunity. Eventually, however, VZV immunity falls below some critical level, permitting latent VZV to reactivate, proliferate within the sensory ganglion, and cause herpes zoster. Noting the relative rarity of second episodes of herpes zoster, Hope-Simpson concluded that virus replication during herpes zoster boosted immunity to VZV, effectively immunizing against a second episode. He calculated that 50% of persons who lived to 85 years of age would experience an episode of herpes zoster, but only 1% would experience another episode. In the Shingles Prevention Study, there were only 2 second episodes of herpes zoster among the 642 placebo recipients who developed herpes zoster [18], indicating that the risk of developing a second episode of herpes zoster was at least 10-fold lower than the risk of developing the first episode.

When Hope-Simpson formulated his remarkable hypothesis, CMI and humoral immunity were not clearly differentiated, but we now recognize that the essential component responsible for protection against herpes zoster is VZV-CMI, which declines progressively with advancing age. It thus seemed possible that if we could mimic the boost in VZV-CMI induced by herpes zoster with a VZV vaccine, we might be able to protect older adults from herpes zoster and PHN.

THE CHALLENGE OF VACCINATING AGAINST HERPES ZOSTER

Varicella vaccine, like other vaccines against common childhood viral diseases, such as measles, mumps, and rubella, is administered to susceptible persons prior to exogenous exposure to the virus, inducing immunity that prevents primary infection and disease. We expect such vaccines to have $\geqslant$95% efficacy and induce herd immunity.

Vaccination against herpes zoster is directed at persons who have already experienced primary VZV infection in whom disease prevention requires changing the host-virus relationship.

Table 2. Pathophysiology of Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Latency and Reactivation

Characteristic	HSV	VZV	References
Primary infection	Primary infections include acute herpetic gingivostomatitis, primary genital herpes, acute herpetic keratoconjunctivitis, herpetic whitlow, and herpes gladiatorum Disease is manifest at the portal of entry (oropharynx, genitalia, skin) The majority of primary infections are asymptomatic The incubation period is short (usually 2–5 days) HSV is able to evade certain innate and adaptive host immune responses HSV replicates in and damages epithelial cells at the portal of entry, where innate and adaptive immune responses eventually control HSV replication	Primary infection causes varicella Disease is manifest at a distance from the portal of entry; >95% of primary infections are symptomatic The incubation period is long (usually ~14 days) VZV is able to evade certain innate and adaptive host immune responses VZV infects T cells in the tonsils T cell–associated viremia spreads VZV to the skin, where innate and adaptive immune responses impede virus replication and delay the onset of the varicella rash Innate and adaptive immune responses eventually control VZV replication	[6, 11, 21–23, 59, 79–104]
Establishment of latency	Retrograde axonal transport from infected skin and/or mucous membranes to sensory neurons innervating the site of primary infection	Retrograde axonal transport from skin lesions to sensory neurons innervating the skin involved in the varicella rash; T cell–associated viremia may also carry VZV to the sensory neurons during the incubation period	[6–11, 21–23, 57–59, 62, 79–83]
Site of latent infection	Sensory neurons, primarily in the trigeminal and/or sacral ganglia; 2%–10% of neurons contain episomal HSV DNA	Sensory neurons in the trigeminal and most dorsal root (sensory) ganglia; 1%–7% of neurons contain episomal VZV DNA	[6, 11–23, 79–81, 83, 105–109]
Viral gene expression during latency	Multiple copies of LATs in the nucleus of the latently infected neuron; no detectable HSV proteins or virus replication	⩾6 immediate early and early VZV transcripts; ⩾6 immediate early and early VZV proteins, but they fail to localize to the nucleus; no late VZV proteins or virus replication	[6, 21–23, 105, 110–123]
Reactivation	Frequent in individual sensory neurons No spread of infection within the sensory ganglion (Figure 1) Anterograde axonal transport to the periphery from one infected sensory neuron	Infrequent Results in lytic infection with spread to satellite cells and other sensory neurons within the ganglion (Figure 1) Anterograde axonal transport to the periphery from multiple infected sensory neurons	(Figure 1) [6, 11–19, 21–23, 62, 79–81, 105, 133, 138–140]
Ganglionic pathology	None	Extensive; hemorrhagic necrosis; later fibrosis	(Figure 1) [6, 11, 21, 23, 133, 138–140]
Postherpetic neuralgia	Virtually never	Common; incidence increases with increasing age	[6, 11, 13, 17–19, 21, 22, 63, 80, 138–144]
Fate of the neuron in which the latent virus reactivates	Sensory neuron survives to undergo repeated reactivation	Sensory neuron is destroyed	[6, 11, 19, 21, 22, 79–81, 129, 133, 138–140]
Proportion of the dermatome affected	Usually the sensory field of a single sensory neuron	A large portion of the dermatome, corresponding to the sensory fields of many sensory neurons	(Figure 1) [6, 11, 19, 21, 22, 79, 80, 133]
Control of reactivation	During latency, activated HSV-specific late effector memory $CD8^+$ T cells cluster around LAT-positive neurons, but without neuronal damage; peripheral shedding and the development of recurrent disease is controlled primarily by HSV-specific $CD8^+$ and $CD4^+$ T cells that infiltrate the skin and/or mucous membranes at the peripheral site of HSV infection; HSV-specific $CD8^+$ T cells persist adjacent to peripheral nerve endings at the dermal-epidermal junction for months after lesion healing, poised to inhibit virus replication and lesion formation when HSV arrives at the periphery	During latency, T cells in the sensory ganglion do not appear to "recognize" neurons latently infected with VZV; VZV-specific CMI may limit reactivation of latent VZV in the sensory neuron; following reactivation, VZV-specific CMI limits the development of herpes zoster by inhibiting the spread of VZV infection from the sensory neuron in which latent VZV reactivates to satellite cells and other neurons within the ganglion; VZV-specific $CD4^+$ and $CD8^+$ T cells are both involved, but $CD4^+$ T cells appear to be predominant	[21–23, 62, 79, 80, 86–105, 110–137, 144–151]
Recurrent infections	Herpes labialis, recurrent genital herpes, recurrent herpetic keratitis, recurrent herpetic whitlow, and recurrent cutaneous herpes Frequent symptomatic and asymptomatic recurrences in immunocompetent persons Most reactivation results in asymptomatic virus shedding The median shedding rate averages 25% of days	Herpes zoster Relatively uncommon; lifetime incidence is ~30% Second episodes are rare in immunocompetent persons	[6, 14–19, 21, 22, 79–81, 145, 146]
Person-to-person transmission	Person-to-person transmission is due primarily to contact with someone experiencing asymptomatic virus shedding	There is no evidence of asymptomatic virus shedding, except under extraordinary circumstances; transmission results from exposure to varicella or herpes zoster (with inhalation of aerosolized virus)	[2, 3, 6, 19, 21, 22, 59, 75, 77, 79, 80, 136, 145, 146, 152]
Effect of Age	Frequency of symptomatic and asymptomatic recurrences decreases over time (measured in years)	Incidence of herpes zoster and postherpetic neuralgia increase with increasing age	[2, 3, 6, 12–19, 21, 22, 59, 79, 138, 141–146, 153]

NOTE. CMI, cell-mediated immunity; LAT, latency-associated transcript.

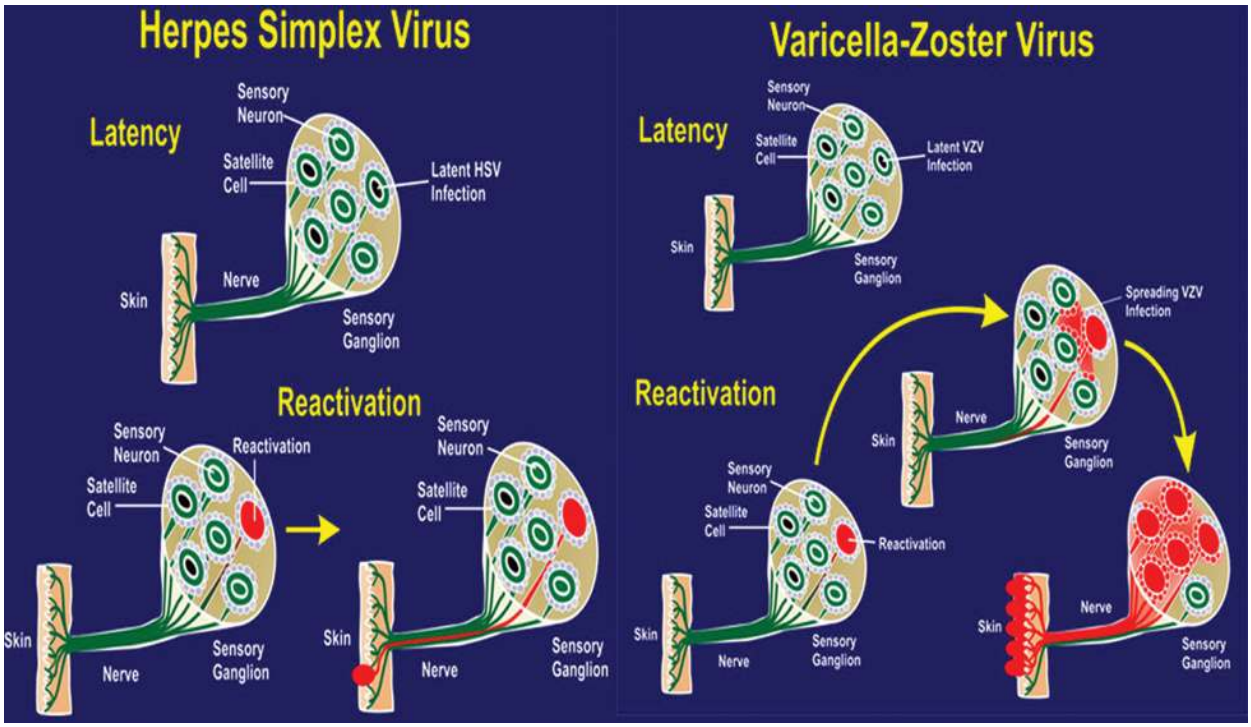

Figure 1. Herpes simplex virus (HSV) and varicella-zoster virus (VZV) latency and reactivation in the sensory ganglion. Neurons with black nuclei are latently infected. Red indicates reactivation and, in the case of VZV, spread of infection within the ganglion.

Zoster vaccine acts by boosting declining levels of preexisting CMI to VZV in older adults, thereby reducing the frequency and severity of a disease caused by reactivation and multiplication of endogenous latent VZV. We do not expect vaccines against such endogenous infections to approach 95% efficacy or to induce herd immunity. The natural history of herpes zoster described by Hope-Simpson [12] provides a model for successful "vaccination" of older adults against herpes zoster [138]. There is no comparable natural resistance to recurrent herpes simplex, which occurs repeatedly in immunocompetent persons [21, 23, 79–81, 145, 146].

EVIDENCE OF EFFICACY: EARLY STUDIES

Oka strains of live, attenuated VZV vaccine have been shown to boost VZV-CMI in older adults (Table 1). In addition, heat-inactivated Oka VZV vaccines were shown to boost VZV-CMI and reduce the frequency and severity of herpes zoster in bone marrow transplant recipients [155, 156]. These and Hope-Simpson's [12] seminal observations provided the impetus for a large-scale efficacy trial of live, attenuated Oka/Merck VZV vaccine (zoster vaccine) in older adults, the VA Cooperative Study 403: "The Shingles Prevention Study."

THE SHINGLES PREVENTION STUDY

Preliminary studies. Pain, the major cause of herpes zoster's morbidity in older persons, is subjective. Consequently, herpes zoster–specific assessment tools, the Zoster Brief Pain Inventory and Zoster Impact Questionnaire, were developed and validated to quantify pain and discomfort (eg, allodynia and severe pruritus) due to herpes zoster and to assess the impact of herpes zoster on activities of daily living and health-related quality of life [157, 158]. It was also necessary to accurately diagnose mild and atypical cases of herpes zoster, both to guarantee a valid natural history study among placebo recipients and to avoid biasing the study in favor of zoster vaccine by missing cases of modified herpes zoster among vaccine recipients [159]. Preliminary studies were conducted to establish the safety and immunogenicity of higher doses of Oka vaccine, select a dose that would boost VZV-CMI with minimal side effects, and verify its safety and efficacy in older subjects with the common comorbidities of diabetes mellitus and chronic obstructive pulmonary disease.

The Shingles Prevention Study. The Shingles Prevention Study was a placebo-controlled, double-blind trial in which 38,546 adults aged ⩾60 years were randomized to receive either Oka/Merck VZV vaccine (zoster vaccine) or placebo. Randomization was stratified by study site and age group (60–69 vs ⩾70 years of age). Subjects were actively observed for herpes zoster with the aid of an automated telephone response system. Details of the study design were published elsewhere [18, 63]. The primary end point was the burden of illness due to herpes zoster (HZ BOI), a severity-by-duration measure representing

the total herpes zoster–associated pain and discomfort in a population of subjects. The secondary end point was the incidence of clinically significant PHN. The incidence of herpes zoster was also determined. Minimum potency of zoster vaccine used in the Shingles Prevention Study was at least 14 times the minimum potency of varicella vaccine [18].

Results. Zoster vaccine reduced the HZ BOI by 61.1%, the incidence of PHN by 66.5%, and the incidence of herpes zoster by 51.3% (Table 3). Zoster vaccine also reduced the negative impact of herpes zoster on activities of daily living and health-related quality of life to a degree comparable to its reduction in HZ BOI (Figure 2) [160, 161], providing independent evidence that HZ BOI is a valid measure of the total adverse impact of herpes zoster on the older adults in the Shingles Prevention Study.

In the younger age stratum, most of the benefit of zoster vaccine resulted from a reduction in the incidence of herpes zoster. In the older age stratum, much of the benefit of zoster vaccine resulted from a reduction in the severity of the disease and in the incidence of PHN (Table 4). However, because of the greater incidence and severity of herpes zoster and PHN in the older age stratum, the absolute benefit of zoster vaccine was greater in these older subjects.

Zoster vaccine was well tolerated and neither induced nor caused herpes zoster [18, 63]. A more detailed analysis of adverse events confirmed the safety of zoster vaccine in the entire Shingles Prevention Study population, including subjects $\geqslant$80 years of age [64]. Zoster vaccine was also safe and well tolerated when administered to 384 placebo recipients who had documented herpes zoster during the Shingles Prevention Study (M. N. Oxman, G. R. Johnson, M. J. Levin, Shingles Prevention Study Group; unpublished data).

Long-term follow-up of a subset of Shingles Prevention Study vaccine recipients continues to determine the duration of zoster vaccine efficacy. Results to date indicate that efficacy is maintained for at least 6 years after vaccination [162].

LABORATORY CORRELATES OF CLINICAL EFFICACY

In the Shingles Prevention Study, analysis of immune responses at baseline demonstrated that the previously well-documented age-related decline in VZV-CMI continued in our older Shingles Prevention Study population, and confirmed that levels of VZV antibody did not decline with age (Table 5 and Figure 3). The VZV-CMI responses to zoster vaccine 6 weeks after vaccination also decreased with age and were significantly lower in the older age stratum. In contrast, there was no significant difference in the VZV antibody response to zoster vaccine in the 2 age strata [154].

Higher levels of VZV-CMI were associated with a reduced risk of herpes zoster in both vaccine and placebo recipients. Although VZV-CMI responses were clearly protective, no threshold level providing protection from herpes zoster was identified [154].

The results of the 2 assays of VZV-CMI (the responder cell frequency assay and the interferon-γ enzyme-linked immunospot assay) were correlated with each other at baseline and at all time points after zoster vaccine or placebo administration (Spearman rank correlations, 0.38 to 0.61), whereas the levels of antibody to VZV (measured by VZV glycoprotein enzyme-linked immunosorbent assay) did not correlate with the results of either VZV-CMI assay at any time point (Spearman rank correlations, -0.05 to 0.13) [154]. This is not surprising, since CMI and antibodies to VZV are induced by different VZV epitopes [22, 149].

In Shingles Prevention Study subjects who developed herpes zoster, higher levels of VZV-CMI at rash onset were associated with reduced herpes zoster severity and decreased occurrence of PHN, whereas increased levels of antibody to VZV correlated with more severe herpes zoster and increased risk of PHN [163]. Of note, herpes zoster and zoster vaccine appeared to induce similar levels of VZV-CMI [163].

The critical dichotomy in the roles of VZV-CMI and antibody to VZV is underlined by experience in immunocompromised patients (Table 5). Diseases and treatments causing significant decrements in VZV-CMI are associated with marked increases in the incidence of herpes zoster and in herpes zoster severity, and in the magnitude and duration of VZV replication (Table 5). Substantial decrements in VZV-CMI are also associated with multiple recurrences, chronic atypical cutaneous lesions, cutaneous and visceral dissemination, and the selection of VZV mutants resistant to antiviral agents [22, 190, 191]. In contrast, congenital and acquired agammaglobulinemias are not associated with increased risk or severity of herpes zoster and its complications, and administration of antibody to VZV does not ameliorate the marked increase in the frequency and severity of herpes zoster in bone marrow allograft recipients and other patients with severely compromised VZV-CMI (Table 5).

THE FALLACY OF USING ANTIBODY TO VZV AS A PROXY FOR ZOSTER VACCINE EFFICACY

The data summarized above and in Table 5 indicate that increased levels of VZV-CMI provide protection against herpes zoster and are associated with less severe disease and a lower risk of PHN. Increased levels of antibody to VZV do not confer protection against herpes zoster or PHN. In fact, increased levels of antibody to VZV after the onset of herpes zoster are associated with more severe disease and greater risk of PHN, probably because they reflect more extensive VZV replication [163]. Thus, the use of VZV antibody response as a proxy for zoster vaccine efficacy is clearly unjustified.

Table 3. Efficacy of Zoster Vaccine in the Shingles Prevention Study

	Zoster vaccine				Placebo				Efficacy of zoster vaccine[b]		
Age group, years[a]	No. of subjects	No. of cases of HZ	No. of cases of PHN	Percentage of HZ patients with PHN	No. of subjects	No. of cases of HZ	No. of cases of PHN	Percentage of HZ patients with PHN	HZ incidence, % (95% CI)	PHN incidence, % (95% CI)	HZ BOI, % (95% CI)[c]
60–69	10,370	122	8	6.6	10,356	334	23	6.9	63.9 (55.5–70.9)	65.7 (20.4–86.7)	65.5 (51.5–75.5)
⩾70	8,884	193	19	9.8	8,891	308	57	18.5	37.6 (25.0–48.1)	66.8 (43.3–81.3)	55.4 (39.9–66.9)
Total	19,254	315	27	8.6	19,247	642	80	12.5	51.3 (44.2–57.6)	66.5 (47.5–79.2)	61.1 (51.1–69.1)

NOTE. Data are from [18]. The analysis was performed on the modified intent-to-treat population, which included all subjects randomized in the study who were observed for at least 30 days after vaccination and who did not develop an evaluable case of herpes zoster (HZ) within the first 30 days after vaccination. For the Shingles Prevention Study end point, postherpetic neuralgia (PHN) was defined as HZ-associated pain and discomfort rated as three or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) using the Zoster Brief Pain Inventory, that persisted or appeared more than 90 days after HZ rash onset. BOI, burden of illness; CI, confidence interval.

[a] Age strata at randomization were 60–69 and ⩾70 years of age.

[b] Vaccine efficacy is expressed as the percentage reduction in vaccine, compared with placebo recipients.

[c] For each evaluable case of HZ, the Zoster Brief Pain Inventory (ZBPI) data were used to calculate an HZ severity-of-illness score, defined as the area under the ZBPI "worst pain" response–versus–time curve during the 182-day minimum follow-up period. The HZ severity-of-illness score was defined as 0 for subjects who did not develop HZ during the study. The primary Shingles Prevention Study end point was the BOI due to HZ, a severity-by-duration measure representing the total HZ-associated pain and discomfort in a population of study subjects. The HZ BOI is the sum of the HZ severity-of-illness scores for all members of the group (vaccine or placebo recipients) and measures any effect of zoster vaccine on the incidence of HZ, the severity of HZ pain and discomfort, and/or the duration of HZ pain and discomfort.

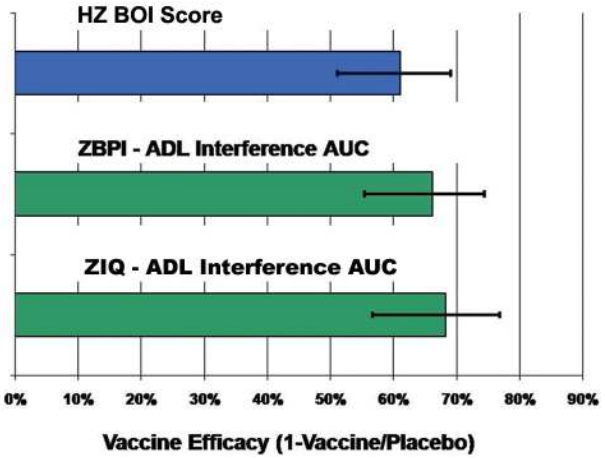

Figure 2. Zoster vaccine efficacy for herpes zoster (HZ) burden of illness (BOI) and activities of daily living (ADL) interference end points among 38,501 subjects. AUC, area under the curve. From [160]

Therefore, in the absence of efficacy trials, decisions regarding new zoster vaccine formulations and use should be based on evidence of the induction of immune responses in humans that are physiologically relevant to herpes zoster—namely, VZV-CMI (Table 5). Attempts to assess the efficacy of vaccines against herpes zoster using VZV antibody assays may provide erroneous information.

POTENTIAL IMPROVEMENTS IN ZOSTER VACCINES AND THEIR USE

Current recommendations. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends zoster vaccine for all persons aged ⩾60 years who have no contraindications, including persons reporting a previous episode of herpes zoster or who have chronic medical conditions [19]. However, in December 2009, the US Food and Drug Administration approved a revision to the Zostavax (Merck) package insert stating that "ZOSTAVAX® and PNEUMOVAX 23® should not be given concurrently because concomitant use resulted in reduced immunogenicity of ZOSTAVAX®" [192, p 1]. This unwarranted decision (the only measure of immunogenicity was antibody to VZV measured by VZV glycoprotein enzyme-linked immunosorbent assay) [193] complicates efforts to follow CDC/ACIP recommendations to administer zoster vaccine to all persons ⩾60 years of age without contraindications [19].

Increased efficacy in immunocompetent persons. The current zoster vaccine provides substantial protection against herpes zoster and PHN [18, 63], but a vaccine with greater efficacy would be desirable. This might be accomplished by administering ⩾1 dose of a higher-potency vaccine [163, 194]. Safety and tolerability of a zoster vaccine containing >8 times the median potency of the zoster vaccine used in the Shingles Prevention Study have been reported [195]. Other approaches might include the design of live attenuated VZV vaccines that selectively express or over-express epitopes that stimulate VZV-CMI [149, 151], the incorporation of those epitopes into other vectors, such as vaccinia, an attenuated cytomegalovirus vaccine, or yellow fever vaccines, and the use of toll-like receptor ligands and cytokines as adjuvants.

Vaccination of immunocompromised patients. Oka vaccine is the most attenuated of all currently licensed live, attenuated virus vaccines, and it has been safely administered to VZV-susceptible and VZV-seropositive children and adults, including susceptible children with human immunodeficiency virus 1 (HIV-1) infection and leukemia [19]. The biology of primary VZV infection provides an additional margin of safety for zoster vaccine; even highly immunocompromised persons with a history of natural varicella rarely develop a second episode when exposed to exogenous virus [6–11, 181, 183–185, 190]. Most cases presumed to be second episodes of varicella in immunocompromised patients have been cases of disseminated herpes zoster, sometimes occurring before or in the absence of a typical dermatomal herpes zoster rash. Thus, it appears that the current zoster vaccine could be safely administered to several groups of adult patients who are moderately immunosuppressed, such as VZV-seropositive HIV-1 infected patients with $CD4^+$ T cell counts ⩾200 cells/μL, or to patients with rheumatoid arthritis or psoriasis receiving moderate doses of methotrexate, corticosteroids, or tumor necrosis factor inhibitors [19, 196–199]. A trial of safety and immunogenicity of zoster vaccine in HIV-1–infected patients who are receiving antiretroviral therapy is underway, but studies involving other immunocompromised patient populations are warranted. The Oka vaccine strain of VZV is fully susceptible to acyclovir, famciclovir, and valacyclovir; thus, effective antiviral therapy is available if complications involving vaccine virus replication occur.

Inactivated zoster vaccines for administration to immunocompromised patients. Heat-inactivated VZV vaccine has been safely administered to autologous bone marrow transplant recipients, in whom it accelerated recovery of VZV-CMI and reduced the occurrence of herpes zoster [155, 156]. Encouraged by these results, several groups are exploring the development of inactivated VZV vaccines, with and without adjuvants, to permit immunization of profoundly immunosuppressed patients.

SPECIAL CONSIDERATIONS AND UNANSWERED QUESTIONS

Immunization with zoster vaccine before immunosuppression. Administration of zoster vaccine is recommended 2 weeks (preferably 4 weeks) before planned therapeutic immunosuppression

Table 4. Efficacy of Zoster Vaccine for the Incidence of Postherpetic Neuralgia (PHN) in the Shingles Prevention Study, by Duration of Pain after Onset of Herpes Zoster (HZ) Rash

Definition of PHN by duration of pain after HZ rash onset	Zoster vaccine		Placebo		Zoster vaccine efficacy, % (95% CI)
	No. of confirmed cases of HZ with PHN	Incidence of PHN per 1000 person-years[a]	No. of confirmed cases of HZ with PHN	Incidence of PHN per 1000 person-years[a]	
>30 days	81	1.39	196	3.39	58.9 (46.6–68.7)
>60 days	45	0.77	113	1.96	60.4 (43.6–72.6)
>90 days	27	0.46	80	1.38	66.5 (47.5–79.2)
>120 days	17	0.29	54	0.93	68.7 (45.2–83.0)
>182 days	9	0.16	33	0.57	72.9 (42.1–88.6)

NOTE. For the Shingles Prevention Study end point, postherpetic neuralgia (PHN) was defined as HZ-associated pain and discomfort rated as ⩾3, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), using the Zoster Brief Pain Inventory, that persisted or appeared more than 90 days after HZ rash onset. Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded persons who withdrew or in whom a confirmed case of herpes zoster developed, within the first 30 days after vaccination. Of the 3 persons who developed >1 confirmed case of HZ, only the first case was included. For additional analyses, PHN was defined as HZ-associated pain and discomfort rated as ⩾3, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), using the Zoster Brief Pain Inventory, that persisted or appeared more than 30, 60, 120, or 182 days after the HZ rash onset. Used with permission from [18]. CI, confidence interval.

[a] The incidence of PHN in each treatment group (vaccine or placebo) was the weighted average of the observed incidence of PHN, with weights proportional to the total number of person-years of follow-up.

[19]. Although the efficacy of zoster vaccine under these circumstances in unknown, the risk is minimal and the potential advantages obvious.

Administration of zoster vaccine to household contacts of immunocompromised patients. Transmission of vaccine virus from recipients of zoster vaccine to susceptible household contacts has not been documented. Thus immunocompetent older adults in contact with immunosuppressed patients should receive zoster vaccine to reduce the risk that they will develop herpes zoster and transmit wild-type VZV to their susceptible immunosuppressed contacts [19]. For the same reasons, adult contacts of susceptible pregnant women and infants should receive zoster vaccine [19]. Eligible residents and personnel in nursing homes and other facilities housing older adults should also be vaccinated against herpes zoster. However, VZV-seronegative persons (eg, health care workers from tropical countries who have not had varicella) should be vaccinated against varicella.

Donation of blood and blood products by recipients of zoster vaccine. There is little evidence of significant or prolonged viremia following administration of zoster vaccine [19, 22]. Consequently, it should be considered safe for immunocompetent zoster vaccine recipients to donate blood and blood products, including platelets, within 3–6 weeks after vaccination. The risk of transmitting vaccine virus is likely far lower than the risk of reactivation and transmission of latent wild-type VZV by older donors.

Administration of zoster vaccine to persons aged <60 years. Currently, zoster vaccine is not licensed for persons aged <60 years [19, 192]. Nevertheless, zoster vaccine would almost certainly be safe and effective in persons aged <60 years [200], although such persons might require a booster dose at a younger age than do persons who are vaccinated at ⩾60 years of age.

Effect on herpes zoster epidemiology of universal childhood immunization with varicella vaccine. Recipients of varicella vaccine have a substantially lower incidence of herpes zoster than persons infected with wild-type VZV [201–204]. If this persists throughout adulthood, recipients of varicella vaccine may be expected to have a lower lifetime risk of herpes zoster than persons who experienced natural varicella.

Second "breakthrough" episodes of varicella are not uncommon in recipients of varicella vaccine, whereas they are very rare in persons with a history of varicella caused by wild-type VZV [59]. Thus, varicella vaccine recipients who later become immunosuppressed may be susceptible to second episodes of varicella.

If exogenous exposure to VZV is important in delaying the age-dependent decline in VZV-CMI, we may expect an increase in the incidence of herpes zoster in younger adults because widespread vaccination against varicella will markedly reduce their exogenous exposure to VZV. Since herpes zoster is less severe in younger adults, this might reduce the total adverse impact of herpes zoster in the population already latently infected with wild-type VZV. However, if the protection against second episodes of herpes zoster is not long lasting, the net result could be many more second episodes of herpes zoster in older adults. The answer to this complex set of related unknowns will only come from careful long-term epidemiological observations of the sort that have been initiated by Jane Seward and her colleagues at the CDC [19, 204]. The availability of

Table 5. Evidence that Varicella-Zoster Virus (VZV)–Specific Cell-Mediated Immunity (CMI), But Not Antibodies to VZV, Correlates with the Risk and Severity of Herpes Zoster (HZ) and Postherpetic Neuralgia (PHN)

Population	Observation	VZV-specific CMI	Antibody to VZV	References
General	Epitopes and mechanisms for induction of CMI and antibodies to pathogens differ	T cell receptors recognize linear peptides produced in host cells by breakdown of proteins of the pathogen, which are bound to MHC molecules, and presented on the cell surface as complexes of the foreign peptide and a MHC molecule	B cell receptors mainly recognize conformational epitopes on surface antigens of extracellular pathogens; the B cell receptor has the same specificity as the antibody produced	[131, 132, 135, 149, 151, 164–169]
Immunocompetent persons of all ages	Incidence and severity of HZ increase with increasing age	Levels of VZV-specific CMI decrease with increasing age	Levels of antibody to VZV are well-maintained in older persons	[12–17, 138, 154, 170–176]
Immunocompetent persons ⩾60 years of age	Incidence and severity of HZ and PHN increase with increasing age	The age-related decline in VZV-specific CMI continues in persons ⩾60 years of age	Levels of antibody to VZV do not decline with increasing age in persons ⩾60 years of age	[154]
Immunocompetent recipients of zoster vaccine or placebo who developed HZ	Correlation of levels of VZV-specific CMI and of antibody to VZV with severity of HZ and incidence of PHN	Higher levels of VZV-specific CMI early after HZ onset correlated with less severe HZ and a lower incidence of PHN	Higher levels of antibody to VZV after HZ onset correlated with more severe HZ and a higher incidence of PHN	[163]
Immunocompromised patients	Markedly increased incidence and severity of HZ	Reduced levels of VZV-specific CMI are correlated with increased risk of HZ	Levels of antibody to VZV are not correlated with increased risk of HZ	[176–181]
Bone marrow transplant recipients	Posttransplantation development of HZ	Posttransplantation development of VZV-specific CMI correlated with reduced risk of post-transplant HZ	Levels of antibody to VZV are not correlated with risk of posttransplantation HZ	[9, 182–185]
Bone marrow transplant recipients immunized with heat-inactivated VZV vaccine or placebo	VZV vaccine recipients have reduced incidence and severity of HZ	Increased levels of VZV-specific CMI are associated with a proportional reduction in the incidence and severity of posttransplantation HZ	Titers of antibody to VZV comparable in vaccine and placebo recipients; titers of antibody to VZV are not predictive of risk or severity of posttransplantation HZ	[155, 156]
Patients with X-linked agammaglobulinemia	In the absence of antibody replacement therapy, no difficulty resolving varicella and no recurrence of varicella on repeated intimate exposure to varicella. Anecdotal experience does not suggest any increased risk of HZ	Intact CMI	Absent antibody production	[186–189]

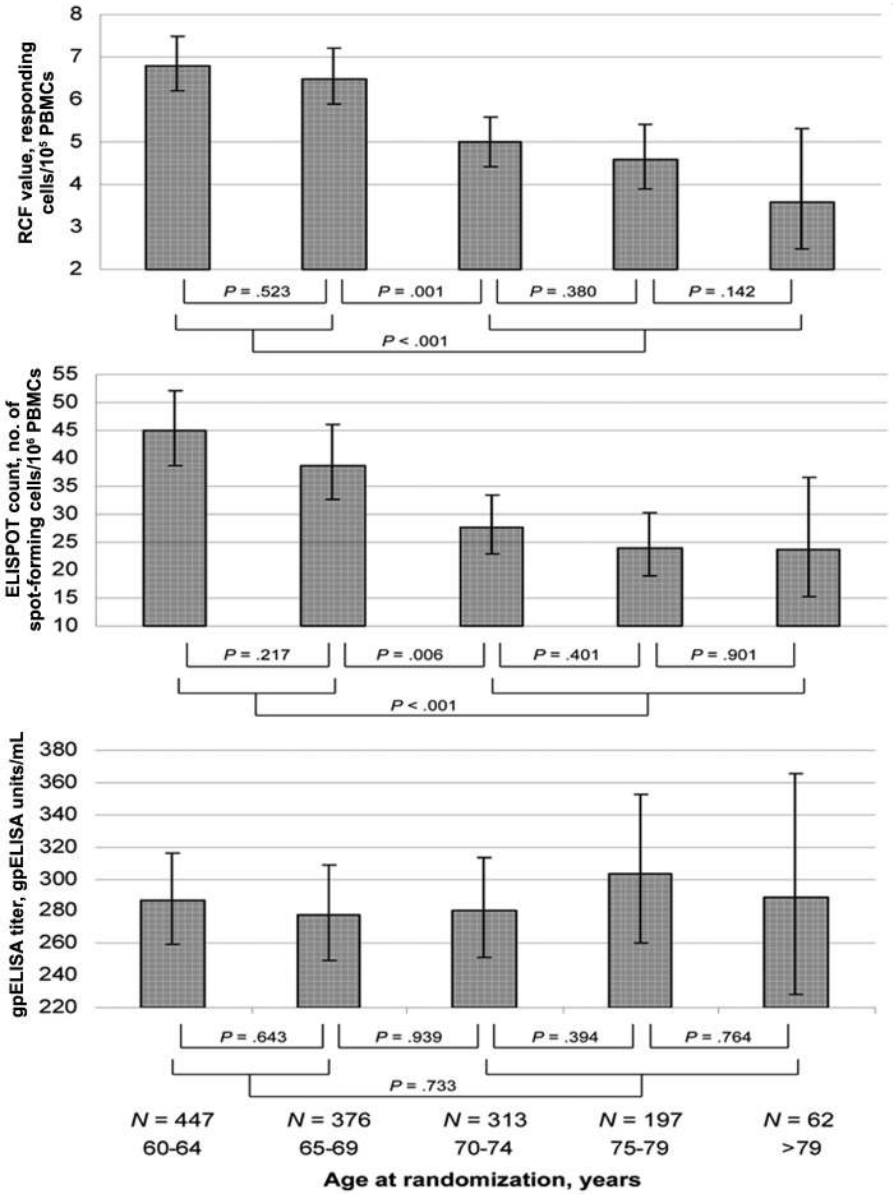

Figure 3. Baseline levels of immunity to varicella-zoster virus in the Shingles Prevention Study. Varicella-zoster virus–specific immune responses are shown at baseline (ie, prior to vaccination), according to age group. *Error bars,* 95% confidence intervals for the geometric mean. *N,* number of subjects who had blood samples collected in the age group. *P* values for differences between age groups are shown below the graphs. Adapted from [154]. ELISPOT, interferon-γ enzyme-linked immunospot assay; gpELISA, VZV glycoprotein enzyme-linked immunosorbent assay; PBMC, peripheral blood mononuclear cell; RCF, responder cell frequency.

effective zoster vaccines should enable us to mitigate any adverse consequences of this changing epidemiology.

BARRIERS TO IMMUNIZATION OF OLDER ADULTS WITH ZOSTER VACCINE

Need to maintain zoster vaccine at temperatures of −15°C or lower. Lyophilized zoster vaccine must be maintained at temperatures of −15°C or lower and reconstituted and administered ≤30 min after removal from the freezer [19, 192]. This presents a significant problem, because physicians caring for older adults often lack ready access to freezers. Fortunately, a refrigerator-stable product appears to be on the horizon [205].

Additional barriers. There are a number of additional barriers to immunization of older adults with zoster vaccine and other recommended vaccines [206–211]. The most important determinant is the health care provider's attitude toward vaccination. If the provider recommends the vaccine, most patients are vaccinated; if not, few are. Reasons for lack of provider advocacy include doubts (shared by many older patients) about vaccine efficacy, related to the fact that, like most vaccines

recommended for adults, zoster vaccine provides only partial protection, in contrast to the almost complete protection provided by most vaccines administered to children. Failure of both physicians and patients to recognize that herpes zoster and PHN cause a significant burden of disease in older adults leads to the conclusion that zoster vaccine is not needed. Lack of information on the duration of protection adds further uncertainty, as do concerns about safety and side effects. Lack of reimbursement for vaccine administration and concerns regarding out-of-pocket costs for the patient, both related to coverage by Medicare Part D, rather than Part B, are additional negative factors. Another concern, reduced immunogenicity and efficacy in older patients, should be offset by the realization that the incidence and severity of herpes zoster, especially PHN, are markedly increased in these older patients. Consequently, despite a relative reduction in vaccine efficacy, the absolute benefit of vaccination for very elderly persons may be comparable or even greater than that obtained by younger vaccine recipients. Finally, the lack of opportunities to immunize older patients can be mitigated by concomitant administration of $\geqslant 2$ vaccines during a single encounter.

FUTURE DIRECTIONS

The immediate future should see the extension of safety and immunogenicity testing of the currently licensed zoster vaccine to populations of moderately immunocompromised patients, hopefully with the inclusion of assays of VZV-CMI to assess physiologically relevant immunogenicity. Also, assessment of the safety and immunogenicity of higher-titer zoster vaccine should occur without delay. Another priority should be the evaluation of inactivated VZV vaccines (with and without adjuvants) in more profoundly immunocompromised patients. Hopefully, adjuvants containing selected toll-like receptor ligands and cytokines will target VZV more specifically and increase relevant immune responses. The next step should be the development of new classes of vaccines and vectors incorporating selected VZV epitopes that induce VZV-CMI rather than antibodies to VZV. The end result should be the virtual elimination of herpes zoster caused by wild-type VZV.

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References

1. Bruusgaard E. The mutual relation between zoster and varicella. Br J Derm **1932**; 44:1–24.
2. Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med **1983**; 309(22):1362–1368.
3. Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med **1983**; 309(23):1434–1440.
4. Straus SE, Reinhold W, Smith HA, et al. Endonuclease analysis of viral DNA from varicella and subsequent zoster infections in the same patient. N Engl J Med **1984**; 311(21):1362–1364.
5. Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. J Med Virol **2003**; 70(suppl 1):S111–S118.
6. Oxman MN. Varicella and herpes zoster. In: Fitzpatrick TB, ed. Dermatology in general medicine. 1st ed. Boston: McGraw-Hill, **1979**: 1600–1616.
7. Gershon AA, Steinberg SP, Gelb L. Clinical reinfection with varicella-zoster virus. J Infect Dis **1984**; 149(2):137–142.
8. Schimpff S, Serpick A, Stoler B, et al. Varicella-zoster infection in patients with cancer. Ann Intern Med **1972**; 76(2):241–254.
9. Ljungman P, Lonnqvist B, Gahrton G, Ringden O, Sundqvist VA, Wahren B. Clinical and subclinical reactivations of varicella-zoster virus in immunocompromised patients. J Infect Dis **1986**; 153(5):840–847.
10. Rusthoven JJ, Ahlgren P, Elhakim T, et al. Varicella-zoster infection in adult cancer patients: a population study. Arch Intern Med **1988**; 148(7):1561–1566.
11. Oxman MN. Clinical manifestations of herpes zoster. In: Arvin AM, Gershon AA, eds. Varicella-zoster virus: virology and clinical management. Cambridge, UK: Cambridge University Press, **2000**:246–275.
12. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med **1965**; 58:9–20.
13. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) **1982**; 61(5):310–316.
14. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med **1995**; 155(15):1605–1609.
15. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect **2001**; 127(2):305–314.
16. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med **2005**; 20(8):748–753.
17. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc **2007**; 82(11):1341–1349.
18. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **2005**; 352(22):2271–2284.
19. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep **2008**; 57(RR-5):1, 30; quiz CE2–4.

20. Pellett P, Roizman B. The family herpesviridae: a brief introduction. In: Knipe D, Howley P, eds. Fields virology. 5th ed. Vol. 2. Philadelphia: Lippincott Williams and Wilkins, **2007**:2479–2499.
21. Roizman B, Knipe DM, Whitley RJ. Herpes simplex viruses. In: Knipe D, Howley P, eds., eds. Fields virology. 5th ed. ed. Vol. Vol. 2. Philadelphia: Lippincott Williams & Wilkins, **2007**:2502–2601.
22. Cohen JI, Straus SE, Arvin AM. Varicella-zoster virus replication, pathogenesis and management. In: Knipe D, Howley P, eds. Fields virology. 5th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins, **2007**:2744–2818.
23. Rouse BT, Kaistha SD. A tale of 2 alpha-herpesviruses: lessons for vaccinologists. Clin Infect Dis **2006**; 42(6):810–817.
24. Gomi Y, Sunamachi H, Mori Y, Nagaike K, Takahashi M, Yamanishi K. Comparison of the complete DNA sequences of the Oka varicella vaccine and its parental virus. J Virol **2002**; 76(22):11447–11459.
25. Quinlivan M, Hawrami K, Barrett-Muir W, et al. The molecular epidemiology of varicella-zoster virus: evidence for geographic segregation. J Infect Dis **2002**; 186(7):888–894.
26. Barrett-Muir W, Scott FT, Aaby P, et al. Genetic variation of varicella-zoster virus: evidence for geographical separation of strains. J Med Virol **2003**; 70(suppl 1):42–47.
27. Loparev VN, Rubtcova EN, Bostik V, et al. Identification of five major and two minor genotypes of varicella-zoster virus strains: a practical two-amplicon approach used to genotype clinical isolates in Australia and New Zealand. J Virol **2007**; 81(23):12758–12765.
28. Norberg P, Liljeqvist JA, Bergstrom T, Sammons S, Schmid DS, Loparev VN. Complete-genome phylogenetic approach to varicella-zoster virus evolution: Genetic divergence and evidence for recombination. J Virol **2006**; 80(19):9569–9576.
29. Breuer J, Grose C, Norberg P, Tipples G, Schmid DS. A proposal for a common nomenclature for viral clades that form the species varicella-zoster virus: summary of VZV Nomenclature Meeting 2008, Barts and the London School of Medicine and Dentistry, 24–25 July 2008. J Gen Virol **2010**; 91(Pt 4):821–828.
30. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet **1974**; 2(7892):1288–1290.
31. Takahashi M, Okuno Y, Otsuka T, Osame J, Takamizawa A. Development of a live attenuated varicella vaccine. Biken J **1975**; 18(1):25–33.
32. Takahashi M, Asano Y, Kamiya H, et al. Development of varicella vaccine. J Infect Dis **2008**; 197(suppl 2):41–44.
33. Gomi Y, Imagawa T, Takahashi M, Yamanishi K. Oka varicella vaccine is distinguishable from its parental virus in DNA sequence of open reading frame 62 and its transactivation activity. J Med Virol **2000**; 61(4):497–503.
34. Gomi Y, Imagawa T, Takahashi M, Yamanishi K. Comparison of DNA sequence and transactivation activity of open reading frame 62 of Oka varicella vaccine and its parental viruses. Arch Virol Suppl **2001**; 17(17):49–56.
35. Gomi Y, Ozaki T, Nishimura N, et al. DNA sequence analysis of varicella-zoster virus gene 62 from subclinical infections in healthy children immunized with the Oka varicella vaccine. Vaccine **2008**; 26(44):5627–5632.
36. Moriuchi M, Moriuchi H, Straus SE, Cohen JI. Varicella-zoster virus (VZV) virion-associated transactivator open reading frame 62 protein enhances the infectivity of VZV DNA. Virology **1994**; 200(1):297–300.
37. Yamanishi K. Molecular analysis of the Oka vaccine strain of varicella-zoster virus. J Infect Dis **2008**; 197(suppl 2):S45–S48.
38. Quinlivan M, Gershon AA, Steinberg SP, Breuer J. An evaluation of single nucleotide polymorphisms used to differentiate vaccine and wild type strains of varicella-zoster virus. J Med Virol **2005**; 75(1):174–180.
39. Parker SP, Quinlivan M, Taha Y, Breuer J. Genotyping of varicella-zoster virus and the discrimination of Oka vaccine strains by TaqMan real-time PCR. J Clin Microbiol **2006**; 44(11):3911–3914.
40. Breuer J, Quinlivan M, Al Bassam M, et al. DNA sequence variability in Oka vaccine isolates. J Infect Dis **2007**; 196(5):801–802.
41. Takahashi M. Clinical overview of varicella vaccine: development and early studies. Pediatrics **1986**; 78(4 Pt 2):736–741.
42. Asano Y, Nagai T, Miyata T, et al. Long-term protective immunity of recipients of the Oka strain of live varicella vaccine. Pediatrics **1985**; 75(4):667–671.
43. Takahashi M, Iketani T, Sasada K, et al. Immunization of the elderly and patients with collagen vascular diseases with live varicella vaccine and use of varicella skin antigen. J Infect Dis **1992**; 166(suppl 1):58–62.
44. Takahashi M, Okada S, Miyagawa H, et al. Enhancement of immunity against VZV by giving live varicella vaccine to the elderly assessed by VZV skin test and IAHA, gpELISA antibody assay. Vaccine **2003**; 21(25–26):3845–3853.
45. Gershon AA. Live-attenuated varicella vaccine. Infect Dis Clin North Am **2001**; 15(1):65, 81, viii.
46. Weibel RE, Neff BJ, Kuter BJ, et al. Live attenuated varicella virus vaccine. efficacy trial in healthy children. N Engl J Med **1984**; 310(22): 1409–1415.
47. Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. Pediatrics **1986**; 78(4 Pt 2):748–756.
48. Gershon AA, Steinberg SP, LaRussa P, Ferrara A, Hammerschlag M, Gelb L. Immunization of healthy adults with live attenuated varicella vaccine. J Infect Dis **1988**; 158(1):132–137.
49. Berger R, Luescher D, Just M. Enhancement of varicella-zoster-specific immune responses in the elderly by boosting with varicella vaccine. J Infect Dis **1984**; 149(4):647–.
50. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis **1992**; 166(2):253–259.
51. Levin MJ, Barber D, Goldblatt E, et al. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis **1998**; 178(suppl 1):109–112.
52. Trannoy E, Berger R, Hollander G, et al. Vaccination of immunocompetent elderly subjects with a live attenuated Oka strain of varicella zoster virus: a randomized, controlled, dose-response trial. Vaccine **2000**; 18(16):1700–1706.
53. Gershon AA, LaRussa P, Steinberg S, Mervish N, Lo SH, Meier P. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. J Infect Dis **1996**; 173(2):450–453.
54. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. J Infect Dis **2006**; 194(2):247–255.
55. Gershon AA, Levin MJ, Weinberg A, et al. A phase I-II study of live attenuated varicella-zoster virus vaccine to boost immunity in human immunodeficiency virus-infected children with previous varicella. Pediatr Infect Dis J **2009**; 28(7):653–655.
56. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis **2003**; 188(9): 1336–1344.
57. Takayama N, Takayama M, Takita J. Herpes zoster in healthy children immunized with varicella vaccine. Pediatr Infect Dis J **2000**; 19(2):169–170.
58. Hardy I, Gershon AA, Steinberg SP, LaRussa P. The incidence of zoster after immunization with live attenuated varicella vaccine: a study in children with leukemia. varicella vaccine collaborative study group. N Engl J Med **1991**; 325(22):1545–1550.
59. Marin M, Guris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep **2007**; 56(RR-4):1–40.
60. Seward JF, Marin M, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. J Infect Dis **2008**; 197(suppl 2): S82–S89.

61. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. Pediatrics **2008**; 122(3): E744–E751.
62. Schmid DS, Jumaan AO. Impact of varicella vaccine on varicella-zoster virus dynamics. Clin Microbiol Rev **2010**; 23(1):202–217.
63. Oxman MN, Levin MJ, Shingles Prevention Study Group. Vaccination against herpes zoster and postherpetic neuralgia. J Infect Dis **2008**; 197(suppl 2):S228–S236.
64. Simberkoff MS, Arbeit RD, Johnson GR, Oxman MN, et al. Safety of zoster vaccine in the shingles prevention study: a randomized trial. Ann Intern Med **2010**; 152(9):545–554.
65. ZOSTAVAX® prescribing information [package insert]. Whitehouse Station, NJ: Merck, **2006**.
66. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the united states, 2007: uptake of the first new vaccine to target seniors. Vaccine **2009**; 27(6):882–887.
67. LaRussa P, Steinberg SP, Shapiro E, Vazquez M, Gershon AA. Viral strain identification in varicella vaccinees with disseminated rashes. Pediatr Infect Dis J **2000**; 19(11):1037–1039.
68. Quinlivan ML, Gershon AA, Steinberg SP, Breuer J. Rashes occurring after immunization with a mixture of viruses in the Oka vaccine are derived from single clones of virus. J Infect Dis **2004**; 190(4):793–796.
69. Loparev VN, Rubtcova E, Seward JF, Levin MJ, Schmid DS. DNA sequence variability in isolates recovered from patients with postvaccination rash or herpes zoster caused by Oka varicella vaccine. J Infect Dis **2007**; 195(4):502–510.
70. Sauerbrei A, Rubtcova E, Wutzler P, Schmid DS, Loparev VN. Genetic profile of an Oka varicella vaccine virus variant isolated from an infant with zoster. J Clin Microbiol **2004**; 42(12):5604–5608.
71. Taha Y, Scott FT, Parker SP, Syndercombe Court D, Quinlivan ML, Breuer J. Reactivation of 2 genetically distinct varicella-zoster viruses in the same individual. Clin Infect Dis **2006**; 43(10):1301–1303.
72. Quinlivan MA, Gershon AA, Nichols RA, LaRussa P, Steinberg SP, Breuer J. Vaccine Oka varicella-zoster virus genotypes are monomorphic in single vesicles and polymorphic in respiratory tract secretions. J Infect Dis **2006**; 193(7):927–930.
73. Quinlivan ML, Gershon AA, Al Bassam MM, et al. Natural selection for rash-forming genotypes of the varicella-zoster vaccine virus detected within immunized human hosts. Proc Natl Acad Sci U S A **2007**; 104(1):208–212.
74. Breuer J, Schmid DS. Vaccine Oka variants and sequence variability in vaccine-related skin lesions. J Infect Dis **2008**; 197(suppl 2):S54–S57.
75. Breuer J. Herpes zoster: New insights provide an important wake-up call for management of nosocomial transmission. J Infect Dis **2008**; 197(5):635–637.
76. Levin MJ, DeBiasi RL, Bostik V, Schmid DS. Herpes zoster with skin lesions and meningitis caused by 2 different genotypes of the Oka varicella-zoster virus vaccine. J Infect Dis **2008**; 198(10):1444–1447.
77. Lopez AS, Burnett-Hartman A, Nambiar R, et al. Transmission of a newly characterized strain of varicella-zoster virus from a patient with herpes zoster in a long-term-care facility, West Virginia, 2004. J Infect Dis **2008**; 197(5):646–653.
78. Quinlivan M, Sengupta N, Breuer J. A case of varicella caused by co-infection with two different genotypes of varicella-zoster virus. J Clin Virol **2009**; 44(1):66–69.
79. Corey L, Wald A. Genital herpes. In: Holmes KK, Sparling PF, Mardh PA, et al, eds. Sexually transmitted diseases. New York: McGraw-Hill, **1999**:285–312.
80. Koelle DM, Corey L. Herpes simplex: insights on pathogenesis and possible vaccines. Annu Rev Med **2008**; 59:381–395.
81. Schiffer JT, Corey L. New concepts in understanding genital herpes. Curr Infect Dis Rep **2009**; 11(6):457–464.
82. LaRussa P. Clinical manifestations of varicella. In: Arvin AM, Gershon AA, eds. Varicella-zoster virus—virology and clinical management. Cambridge, United Kingdom: Cambridge University Press, **2000**:206–218.
83. Arvin AM. Investigations of the pathogenesis of varicella zoster virus infection in the SCIDhu mouse model. Herpes **2006**; 13(3):75–80.
84. Ku CC, Padilla JA, Grose C, Butcher EC, Arvin AM. Tropism of varicella-zoster virus for human tonsillar CD4(+) T lymphocytes that express activation, memory, and skin homing markers. J Virol **2002**; 76(22):11425–11433.
85. Ku CC, Besser J, Abendroth A, Grose C, Arvin AM. Varicella-zoster virus pathogenesis and immunobiology: new concepts emerging from investigations with the SCIDhu mouse model. J Virol **2005**; 79(5): 2651–2658.
86. Jones L, Black AP, Malavige GN, Ogg GS. Persistent high frequencies of varicella-zoster virus ORF4 protein-specific CD4+ T cells after primary infection. J Virol **2006**; 80(19):9772–9778.
87. Jones L, Black AP, Malavige GN, Ogg GS. Phenotypic analysis of human CD4+ T cells specific for immediate-early 63 protein of varicella-zoster virus. Eur J Immunol **2007**; 37(12):3393–3403.
88. Milikan JC, Baarsma GS, Kuijpers RW, Osterhaus AD, Verjans GM. Human ocular-derived virus-specific CD4+ T cells control varicella zoster virus replication in human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci **2009**; 50(2):743–751.
89. Huch JH, Cunningham AL, Arvin AM, et al. Impact of varicella zoster virus on dendritic cell subsets in human skin during natural infection. J Virol **2010**; 84(8):4060–4072.
90. Koelle DM, Chen HB, Gavin MA, Wald A, Kwok WW, Corey L. CD8 CTL from genital herpes simplex lesions: Recognition of viral tegument and immediate early proteins and lysis of infected cutaneous cells. J Immunol **2001**; 166(6):4049–4058.
91. Koelle DM, Posavad CM, Barnum GR, Johnson ML, Frank JM, Corey L. Clearance of HSV-2 from recurrent genital lesions correlates with infiltration of HSV-specific cytotoxic T lymphocytes. J Clin Invest **1998**; 101(7):1500–1508.
92. Gonzalez JC, Kwok WW, Wald A, McClurkan CL, Huang J, Koelle DM. Expression of cutaneous lymphocyte-associated antigen and E-selectin ligand by circulating human memory CD4+ T lymphocytes specific for herpes simplex virus type 2. J Infect Dis **2005**; 191(2):243–254.
93. Vleck SE, Oliver SL, Reichelt M, et al. Anti-glycoprotein H antibody impairs the pathogenicity of varicella-zoster virus in skin xenografts in the SCID mouse model. J Virol **2010**; 84(1):141–152.
94. Abendroth A, Arvin AM. Immune evasion as a pathogenic mechanism of varicella zoster virus. Semin Immunol **2001**; 13(1):27–39.
95. Abendroth A, Lin I, Slobedman B, Ploegh H, Arvin AM. Varicella-zoster virus retains major histocompatibility complex class I proteins in the golgi compartment of infected cells. J Virol **2001**; 75(10):4878–4888.
96. Black AP, Jones L, Malavige GN, Ogg GS. Immune evasion during varicella zoster virus infection of keratinocytes. Clin Exp Dermatol **2009**; 34(8):e941–e944.
97. Peng T, Zhu J, Klock A, et al. Evasion of the mucosal innate immune system by herpes simplex virus type 2. J Virol **2009**; 83(23):12559–12568.
98. Eidson KM, Hobbs WE, Manning BJ, Carlson P, DeLuca NA. Expression of herpes simplex virus ICP0 inhibits the induction of interferon-stimulated genes by viral infection. J Virol **2002**; 76(5):2180–2191.
99. Leib DA. Counteraction of interferon-induced antiviral responses by herpes simplex viruses. Curr Top Microbiol Immunol **2002**; 269:171–185.
100. Hill A, Jugovic P, York I, et al. Herpes simplex virus turns off the TAP to evade host immunity. Nature **1995**; 375(6530):411–415.
101. Perkins D, Pereira EF, Gober M, Yarowsky PJ, Aurelian L. The herpes simplex virus type 2 R1 protein kinase (ICP10 PK) blocks apoptosis in hippocampal neurons, involving activation of the MEK/MAPK survival pathway. J Virol **2002**; 76(3):1435–1449.
102. Nagashunmugam T, Lubinski J, Wang L, et al. In vivo immune evasion mediated by the herpes simplex virus type 1 immunoglobulin G Fc receptor. J Virol **1998**; 72(7):5351–5359.

103. Sloan DD, Zahariadis G, Posavad CM, Pate NT, Kussick SJ, Jerome KR. CTL are inactivated by herpes simplex virus-infected cells expressing a viral protein kinase. J Immunol **2003**; 171(12):6733–6741.
104. Hosken N, McGowan P, Meier A, et al. Diversity of the CD8+ T-cell response to herpes simplex virus type 2 proteins among persons with genital herpes. J Virol **2006**; 80(11):5509–5515.
105. Cohen JI. VZV: Molecular basis of persistence (latency and reactivation). In: Arvin A, Campadelli-Fiume G, Mocarski E, et al, eds. Human herpesviruses: biology, therapy, and immunoprophylaxis. Cambridge, UK: Cambridge University Press, **2007**:689–699.
106. LaGuardia JJ, Cohrs RJ, Gilden DH. Prevalence of varicella-zoster virus DNA in dissociated human trigeminal ganglion neurons and nonneuronal cells. J Virol **1999**; 73(10):8571–8577.
107. Cohrs RJ, Laguardia JJ, Gilden D. Distribution of latent herpes simplex virus type-1 and varicella zoster virus DNA in human trigeminal ganglia. Virus Genes **2005**; 31(2):223–237.
108. Wang K, Lau TY, Morales M, Mont EK, Straus SE. Laser-capture microdissection: Refining estimates of the quantity and distribution of latent herpes simplex virus 1 and varicella-zoster virus DNA in human trigeminal ganglia at the single-cell level. J Virol **2005**; 79(22): 14079–14087.
109. Levin MJ, Cai G, Manchak MD, Pizer LI. Varicella-zoster virus DNA in cells isolated from human trigeminal ganglia. J Virol **2003**; 77(12): 6979–6987.
110. Meier JL, Holman RP, Croen KD, Smialek JE, Straus SE. Varicella-zoster virus transcription in human trigeminal ganglia. Virology **1993**; 193(1):193–200.
111. Debrus S, Sadzot-Delvaux C, Nikkels AF, Piette J, Rentier B. Varicella-zoster virus gene 63 encodes an immediate-early protein that is abundantly expressed during latency. J Virol **1995**; 69(5):3240–3245.
112. Cohrs RJ, Barbour M, Gilden DH. Varicella-zoster virus (VZV) transcription during latency in human ganglia: detection of transcripts mapping to genes 21, 29, 62, and 63 in a cDNA library enriched for VZV RNA. J Virol **1996**; 70(5):2789–2796.
113. Cohrs RJ, Gilden DH, Kinchington PR, Grinfeld E, Kennedy PG. Varicella-zoster virus gene 66 transcription and translation in latently infected human ganglia. J Virol **2003**; 77(12):6660–6665.
114. Cohrs RJ, Randall J, Smith J, et al. Analysis of individual human trigeminal ganglia for latent herpes simplex virus type 1 and varicella-zoster virus nucleic acids using real-time PCR. J Virol **2000**; 74(24): 11464–11471.
115. Kennedy PG, Grinfeld E, Gow JW. Latent varicella-zoster virus in human dorsal root ganglia. Virology **1999**; 258(2):451–454.
116. Kennedy PG, Grinfeld E, Bell JE. Varicella-zoster virus gene expression in latently infected and explanted human ganglia. J Virol **2000**; 74(24): 11893–11888.
117. Mahalingam R, Wellish M, Cohrs R, et al. Expression of protein encoded by varicella-zoster virus open reading frame 63 in latently infected human ganglionic neurons. Proc Natl Acad Sci U S A **1996**;93: 2122–2424.
118. Lungu O, Panagiotidis CA, Annunziato PW, Gershon AA, Silverstein SJ. Aberrant intracellular localization of varicella-zoster virus regulatory proteins during latency. Proc Natl Acad Sci U S A **1998**; 95(12): 7080–7085.
119. Krause PR, Croen KD, Straus SE, Ostrove JM. Detection and preliminary characterization of herpes simplex virus type 1 transcripts in latently infected human trigeminal ganglia. J Virol **1988**; 62(12):4819–4823.
120. Kent JR, Kang W, Miller CG, Fraser NW. Herpes simplex virus latency-associated transcript gene function. J Neurovirol **2003**; 9(3):285–290.
121. Bloom DC. HSV LAT and neuronal survival. Int Rev Immunol **2004**; 23(1–2):187–198.
122. Stevens JG, Haarr L, Porter DD, Cook ML, Wagner EK. Prominence of the herpes simplex virus latency-associated transcript in trigeminal ganglia from seropositive humans. J Infect Dis **1988**; 158(1):117–123.
123. Zerboni L, Sobel RA, Ramachandran V, et al. The expression of varicella-zoster virus immediate early regulatory protein IE63 in neurons of latently infected human sensory ganglia. J Virol **2010**; 84(7):3421–3430.
124. Decman V, Freeman ML, Kinchington PR, Hendricks RL. Immune control of HSV-1 latency. Viral Immunol **2005**; 18(3):466–473.
125. Khanna KM, Bonneau RH, Kinchington PR, Hendricks RL. Herpes simplex virus-specific memory CD8+ T cells are selectively activated and retained in latently infected sensory ganglia. Immunity **2003**; 18(5):593–603.
126. Hufner K, Derfuss T, Herberger S, et al. Latency of alpha-herpes viruses is accompanied by a chronic inflammation in human trigeminal ganglia but not in dorsal root ganglia. J Neuropathol Exp Neurol **2006**; 65(10):1022–1030.
127. Theil D, Derfuss T, Paripovic I, et al. Latent herpesvirus infection in human trigeminal ganglia causes chronic immune response. Am J Pathol **2003**; 163(6):2179–2184.
128. Liu T, Khanna KM, Chen X, Fink DJ, Hendricks RL. $CD8^+$ T cells can block herpes simplex virus type 1 (HSV-1) reactivation from latency in sensory neurons. J Exp Med **2000**; 191(9):1459–1466.
129. Verjans GM, Hintzen RQ, van Dun JM, et al. Selective retention of herpes simplex virus-specific T cells in latently infected human trigeminal ganglia. Proc Natl Acad Sci U S A **2007**; 104(9):3496–3501.
130. Suvas S, Azkur AK, Rous BT. Qa-1b and CD94-NKG2a interactions regulate cytolytic activity of herpes simplex virus-specific memory CD8+ T cells in the latently infected trigeminal ganglia. J Immunol **2006**; 176:1703–1711.
131. Arvin AM, Sharp M, Moir M, et al. Memory cytotoxic T cell responses to viral tegument and regulatory proteins encoded by open reading frames 4, 10, 29, and 62 of varicella-zoster virus. Viral Immunol **2002**; 15(3):507–516.
132. Arvin AM, Sharp M, Smith S, et al. Equivalent recognition of a varicella-zoster virus immediate early protein (IE62) and glycoprotein I by cytotoxic T lymphocytes of either CD4+ or CD8+ phenotype. J Immunol **1991**; 146(1):257–264.
133. Reichelt M, Zerboni L, Arvin AM. Mechanisms of varicella-zoster virus neuropathogenesis in human dorsal root ganglia. J Virol **2008**; 82(8):3971–3983.
134. Frey CR, Sharp MA, Min AS, Schmid DS, Loparev V, Arvin AM. Identification of CD8+ T cell epitopes in the immediate early 62 protein (IE62) of varicella-zoster virus, and evaluation of frequency of CD8+ T cell response to IE62, by use of IE62 peptides after varicella vaccination. J Infect Dis **2003**; 188(1):40–52.
135. Bergen RE, Sharp M, Sanchez A, Judd AK, Arvin AM. Human T cells recognize multiple epitopes of an immediate early/tegument protein (IE62) and glycoprotein I of varicella zoster virus. Viral Immunol **1991**; 4(3):151–166.
136. Cunningham AL, Turner RR, Miller AC, Para MF, Merigan TC. Evolution of recurrent herpes simplex lesions. an immunohistologic study. J Clin Invest **1985**; 75(1):226–233.
137. Sadzot-Delvaux C, Kinchington PR, Debrus S, Rentier B, Arvin AM. Recognition of the latency-associated immediate early protein IE63 of varicella-zoster virus by human memory T lymphocytes. J Immunol **1997**; 159(6):2802–2806.
138. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology **1995**; 45(12 suppl 8): S41–S46.
139. Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. Brain **1900**; 23:353–523.
140. Watson CP, Deck JH, Morshead C, Van dK, Evans RJ. Post-herpetic neuralgia: Further post-mortem studies of cases with and without pain. Pain **1991**; 44(2):105–117.
141. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract **1975**; 25(157):571–575.
142. Kost RG, Straus SE. Postherpetic neuralgia–pathogenesis, treatment, and prevention. N Engl J Med **1996**; 335(1):32–42.
143. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med **2000**; 342(9):635–645.

144. Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R. Risk factors for postherpetic neuralgia. Arch Intern Med **1997**; 157(11): 1217–1224.
145. Sacks SL, Griffiths PD, Corey L, et al. HSV shedding. Antiviral Res **2004**; 63(suppl 1):S19–S26.
146. Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. J Infect Dis **2008**; 198(8):1141–1149.
147. Donaghy H, Bosnjak L, Harman AN, et al. Role for plasmacytoid dendritic cells in the immune control of recurrent human herpes simplex virus infection. J Virol **2009**; 83(4):1952–1961.
148. Zhu J, Koelle DM, Cao J, et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. J Exp Med **2007**; 204(3):595–603.
149. Arvin AM. Humoral and cellular immunity to varicella-zoster virus: an overview. J Infect Dis **2008**; 197(suppl 2):S58–60.
150. Malavige GN, Jones L, Black AP, Ogg GS. Varicella zoster virus glycoprotein E-specific CD4+ T cells show evidence of recent activation and effector differentiation, consistent with frequent exposure to replicative cycle antigens in healthy immune donors. Clin Exp Immunol **2008**; 152(3):522–531.
151. Jones L, Malavige G, Jeffery K, et al. Tracking epitope-specific antiviral CD4+ T cell responses to a live attenuated vaccine reveals ongoing functional responses. Vaccine **2009**; 27(52):7398–7401.
152. Cohrs RJ, Mehta SK, Schmid DS, Gilden DH, Pierson DL. Asymptomatic reactivation and shed of infectious varicella zoster virus in astronauts. J Med Virol **2008**; 80(6):1116–1122.
153. Crespi CM, Cumberland WG, Wald A, Corey L, Blower S. Longitudinal study of herpes simplex virus type 2 infection using viral dynamic modelling. Sex Transm Infect **2007**; 83(5):359–364.
154. Levin MJ, Oxman MN, Zhang JH, et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. J Infect Dis **2008**; 197(6):825–835.
155. Redman RL, Nader S, Zerboni L, et al. Early reconstitution of immunity and decreased severity of herpes zoster in bone marrow transplant recipients immunized with inactivated varicella vaccine. J Infect Dis **1997**; 176(3):578–585.
156. Hata A, Asanuma H, Rinki M, et al. Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med **2002**; 347(1):26–34.
157. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. J Pain **2004**; 5(6):344–356.
158. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. Clin J Pain **2007**; 23(6):490–496.
159. Harbecke R, Oxman MN, Arnold BA, et al. A real-time PCR assay to identify and discriminate among wild-type and vaccine strains of varicella-zoster virus and herpes simplex virus in clinical specimens, and comparison with the clinical diagnoses. J Med Virol **2009**; 81(7): 1310–1322.
160. Schmader K, Saddier P, Johnson G, et al; the Shingles Prevention Study Group. The effect of a zoster vaccine on interference of herpes zoster with activities of daily living (ADL). In: Program and abstracts of the 44th Annual Meeting of the Infectious Diseases Society of America. Alexandria, VA: Infectious Diseases Society of America, **2006**. Abstract 859.
161. Schmader KE, Johnson GR, Saddier P, et al. Effect of a zoster vaccine on herpes zoster–related interference with functional status and health-realted quality of life measures in older adults. J Am Geritatr Soc (in press).
162. Schmader K, Oxman M, Levin M, et al. Persistence of zoster vaccine efficacy. In: Program and abstracts of the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and 46th Annual Infectious Diseases Society of America Meeting. Alexandria, VA: Infectious Diseases Society of America, **2008**. Abstract G-409.
163. Weinberg A, Zhang JH, Oxman MN, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis **2009**; 200(7): 1068–1077.
164. Murphy K, Travers P, Walport M. Janeway's immunobiology. 7th ed. New York, NY, and Abingdon, UK: Garland Science, Taylor & Francis Group, **2008**.
165. Hammer GE, Kanaseki T, Shastri N. The final touches make perfect the peptide-MHC class I repertoire. Immunity **2007**; 26(4):397–406.
166. Ramachandra L, Simmons D, Harding CV. MHC molecules and microbial antigen processing in phagosomes. Curr Opin Immunol **2009**; 21(1):98–104.
167. Watts C. The exogenous pathway for antigen presentation on major histocompatibility complex class II and CD1 molecules. Nat Immunol **2004**; 5(7):685–692.
168. Amanna IJ, Slifka MK, Crotty S. Immunity and immunological memory following smallpox vaccination. Immunol Rev **2006**; 211:320–337.
169. Sette A, Grey H, Oseroff C, et al. Definition of epitopes and antigens recognized by vaccinia specific immune responses: Their conservation in variola virus sequences, and use as a model system to study complex pathogens. Vaccine **2009**; 27(suppl 6):G21–G26.
170. Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. Neurology **1980**; 30(6):582–587.
171. Berger R, Florent G, Just M. Decrease of the lymphoproliferative response to varicella-zoster virus antigen in the aged. Infect Immun **1981**; 32(1):24–27.
172. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ. Immune responses to varicella-zoster in the aged. Arch Intern Med **1982**; 142(2):291–293.
173. Hayward AR, Herberger M. Lymphocyte responses to varicella zoster virus in the elderly. J Clin Immunol **1987**; 7(2):174–178.
174. Hayward A, Levin M, Wolf W, Angelova G, Gilden D. Varicella-zoster virus-specific immunity after herpes zoster. J Infect Dis **1991**; 163(4): 873–875.
175. Gershon AA, Steinberg SP. Antibody responses to varicella-zoster virus and the role of antibody in host defense. Am J Med Sci **1981**; 282(1): 12–17.
176. Stevens DA, Merigan TC. Interferon, antibody, and other host factors in herpes zoster. J Clin Invest **1972**; 51(5):1170–1178.
177. Arvin A. Aging, immunity, and the varicella-zoster virus. N Engl J Med **2005**; 352(22):2266–2267.
178. Arvin AM, Pollard RB, Rasmussen LE, Merigan TC. Selective impairment of lymphocyte reactivity to varicella-zoster virus antigen among untreated patients with lymphoma. J Infect Dis **1978**; 137(5): 531–540.
179. Dolin R, Reichman RC, Mazur MH, Whitley RJ. NIH conference. herpes zoster-varicella infections in immunosuppressed patients. Ann Intern Med **1978**; 89(3):375–388.
180. Ruckdeschel JC, Schimpff SC, Smyth AC, Mardiney MR Jr. Herpes zoster and impaired cell-associated immunity to the varicella-zoster virus in patients with Hodgkin's disease. Am J Med **1977**; 62(1):77–85.
181. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis **1992**; 166(5):1153–1156.
182. Webster A, Grint P, Brenner MK, Prentice HG, Griffiths PD. Titration of IgG antibodies against varicella zoster virus before bone marrow transplantation is not predictive of future zoster. J Med Virol **1989**; 27(2):117–119.
183. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. J Infect Dis **1985**; 152(6):1172–1181.
184. Meyers JD, Flournoy N, Thomas ED. Cell-mediated immunity to varicella-zoster virus after allogeneic marrow transplant. J Infect Dis **1980**; 141(4):479–487.
185. Wilson A, Sharp M, Koropchak CM, Ting SF, Arvin AM. Subclinical varicella-zoster virus viremia, herpes zoster, and T lymphocyte im-

munity to varicella-zoster viral antigens after bone marrow transplantation. J Infect Dis **1992**; 165(1):119–126.
186. Good RA, Zak SJ. Disturbances in gamma globulin synthesis as experiments of nature. Pediatrics **1956**; 18(1):109–149.
187. Janeway CA, Apt L, Gitlin D. Agammaglobulinemia. Trans Assoc Am Physicians **1953**; 66:200–202.
188. Rosen FS, Janeway CA. The gamma globulins. 3. the antibody deficiency syndromes. N Engl J Med **1966**; 275(13):709–715.
189. Conley ME, Rohrer J, Minegishi Y. X-linked agammaglobulinemia. Clin Rev Allergy Immunol **2000**; 19(2):183–204.
190. Gnann JW, Whitley RJ. Natural history and treatment of varicella-zoster virus in high-risk populations. J Hosp Infect **1991**; 18:317–329.
191. Glesby MJ, Moore ED, Chaisson RE. Clinical spectrum of herpes zoster in adults infected with human immunodeficiency virus. Clin Infect Dis **1995**; 21:370–375.
192. ZOSTAVAX® prescribing information [package insert]. Whitehouse Station, NJ: Merck, **2009**. http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf.
193. Macintyre R, Egerton T, McCaughey M, et al. Concomitant administration of zoster and pneumococcal vaccines in adults ⩾60 years old. In: Program and abstractso the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Infectious Diseases Society of America Meeting. Alexandria, VA: Infectious Diseases Society of America, **2008**. Poster G 399d.
194. Smith JG, Levin M, Vessey R, et al. Measurement of cell-mediated immunity with a varicella-zoster virus-specific interferon-gamma ELISPOT assay: responses in an elderly population receiving a booster immunization. J Med Virol **2003**; 70(suppl 1):S38–S41.
195. Tyring SK, Diaz-Mitoma F, Padget LG, et al. Safety and tolerability of a high-potency zoster vaccine in adults ⩾50 or years of age. Vaccine **2007**; 25(10):1877–1883.
196. Cohen JI. Rheumatoid arthritis and the incidence of herpes zoster: risky business. Clin Infect Dis **2009**; 48(10):1372–1374.
197. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis **2009**; 48(10):1364–1371.
198. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA **2009**; 301(7):737–744.
199. Whitley RJ, Gnann JW. Herpes zoster in the age of focused immunosuppressive therapy. JAMA **2009**; 301(7):774–775.
200. Sutradhar SC, Wang WW, Schlienger K, et al. Comparison of the levels of immunogenicity and safety of Zostavax in adults 50 to 59 years old and in adults 60 years old or older. Clin Vaccine Immunol **2009**; 16(5):646–652.
201. Brunell PA, Taylor-Wiedeman J, Geiser CF, Frierson L, Lydick E. Risk of herpes zoster in children with leukemia: varicella vaccine compared with history of chickenpox. Pediatrics **1986**; 77(1):53–56.
202. Sharrar RG, LaRussa P, Galea SA, et al. The postmarketing safety profile of varicella vaccine. Vaccine **2000**; 19(7–8):916–923.
203. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. J Infect Dis **2008**; 197(suppl 2):S165–S169.
204. Civen R, Chaves SS, Jumaan A, et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. Pediatr Infect Dis J **2009**; 28(11):954–959.
205. Gilderman LI, Lawless JF, Nolen TM, et al. A double-blind, randomized, controlled, multicenter safety and immunogenicity study of a refrigerator-stable formulation of Zostavax. Clin Vaccine Immunol **2008**; 15(2):314–319.
206. Liesegang TJ. Varicella zoster virus vaccines: Effective, but concerns linger. Can J Ophthalmol **2009**; 44(4):379–384.
207. High KP. Overcoming barriers to adult immunization. J Am Osteopath Assoc 2009; 109(6 suppl 2):S25–S28.
208. High K. Immunizations in older adults. Clin Geriatr Med **2007**; 23(3): 669–685.
209. Orenstein WA, Mootrey GT, Pazol K, Hinman AR. Financing immunization of adults in the United States. Clin Pharmacol Ther **2007**; 82(6):764–768.
210. Lieu TA, Ortega-Sanchez I, Ray GT, et al. Community and patient values for preventing herpes zoster. Pharmacoeconomics **2008**; 26(3): 235–249.
211. Hurley LP, Lindley MC, Harpaz R, et al. Barriers to the use of herpes zoster vaccine. Ann Intern Med **2010**; 152(9):555–560.