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Varicella zoster vaccines and their implications for development of HSV vaccines☆

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Abstract

Live attenuated vaccines to prevent varicella and zoster have been available in the US for the past 17 years, with a resultant dramatic decrease in varicella incidence and a predicted future decrease in the incidence of zoster. The pathogenesis and immune responses to varicella zoster virus (VZV) as well as the safety and effectiveness of VZV vaccines are reviewed. The lack of sterilizing immunity provided by VZV vaccines has not prevented them from being safe and effective. Virological and pathological information concerning parallels and differences between VZV and herpes simplex virus (HSV) are highlighted. Although VZV and HSV are distinct pathogens, they appear to have similarities in target organs and immunity that provide an expectation of a high likelihood for the success of vaccination against HSV, and predicted to be similar to that of VZV.

Keywords

Varicella zoster virus; Herpes simplex virus; Vaccination; Vaccine safety; Vaccine efficacy

Introduction

For many years, varicella zoster virus (VZV) and herpes simplex virus (HSV) were thought to be such similar viruses that it was almost unnecessary to study each of them; research on HSV would mostly suffice for both viruses. HSV was recognized to have the great advantage of being easier to propagate than VZV, so it was "chosen" as the reference virus. In 1989, however, Straus enumerated several critical biological and clinical differences between the two pathogens (Straus, 1989). These included characteristics of latent infection and reactivation, such as numbers of skin lesions and frequency of recurrences, and pain symptoms. After that time, it began to be appreciated that VZV deserved study on its own. Today it is clear that while these herpesviruses may look alike, they are different in many aspects. Perhaps the most important difference is that safe and effective live attenuated vaccines were developed for VZV: against varicella in 1974 (Takahashi et al., 1974), and against herpes zoster (HZ) in 2005 (Oxman et al., 2005). Because of the absence of suitable animal models for varicella disease, it was necessary to carry out even the earliest tests of vaccine efficacy directly in humans, although safety testing was first performed in various animals (Takahashi et al., 1974). Effective vaccines against HSV, however, remain elusive.

Usually VZV does not cause severe illness. However a number of complications are associated with this virus, including those involving the respiratory (pneumonia) and

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nervous systems (meningitis, encephalitis, vascuopathy/stroke, retina), and the skin (Gilden et al., 2010).

VZV vaccines were licensed for routine use against varicella in the United States in 1995 (Centers-for-Disease-Control, 1996), and against HZ in 2006 (Mitka, 2006). They have been extremely effective in preventing both diseases (Gershon and Gershon, 2010; Hambleton et al., 2008; Hardy et al., 1991; Marin et al., 2011; Oxman et al., 2005; Shapiro et al., 2011).

Selected important unique aspects of VZV infection

Pathogenesis—VZV is spread via the airborne route (Gustafson et al., 1982, Leclair et al., 1980). Although it was assumed for years that VZV spreads from the respiratory tract of infected individuals, evidence for this is minimal (Brunell, 1989; Gold, 1966). The main route of spread appears to be aerosolization of cell free VZV present in vesicular skin lesions in both varicella (primary infection) and HZ (secondary infection due to reactivation of VZV from latency) (Chen et al., 2004; Tsolia et al., 1990). Infectious VZV is carried in CD4+ and CD8+ T lymphocytes during viremia (Arvin et al., 2010) and seems to spread primarily from one cell to another without exiting into the extracellular space (Weller, 1983), with exceptions involving the superficial layer of the skin and T lymphocytes. Mostly, VZV exists as an intracellular pathogen, which may explain why cell mediated immunity (CMI) rather than antibody is critical for host defense.

VZV is cell-associated because N-linked glycoproteins of its envelope contain exposed mannose-6 phosphate (Man 6 P) moieties (Gabel et al., 1989), which enable the virus to bind to Man 6 P receptors (MPRs). When VZV is enveloped in the *trans*-Golgi network, therefore, newly enveloped virions follow the itinerary of MPRs and traffic to late endosomes, within which the environment is acidic and VZV is inactivated. Subsequent exocytosis is of non-infectious viral particles. Cell-to-cell spread, which involves fusion of infected cells with neighbors, thus becomes the main means by which VZV can infect naive cells in vitro. In skin lesions, however, VZV-infected cells secrete fully infectious varicella virions into the extracellular space. They are able to do this because MPR expression is shut down as suprabasal cells of the epidermis mature into squames; therefore, infected suprabasal epidermal cells do not divert newly enveloped VZV to acidic endosomes, but instead package virions in secretory vesicles that carry it to the plasma membrane for exocytosis (Chen et al., 2004). When VZV initially contacts the respiratory mucosa of a susceptible individual, therefore, it arrives as a cell-free virion; during this time antibodies, delivered by passive immunization can prevent or modify infection (Gershon, Steinberg, and Brunell, 1974).

In establishing latency, VZV may be directly transferred from skin lesions to neuronal cell bodies via axons projecting to infected areas, by the process of retrograde axonal transport. In addition, infected T cells may pass VZV to neurons during T cell viremia, although it is not clear exactly how this transfer is accomplished. Spread of VZV to neurons by viremia was also demonstrated in simian varicella virus (Ouwendijk et al., 2012b). T cells may release cell free virions (Moffat et al., 1995) or may release VZV in exosomes, which fuse with neurons. Electron micrographs of lymphocytes infected with VZV suggest that virions may not be inactivated within endosomes but are well formed and packaged individually in secretory vesicles, as seen in suprabasal epidermal cells (Chen et al., 2011).

Varicella has an average incubation period of 2 weeks; during this time innate immunity protects the skin from the viremic phase of the illness, but eventually the virus overcomes this immune response. At that point, however the adaptive immune system is activated in host defense (Ku et al., 2005; Ku et al., 2004). In addition, the transfer of VZV from one infected cell to another cell probably contributes to slow viral replication, which might be

important in host survival (Chen et al., 2004). It seems likely that the rather long incubation period may enable disease prevention by vaccination. Although VZV has capabilities to effect immune evasion, this phenomenon seems not to be as well developed as it is for HSV (Abendroth and Arvin, 2001; Johnston et al., 2011; Laing et al.; Peng et al., 2009).

Immunity to VZV—There is only one serotype of VZV, although there are at least 7 viral clades, which have been identified from different geographic areas of the world (Breuer et al., 2010). Nevertheless, natural infection with VZV provides life-long protection against a second attack of varicella in most people; second attacks are unusual or rare (Gershon et al., 1984a; Junker, Angus, and Thomas, 1991). Almost simultaneously with the development of the live attenuated vaccine against varicella (Oka strain) (Takahashi et al., 1974), a sensitive and specific serologic test for VZV antibodies was described (Williams et al., 1974). Over time, this assay, the fluorescent antibody to membrane antigen (FAMA) test has proven to be an excellent indicator of protective immunity to varicella (Gershon et al., 2007; Gershon et al., 1984b; Michalik et al., 2008). Our laboratory has tested and followed numerous individuals who have undergone FAMA testing. Of persons with a FAMA titer of ≥1: 4 (n=131), fewer than 2% developed varicella after a household exposure to VZV; by contrast, the attack rate after household exposure in individuals with a titer of <1:4 was 59% (n=68) (Michalik et al., 2008). The availability of the FAMA test as a correlate of immunity, and the high attack rate of varicella following exposure to VZV among susceptibles were extremely helpful in the early evaluation of the efficacy of varicella vaccine (Asano et al., 1983, 1994; Gershon et al., 1984b). ELISA testing proved to be less useful regarding protection from illness, although early results showed seroconversion rates over 90% following one dose of vaccine (Gershon et al., 2012).

Latency and reactivation of VZV—VZV becomes latent in the dorsal root ganglia (DRG), cranial nerve ganglia (CNG) and enteric ganglia (EG) following chickenpox and vaccination. In contrast to latency with HSV, during latent VZV infection, transcripts and proteins of at least 6 of the 71 viral genes are expressed in neurons harboring latent VZV (Chen et al., 2011; Gershon et al., 2012; Kennedy and Cohrs, 2011).

Abundant clinical evidence indicates that some aspect of CMI is involved in preventing VZV reactivation disease (Arvin et al., 1978; Hardy et al., 1991). Exactly what controls VZV reactivation itself remains unclear. In contrast to HSV, infiltrating T cells are not found surrounding neurons that are infected with VZV (Verjans et al., 2007). The incidence of HZ begins to increase in individuals at the age of 50, at the same time that CMI to VZV begins to decrease (Berger et al., 2000; Burke et al., 1982). Presumably this loss of CMI is due to immunoscenescence secondary to aging. Immunocompromised patients are also at increased risk to develop HZ compared to healthy persons of the same age (Cohen et al., 2007). Children and adolescents who develop HZ may have transient decreases in CMI to VZV, possibly due to preceding viral infections that were asymptomatic, or to stress (Mehta et al., 2004).

In addition to being latent in CNG and DRG, RNA transcripts of wild type (WT) and Oka VZV and associated proteins have been demonstrated in enteric neurons in fresh surgical specimens removed from the intestines of children and adults (Chen et al., 2011). The demonstration of latency of VZV in EG is important because reactivation in intestinal ganglia may lead to a number of gastrointestinal diseases ascribed to VZV, such as achalasia, gastric ulcers, and colonic pseudoobstruction, also known as Oglivie's syndrome (Castex et al., 1995; Edelman et al., 2009; Pui et al., 2001; Roberetson et al., 1993; Stratman, 2002; Ussery et al., 1998). With the identification of latency of VZV in the ENS, and the potential for reactivation there, the pathogenesis of gastrointestinal disease due to VZV becomes clearer. Both WT and the Oka strain become latent in the ENS (Chen et al.,

2011). We recently identified an adolescent male with a severe gastric ulcer caused by Oka VZV, which must have been due to reactivation from latency, following 2 doses of varicella vaccine (Cohrs and Gilden, 2012). The demonstration of VZV RNA transcripts in fresh intestinal neuronal tissues (Chen et al., 2011) avoids the confounding possibility of reactivation of VZV after death in autopsy specimens (Ouwendijk et al., 2012a). The molecular capacity to differentiate between vaccine and wild type VZVs is an important aspect of studies on recipients of varicella vaccine in documenting reactivation and reinfection (Gershon et al., 1984b; LaRussa et al., 1992; Quinlivan et al., 2012).

Reactivation of VZV can occur following stress (Cohrs and Gilden, 2012; Mehta et al., 2004; Schmader et al., 1990). Following space travel, ~30% of astronauts developed asymptomatic reactivation of VZV, manifested by the transient appearance of VZV DNA in their saliva (Mehta et al., 2004). On occasion infectious VZV was also found in saliva, but this shedding is probably quite rare and has not been associated with viral transmission (Cohrs et al., 2008). VZV reactivation usually presents with rash, but rash may not invariably occur (Cohrs and Gilden, 2012; Gilden et al., 2010, 1994). When there is no rash, the virus may be demonstrated by the presence of VZV DNA in saliva (Cohrs and Gilden, 2012) or cerebrospinal fluid (CSF) (Gilden et al., 2010).

Selected aspects of Immunization with live attenuated varicella vaccine

Varicella vaccine—Live attenuated varicella vaccine is licensed for routine use in many countries in the world. Originally, in the United States, one dose was recommended for children (Centers-for-Disease-Control, 1996). Due to failure of seroconversion after 1 dose in roughly 20% of children, shown by FAMA testing (Michalik et al., 2008), and also due to continuing outbreaks of varicella in day care facilities and schools (Gershon et al., 2012), a two dose regimen was recommended by the Centers for Disease Control and Prevention (CDC) in 2006 (Centers-for-Disease-Control, 2007a). One dose of vaccine was shown to protect roughly 85% of children (Shapiro et al., 2011; Vazquez et al., 2001); this increased to 98% protection after a second dose was administered (Shapiro et al., 2011). There appears to be little laboratory documented loss of immunity with time even after receipt of only 1 dose (Vazquez et al., 2004). Although one study purported to show waning immunity to varicella, its validity is unproven because diagnoses were made only on clinical grounds, and primary vaccine failure was not taken into account (Chaves et al., 2007).

Development of clinical HZ following varicella vaccination is significanty lower than after natural infection in immunocompromised and healthy vaccinees (Hardy et al., 1991; Son et al., 2010; Tseng et al., 2009). The rate in vaccinated adults is extremely low, 0.9/1000 person-years of observation, which is also less than would be seen after natural infection (Hambleton et al., 2008). The reported rate in healthy vaccinated children is 0.33/1000 person-years, which may be as much as 10 times lower than would be expected after natural varicella (Tseng et al., 2009). After varicella vaccination of HIV-infected children, no cases of HZ were observed (Son et al., 2010).

Interestingly, WT VZV rather than the Oka strain is the cause of HZ in about 1/3 of vaccinated children who develop this illness (Galea et al., 2008; Vazquez, 2012). This is may be the result of asymptomatic VZV viremia occurring after exposure to WT VZV; most of these children have had no history of breakthrough varicella. Usually HZ in vaccinees is not serious, although there appears to be no difference in severity of the illness between Oka and WT (Vazquez, 2012). In autopsy studies of children who received 1 dose of Oka vaccine who subsequently died suddenly in accidents, studies of sensory ganglia revealed widespread latency with WT VZV (Gershon et al., 2012). None of the autopsied children had experienced varicella or HZ. Possibly they developed a subclinical VZV WT viremia upon exposure to WT VZV, but the viral burden was low and no reactivation was observed

during the lifetimes of the children (Gershon et al., 2012) (Table 1). It is impossible to know if this infection occurred before or after vaccination, but in any case it was subclinical. Presumably at least some children were infected with WT after vaccination.

Prior to widespread vaccination in the United States, there were about 100 annual deaths from varicella, mostly in otherwise healthy children and adults. Today, not only has the incidence of varicella declined dramatically but also the rate of hospitalizations from this disease has fallen, and deaths from varicella in the years between 1995–2007, have become rare (Marin et al., 2008, 2011). (Fig. 1) These encouraging data were obtained during the period when only 1 dose of varicella vaccine was given; presumably the situation will improve even further now that 2 doses are routinely given.

There is ample evidence that universal deployment of live attenuated varicella vaccine has decreased transmission of VZV in the U.S. As mentioned, there are now fewer hospitalizations, fatalities, and reported outbreaks of varicella in schools. In is unusual to see patients with varicella today, and young American clinicians have little or no experience in managing this infection. The decrease in VZV transmission has occurred despite observations that sterilizing immunity has not always been achieved by vaccination. The vaccine commonly protects against disease but reinfections and viral latency have not entirely disappeared. As seen in Table 1, silent reinfections can occur with accompanying latency of WT VZV. Latency due to silent WT infection is also indicated by the observation that in 1/3 of vaccinees who develop HZ, WT VZV is the cause. The ~15% breakthrough infection rate of mild to moderate (but not severe) varicella after 1 dose is additional evidence that vaccination does not completely protect against disease, despite reports of over 90% seroconversion by ELISA. Data regarding FAMA seroconversions in healthy child vaccinees are limited, but show that only about 80% of children seroconvert by this assay, following 1 dose. There are no published data regarding seroconversions by FAMA after 2 doses. The best indications of the efficacy of varicella vaccine come from studies that have assessed the proportion of exposed vaccinees who were protected after intimate exposures to the virus (Asano et al., 1983, 1994; Gershon et al., 1984b, 2012).

Varicella vaccine has been shown to be extremely safe. In contrast to ~100 varicella deaths annually from WT disease in the pre-vaccine era in the United States, there is only one varicella death from the Oka strain on record in the world literature, in an English child with underlying leukemia (Ulloa-Gutierrez, 2007), in the past 15 years. The most frequently reported adverse reaction to vaccination is a mild rash that appears several weeks later in about 5 percent of healthy children, particularly after a first vaccine dose (Chaves et al., 2008; Galea et al., 2008; Gershon and Gershon, 2010; Gershon et al., 1991, 1988; Sharrar et al., 2000). Extensive rashes, with occasional pneumonia or neurologic symptoms have been reported rarely in immunocompromised children who were inadvertently vaccinated, such as those with undiagnosed AIDS, natural killer (NK) cell deficiency, and other immunodeficiency diseases. They have been treated successfully with antiviral therapy (Gershon, 2003; Jean-Philippe et al., 2007; Kramer et al., 2001; Levy et al., 2003). There is a potential for transmission of the vaccine virus if vaccinees develop rash from the Oka strain, but transmission is extremely rare from healthy individuals; fewer than 10 instances of transmission have been reported since 1995, during which time as many as 60 million children in the United States were vaccinated (Centers-for-Disease-Control, 2007b; Chaves et al., 2008; Galea et al., 2002; Sharrar et al., 2000). A few notable neurologic events were related to varicella vaccine. There are 9 reports of HZ due to the Oka strain with accompanying meningitis, in which VZV DNA was found in CSF by polymerase chain reaction (PCR). The patients were a mixture of healthy and immunocompromised children; most received antiviral therapy and all recovered (Pahud et al., 2011). (Table 2) This form of meningitis has also been reported as being caused by WT VZV (De La Blanchardiere et al.,

2000; Dueland et al., 1991; Gilden et al., 2010; Levin et al., 2008; Pahud et al., 2011; Spiegel et al., 2010). It is therefore unclear whether or not these 9 Oka meningitis patients should be classified as having a vaccine-associated adverse event. There is no known denominator for meningitis caused by WT or Oka VZV; therefore the incidence of these complications is not known, but this illness in vaccinees appears to be rare. Transient cerebellar ataxia has been reported following vaccination, but its connection to VZV, if any, has not been proven (Chaves et al., 2008; Galea et al., 2008; Sharrar et al., 2000).

Zoster vaccine—In addition to the preventive vaccination against varicella, a therapeutic vaccine was developed to prevent HZ, composed of the Oka strain of VZV, but at a dose ~14 times greater than that used to prevent varicella. The rationale is to revive the CMI response to VZV in the aged, and thus to prevent VZV from reactivating and causing disease. This vaccine is roughly 60% effective in preventing HZ and post herpetic neuralgia in healthy persons over the age of 60 years (Oxman et al., 2005). Because of its recently demonstrated safety and efficacy in a younger age group, it has now been recommended for individuals over the age of 50 years, in whom it is 70% effective if given between 50–59 years (Schmader et al., 2012b). A subunit zoster vaccine composed of adjuvanted glycoprotein E of VZV has been developed and appears to be highly immunogenic in Phase 2 studies (Leroux-Roels et al., 2012). This vaccine is currently in Phase 3 clinical trials, but as yet there are no data available regarding its safety or efficacy. (http://clinicaltrials.gov/ct2/show/NCT01165203).

The issue of whether or not decreased exposure to WT VZV will lead to an increase in the incidence of HZ in the unvaccinated population has been heatedly discussed (Crumpacker, 2011; Goldman and King, 2012). Certain investigators proposed that exposure to WT VZV is essential to maintain long term immunity to VZV (Thomas et al., 2002), while data of others disputes this idea (Gaillat et al., 2011). It is clear that the incidence of HZ is increasing in the United States, but this has been occurring over a period of more than 50 years (Donahue et al., 1995; Ragozzino et al., 1982), long before the advent of varicella vaccine. Undoubtedly the increase in zoster incidence is multifactorial and includes increases in ascertainment and diagnosis, as well as increases in numbers of immunocompromised and elderly individuals, and possibly increases in other factors such as stress. Whether vaccination has contributed to this rise in HZ incidence is difficult to sort out, but varicella vaccination cannot be the only cause since it was licensed in the United States only in 1995, long after the increase in incidence began. A computer modeling study predicted an increase in the incidence of HZ in the vaccine era that would lead to an epidemic of HZ in the population with 50% of young and middle-aged adults developing HZ, and 5000 deaths (Brisson et al., 2002). Clearly this has not happened. The most recent estimated death rate from HZ in the United States is less than 100 patients annually (Mahamud et al., 2012).

Another putative mechanism for maintaining long-term immunity to VZV is by subclinical reactivation from latency. This possibility was suspected years ago (Luby et al., 1977) but could not be firmly documented until molecular techniques such as PCR became available. Now more and more evidence for the occurrence of subclinical reactivation of VZV is accumulating in immunocompromised and immunocompetent individuals (Birlea et al., 2011; Cinque et al., 1997; Ljungman et al., 1986; Mehta et al., 2004; Wilson et al., 1992). It seems that VZV reactivation has a spectrum ranging from subclinical to zoster without rash or zoster sine herpete (Blumenthal et al., 2011; Cohrs and Gilden, 2012; Gilden et al., 2010) to localized unilateral dermatomal vesicular skin lesions, to widespread skin vesicles with visceral involvement resembling severe varicella.

Why then has the development of varicella vaccine so successful in reducing disease from this infection? The vaccine is clearly attenuated (Gershon et al., 2012; Tsolia et al., 1990) and very safe, even in selected immunocompromised patients (Gershon et al., 1984b; Son et al., 2010). From the beginning of vaccine testing there was an immune correlate, the FAMA test, which was immensely helpful in evaluating vaccine efficacy. The Oka strain has limited transmissibility, and it is susceptible to standard antiviral drugs (Preblud et al., 1984). While Oka can cause latent infection, the potential for reactivation disease (HZ) is lower that for WT VZV. There is the potential to boost immunity for those whose CMI is waning due to aging with an Oka based vaccine (Oxman et al., 2005; Schmader et al., 2012a). There is also the possibility that boosting of immunity may be accomplished by non-infectious subunit vaccines, which are still under investigation. (http://clinicaltrials.gov/ct2/show/NCT01165203)

In summary, VZV vaccines have proven remarkably effective and safe. The incidence of varicella and its complications has decreased dramatically in the United States by its use. In one study of unvaccinated HIV-infected children, the incidence of varicella decreased by over 60% in the post-vaccine era, indicating decreased viral transmission and herd immunity (Son et al., 2008). Currently over 90% of young children have been immunized, and hospitalizations and deaths from varicella have fallen dramatically (Marin et al., 2011; Shah et al., 2011). Inroads into the conquest of HZ are also being made, both by varicella vaccine use and the therapeutic vaccine to prevent HZ. Interestingly, this success with VZV vaccines has occurred although the vaccines do not achieve the ideal of “sterilizing” immunity. With all of the available approaches, and despite the vagaries, perhaps it has actually been possible to improve on Mother Nature with prevention of varicella and zoster by vaccination.

Development of vaccines against HSV

Given that HSV is much easier to propagate and historically at least to produce mutant viruses than VZV, one might have predicted that a vaccine for HSV 1 and 2 would have been developed long before VZV vaccines, but we are still awaiting the availability of successful vaccines for HSV. Some of the differences between HSV and VZV might help to explain problems encountered with vaccine development of HSV. One important difference between the viruses is in their incubation periods for causing primary disease; this period is as much as 10 times longer for VZV than for HSV (Gershon et al., 2012). This phenomenon probably partially relates to the mode of infection: varicella has a fairly long viremic phase before causing skin disease while HSV infects directly at the mucosal level where disease appears, such as the genitalia and the oral cavity. Viremia is also thought to be rare in HSV infections. On the other hand influenza, which is vaccine-preventable, has a very short incubation period and also directly infects the organ system involved in disease.

Additional factors may be involved. HSV appears to have more fully developed strategies for immune evasion than VZV (Johnson et al., 2011). Prolonged immunity is the rule following varicella, with reinfections being unusual. In contrast, reinfections with HSV are not uncommon, and frequent subclinical shedding of infectious virus occurs (Johnston et al., 2011). The protective immune responses for HSV are not well understood, although it is known that persistent infiltrates of CD4+ and CD8+ T cells directed towards HSV are present in the mucosa and at nerve endings (Johnston et al., 2011; Zhu et al., 2007). Almost constant genital shedding of HSV 2 suggests that natural immunity to HSV is not very effective, at least in some individuals. In contrast, an immune correlate, the FAMA assay, indicates whether an individual is immune to varicella or not (Michalik et al., 2008). Interestingly, while there are many animal models of HSV infections, varicella vaccine was developed in the absence of such a model. Possibly because immunity to viruses may be mediated differently in humans than in small laboratory animals, which have not evolved

adaptive responses to HSV such as immune evasion, over the millennia as have humans, animal models may complicate vaccine development rather than simplify it.

Outsmarting HSV has not proven to be an easy task. But since VZV vaccination seems to have improved on Mother Nature, perhaps this can be accomplished for HSV as well. Certainly there are many candidate vaccines for testing, and these might be used, possibly even in combinations, to produce strong immune responses to HSV. Reasoning from VZV vaccines, the phenomenon of latency and reactivation can be improved from the human perspective by vaccines. While sterilizing immunity is the ideal, some degree of immune failure is likely but should not in itself preclude vaccination against HSV. Decreasing viral transmission of HSV along with herd immunity, even if imperfect, would seem to be the most important goals of vaccination. Mathematical models suggest that even non-sterilizing vaccines may decrease viral shedding and transmission of HSV 2 (Garnett et al., 2004). A successful vaccine should protect both mucosal and epidermal sites, and ideally not infect neurons (Johnston et al., 2011).

While significant protective immune responses against HSV are not yet fully identified, it is clear that innate and adaptive immunity play roles in control of HSV infections and therefore could be manipulated by vaccination. For example, individuals have been identified in HSV discordant relationships who appear to resist HSV infection, likely due to T cell responses to certain immediate early viral proteins (Posavad et al., 2010).

While antivirals are important for disease control, they cannot substitute for a vaccine; they are useful however when vaccines are not as protective as one would like them to be or if there are adverse events that require therapy. Antivirals can certainly play an adjunct role to vaccination, as they have for varicella vaccine.

Why is it important to develop vaccines against HSV? Most children and adults who are infected with HSV manifest self-limited infections. On the other hand, HSV causes life-threatening disease including neonatal infections, encephalitis, and eczema herpeticum, as well as sight-threatening keratitis. Host immune defenses such as cytotoxic T cells and natural killer (NK) cells are not fully matured in the neonate, which may explain the inability of infected newborns to contain HSV infections (Corey and Wald, 2009; Kimberlin and Whitley, 2005). While HSV encephalitis and neonatal HSV can be treated with antiviral drugs, these are not always completely effective and survivors often have significant morbidity (Corey and Wald, 2009; Kimberlin and Whitley, 2005).

Patients with abnormalities in innate immunity are predisposed to develop severe or persistent HSV infections. HSV encephalitis has been associated with genetic abnormalities involving toll like receptors (TLR3), UNC93B1, and STAT1 signaling in children (Casanova et al., 2011; Casrouge et al., 2006; Zhang et al., 2007). In addition, single nucleotide polymorphisms (SNPs) in TLR2 in humans have been associated with high levels of HSV mucosal shedding, and low interferon-alpha responses (Bochud et al., 2007). One can speculate that by improving adaptive immune responses through a vaccine, deficiencies in innate immunity might be overcome.

It is possible that effective vaccines against HSV might also benefit certain other individuals, including immunocompromised patients. Varicella vaccine was successfully used to prevent chickenpox in children with underlying leukemia in the 1980 s, before herd immunity had developed in the United States due to widespread vaccination of healthy children and adults (Gershon et al., 1984b). An inactivated VZV vaccine was used to protect immunocompromised persons against HZ (Hata et al., 2002). Vaccination against HSV might also offer indirect protection against HIV infection, because the risk of HIV-1 infection is increased by a factor of 3 in HSV- 2 seropositives (Freeman et al., 2006).

It is beyond the scope of this review to delineate the many candidate vaccines against HSV. Suffice it to say that these consist of live attenuated vaccines with various mutations such as deletion of immune evasion genes, subunit adjuvanted vaccines, DNA vaccines that encode various HSV proteins, and replication incompetent vaccines. Ideally it would be best to vaccinate against both HSV 1 and HSV 2, even though HSV 2 seems to protect partially against HSV 1. Based upon experience with other viral vaccines, live attenuated viruses seem to be the most dependable to stimulate long lasting immunity. Immunization of children and adolescents before onset of sexual activity would seem appropriate.

In summary, vaccination against HSV is a worthwhile goal, and one that with available molecular virologic techniques seems achievable.

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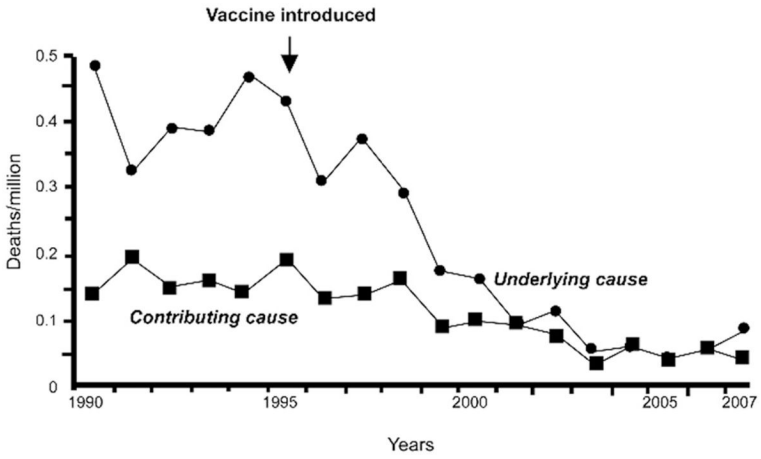

Fig. 1.

Annual age-specific mortality rates for varicella due to varicella as the underlying cause were reduced 88% by 2004–2007, after introduction of varicella vaccine in 1995. Based on figure in Marin et al, 2011.

Table 1

Latent VZV (DNA/RNA) was found by PCR in ganglia at multiple levels, often bilaterally. Distribution of VZV DNA/RNA in ganglia of vaccinated patients. *Source*: Gershon et al. (2012).

Patient Age	Vaccinated	Trigeminal		Cervical		Thoracic		Lumbar		Type
		Right	Left	Right	Left	Right	Left	Right	Left	
1.75	Yes	0	0	0	0	0	+	+	0	Oka
2	Yes	0	0	0	0	+	0	+	0	Wild
2	?	+	+	0	0	+	0	0	+	Wild
2	Yes	+	+	+	+	+	+	+	+	Wild
4	Yes	0	0	+	+	+	+	+	0	Wild
8	Yes	0	0	0	0	+	0	0	0	Wild
10	Yes	+	+	0	0	+	0	+	0	Wild

DNA examined: ORFs 4, 31, 63, 66, 67; RNA examined: ORFs 4, 40, 63, 66.

Table 2

Meningitis caused by the Oka strain of VZV, diagnosed by PCR on CSF in children vaccinated at ~1 year of age.

Case	Report year	Author	Medical history	ORFs tested	Age	Location of zoster rash
1	2003	Levin	Neuroblastoma[a]	62	1 yr	R. thigh
2	2008	Bryan	Neuroblastoma[a]	62	21[b] mo	hands, R leg, abdomen
3	2008	Galea; Chavez	Leukemia chemotherapy[a]	38, 54	4 yr	arm
4	2008	Chavez	Healthy	38,54	4 yr[c]	R. arm
5	2008	Levin	Healthy	38, 54, 62[d]	8 yr	L. shoulder
6	2009	Iyer	Healthy	38, 54, 62	9 yr	L. arm
7	2010	Chouliaras; Goulleret	Healthy	62	3 yr	Face [e] (trigeminal)
8	2011	Han	Healthy	38, 54, 62	7 yr.	R. arm, shoulder
9	2011	Pahud	Healthy	38, 54, 62[d]	12 yr	neck

[a] healthy when immunized.

[b] immunized at 20 mo.

[c] immunized at 32 mos.

[d] and other ORFs.

[e] also had encephalitis.