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Herpes zoster and the search for an effective vaccine

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Summary

Primary infection with varicella zoster virus (VZV), an exclusively human neurotrophic alphaherpesvirus, results in varicella, known more commonly as chickenpox. Like other alphaherpesviruses, VZV establishes latency in the sensory ganglia and can reactivate to cause herpes zoster (also known as shingles), a painful and debilitating disease, especially in elderly and immunocompromised individuals. The overall incidence of herpes zoster in Europe and the United States is three per 1000 people, but increases sharply after 60 years of age to 10 per 1000 people. Zostavax® is a vaccine approved by the Federal Drug Administration for the prevention of herpes zoster. Unfortunately, this vaccine reduces the incidence of disease by only 51% and the incidence of post-herpetic neuralgia by 66·5% when administered to those aged 60 and older. Moreover, it is contraindicated for individuals who are immunocompromised or receiving immunosuppressant treatments, although they are at higher risk for herpes zoster compared to immune-competent older individuals. This paper reviews VZV pathogenesis, host responses and current vaccines available to prevent herpes zoster.

Keywords: herpesvirus, reactivation, shingles, vaccine, Zostavax®

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Varicella zoster virus

Varicella zoster virus (VZV) is one of eight human herpesviruses that belongs to the alphaherpesvirus family, together with HSV1 and HSV2. It has a linear double-stranded DNA genome that is 124 885 base pairs long and encodes 71 unique open reading frames (ORFs) [1]. The VZV genome has two isomeric forms consisting of one long and one short covalently linked segments with unique sequences bounded by inverted terminal repeats (ORF69 and ORF70). VZV shares approximately 40 conserved genes with other human herpesviruses that are essential for: viral replication (ORF18 and ORF19), DNA packaging (ORFs 25, 26, 30, 34, 42/45, 43 and 54) tegument proteins (ORF9-ORF12, 22, 38, 44, 46, 53, 57, 64 and 69), capsid assembly (ORFs 20, 21, 23, 33, 40 and 41) and glycoproteins [gB(ORF31), gC(ORF14), gE(ORF68), gH(ORF37), gI (ORF67), gK(ORF5), gL(ORF60) and gN (ORF9a)] [1–3]. Like other herpesviruses, the VZV virion contains an icosahedral-shaped nucleocapsid that encloses the viral DNA genome and a lipid envelope containing glycoproteins that facilitate viral entry [1].

VZV entry into cells is not well understood, but is believed to occur through direct fusion with the plasma membrane or endocytosis [4]. After viral entry, the virions are uncoated and nucleocapsids attach to nuclear pores and inject their genomic DNA into the nucleus, where it circularizes. Gene expression occurs in a temporal manner with transcription of immediate early, early and then late genes [5]. Immediate early and early genes encode for proteins involved in the regulation of gene expression and viral replication, while late genes encode for structural proteins such as nucleocapsids and glycoproteins [6]. Viral mRNAs are transported to the cytoplasm, where they undergo translation into proteins that are transported back into the nucleus and used for the viral replication and gene expression to generate viral progeny. Nucleocapsids are then assembled in the nuclei of infected

cells. Tegument proteins and glycoproteins are added in the cisternae of the trans-Golgi network [7]. The virus is then released into the cytosol where it fuses with the plasma membrane to bud off. The replication cycle followed by the release of viral progeny only takes 9–12 h in human fibroblasts [5].

Acute VZV infection

Clinical manifestation of varicella

VZV is a highly contagious virus that is spread through the inhalation of saliva droplets containing viral particles or by direct contact with infectious fluid from either varicella or herpes zoster (HZ) vesicles [8,9]. It has an incubation period of 10–21 days, but shorter incubation periods have been observed in immunocompromised people [8,10]. It is believed that VZV replicates initially in the upper respiratory tract and tonsillar lymph nodes before dissemination to the skin. Previous studies proposed a dual viraemia model, where the virus first undergoes amplification in organs such as the liver and spleen followed by a secondary viraemia during which the virus is transported to the skin [11]. However, subsequent studies have shown that viral amplification in the spleen and liver is not necessary for viral dissemination to the skin. Studies using fetal human skin xenografts in the severe combined immunodeficiency (SCID) mouse model showed that VZV can disseminate to the skin by infected tonsillar $CD4^+$ T cells that express skin-homing markers but not by infected skin fibroblasts [12–14]. Other studies suggest that dendritic cells infected at the respiratory mucosa transport VZV to the draining lymph nodes, where they infect T cells that can acquire memory and homing markers and travel to the skin [13,15]. Indeed, more recent studies using time-of-flight mass cytometry show that *in-vitro* VZV infection VZV remodels tonsillar T cells into activated skin-homing cells [16,17]. Once infected T cells reach the skin, they are believed to transfer VZV to keratinocytes and skin epidermal cells, resulting in a widespread vesicular rash together with fatigue, fever and itching.

Primary infection of VZV in immune-competent individuals usually resolves with no complications. However, in individuals who are immunocompromised varicella can be severe and, in some cases, fatal [18,19]. Bacterial infection of skin lesions and pneumonia are the most common complications in both immune-competent and immunocompromised children [18]. Neurological complications are very rare, and occur in one to three per 10 000 cases during acute infection [20]. The most serious varicella-associated neurological complication is acute cerebellar ataxia, which can occur in one in 4000–1 : 100 000 varicella cases in children (depending upon the age of the population studied) [21–23]. Primary infection of varicella has also been associated with increased susceptibility to stroke in immune-competent children [24] due to VZV infecting endothelial cells lining the cerebral arteries causing inflammation [25]. Primary VZV infection in seronegative women during the first 8–20 weeks of gestation could result in fetal varicella syndrome, characterized by cutaneous scars, ocular malformations and limb and central nervous system defects [26]. This syndrome occurs in only 1–2% of births to mothers who contract varicella during pregnancy [27]. In addition, acute VZV infection during the last 2 weeks of gestation can lead to congenital or neonatal varicella [26]. Because of this risk, women of childbearing age are screened for VZV-specific antibodies, and vaccination is recommended if titres are below detection. People who are at increased risk of severe varicella are often administered anti-virals such as acyclovir or VZV-specific immunoglobulins (VariZIG) as prophylaxis following suspected exposure [28].

Immune response during primary infection

Both the innate and adaptive immune responses play a critical role in controlling viral replication during acute infection. The first mechanism of defence is mediated through natural killer (NK) cells and type 1 interferons (IFNs). Indeed, patients who are deficient in NK cells or lack activated NK cells are at increased risk of severe or fatal varicella [29–32]. NK cells can kill VZV-infected cells by secreting the anti-viral factor granulysin, which induces apoptosis in infected cells [33]. Type 1 and type 2 IFNs have also been shown to inhibit VZV replication in human skin xenografts [14]. Moreover, IFN-α treatment reduces the number of new varicella lesions in cancer paediatric patients when administered within 72 h after the appearance of the rash [34].

Complete resolution of acute infection requires adaptive immune responses [35]. Subjects with T cell deficiencies such as those with lymphoma, undergoing chemotherapy or infected with human immunodeficiency virus (HIV) experience severe varicella [36,37]. VZV-specific T cells can be detected in the blood 3–7 days after the appearance of rash and peak 1–2 weeks later followed by a gradual decline [35–38]. T cell immunity to VZV is primarily a T helper type 1 (Th1) response, with interleukin (IL)-2, IL-12, tumour necrosis factor (TNF)-α and IFN-γ being the primary cytokines produced [39]. IFN-γ has been shown to induce the clonal expansion of VZV-specific T cells [40]. Although a comprehensive analysis of the specificity of the anti-VZV T cell response has yet to be conducted, CD8 T cell responses to VZV immediate early genes ORF4, ORF62 and ORF63, tegument protein ORF10, single-stranded DNA binding protein ORF29 and glycoproteins ORF67 (gI) and ORF68 (gE) have been described [1,41–44].

Humoral immunity can be measured within 3 days after the appearance of the rash with the production of immunoglobulin (Ig)M, IgG and IgA antibodies [45]. The specificity of the antibody responses was determined using a protein microarray that contained 69 distinct VZV proteins

and sera from subjects ranging from 2 to 70 years of age with no current symptoms of varicella or HZ. This analysis showed that antibodies are directed primarily against VZV glycoproteins (ORF5, ORF14, ORF31, ORF37 and ORF68), capsid proteins (ORF20, ORF23, ORF40), tegument proteins (ORF53, ORF9, ORF11) genes involved in replication and virion assembly (ORF25, ORF26, ORF28), immediate early transactivators ORF12, ORF62 and ORF63 and membrane proteins ORF2 and ORF24 [46]. ORF2, ORF12 and ORF62 were shown to induce the highest antibody responses [46].

Although both T and B cell responses are generated during acute varicella, early production of VZV-specific T cells, but not antibodies, correlates with reduced severity of clinical symptoms [35]. In line with this observation, patients with agammaglobulinaemia have uncomplicated varicella and are equally protected against a second episode of varicella as individuals with normal B cell responses [47]. Moreover, treatment with varicella zoster immunoglobin (VariZIG) is most effective when given within 96 h of exposure and recommended to be administered within 10 days of exposure [48].

VZV latency

Like herpes simplex 1 (HSV-1) and HSV-2, VZV establishes latency in sensory ganglia, and co-infection of the same neurone by multiple herpesviruses has been described [49,50]. There are two (non-mutually exclusive) theories on how VZV reaches the ganglia: (1) VZV enters into the nerve terminals from the vesicular rash hijacking the retrograde transport mechanism to the ganglia [51,52]; and (2) VZV accesses the distal neurones through the haematogenous route, carried by infected T cells that gain access to the ganglia [53].

During latency, VZV DNA is found in both satellite and neurone cells in sensory ganglia [54] as a circular episomal genome with limited viral gene transcription [55,56]. The most frequently expressed genes found during latency include ORF4, ORF21, ORF29, ORF62, ORF63 and ORF66 [57–59]. ORF4 and ORF63 were found to be required for the establishment of latency in a rat model where VZV-infected melanoma cells were injected directly into the spine [60,61]. Additional studies using rat neurones have shown that ORF63 may also play a role in preventing cell apoptosis [62]. Interestingly, during latency, transcripts associated with these ORFs are found in the cytoplasm of neurones, whereas during acute replication in fibroblasts they are found in the nucleus of the cell [63,64].

VZV reactivation

VZV reactivation results in HZ, a painful and often debilitating disease that affects 1 million individuals per year in the United States alone [65]. During VZV reactivation, the virus travels ante-retrograde from the sensory ganglia to the skin nerve terminals, where it infects and replicates in keratinocytes, and epithelial cells, causing polykaryocytes [53] (Fig. 1). The first symptom of HZ is usually severe prodromal pain and burning which precedes the rash [66]. Unlike varicella, the HZ rash is restricted to the dermatome innervated by the ganglia from which the virus reactivated [67]. VZV can also reactivate without resulting in a rash. When accompanied by pain this is referred to as zoster sine herpete [68], which is difficult to diagnose and can be confirmed only by measuring VZV DNA in the cerebrospinal fluid [69]. Asymptomatic reactivations can also occur during episodes of mild stress or immune suppression. For instance, infectious VZV DNA has been recovered from the saliva of astronauts during and after spaceflight in the absence of disease [70].

The incidence of HZ increases dramatically after the age of 50 years from an average of three cases per 1000 adults aged 40–50 years to 10 cases of HZ per 1000 adults aged 80 years or above [71]. HZ also occurs frequently in individuals with autoimmune diseases, cancer and organ transplant recipients receiving immunosuppressive drugs [31]. Increased incidence of HZ has also been linked to physical trauma, inflammatory bowel disease and diabetes [72,73]. Interestingly, African Americans are significantly less susceptible to HZ compared to Caucasians [74]. In contrast, numerous studies in the United States and Europe have demonstrated that the incidence of HZ is significantly higher in women than men [75–79].

As described for acute infection, VZV-specific T cell immunity plays a more critical role in the prevention of VZV reactivation than antibodies [38]. VZV antibody responses have been shown to be extremely stable, with half-lives of approximately 50 years, whereas the frequency of VZV-specific T cells declines dramatically with age [80,81]. Overall, the frequency of VZV-specific CD4 T cells declines more dramatically with age compared to VZV-specific CD8 T cells [65,82]. Moreover, CD4 T cell responses in women are smaller than those observed in men, which may account for the increased incidence of HZ in this segment of the population [83]. Whether all T cell responses are lost equally or if there is preferential loss of some clonotypes is not currently known, but limited investigations have shown that CD8 T cell responses against the immediate early transactivators ORF62 and ORF63 are reduced in older individuals [42] and patients with malignancies [84], respectively.

VZV reactivation results in a local immune response in the ganglia (Fig. 1). A study that examined ganglia collected from people who suffered from zoster 1–4·5 months before they died from other causes reported the presence of T cells (75% of which were non-cytolytic CD8 T cells), B cells, macrophages and NK cells, but no dendritic cells in the ganglia [85]. The recruitment of T and NK cells to the ganglia could, potentially, be due to VZV-induced expression of chemokine CXCL10 from neurones, which binds to

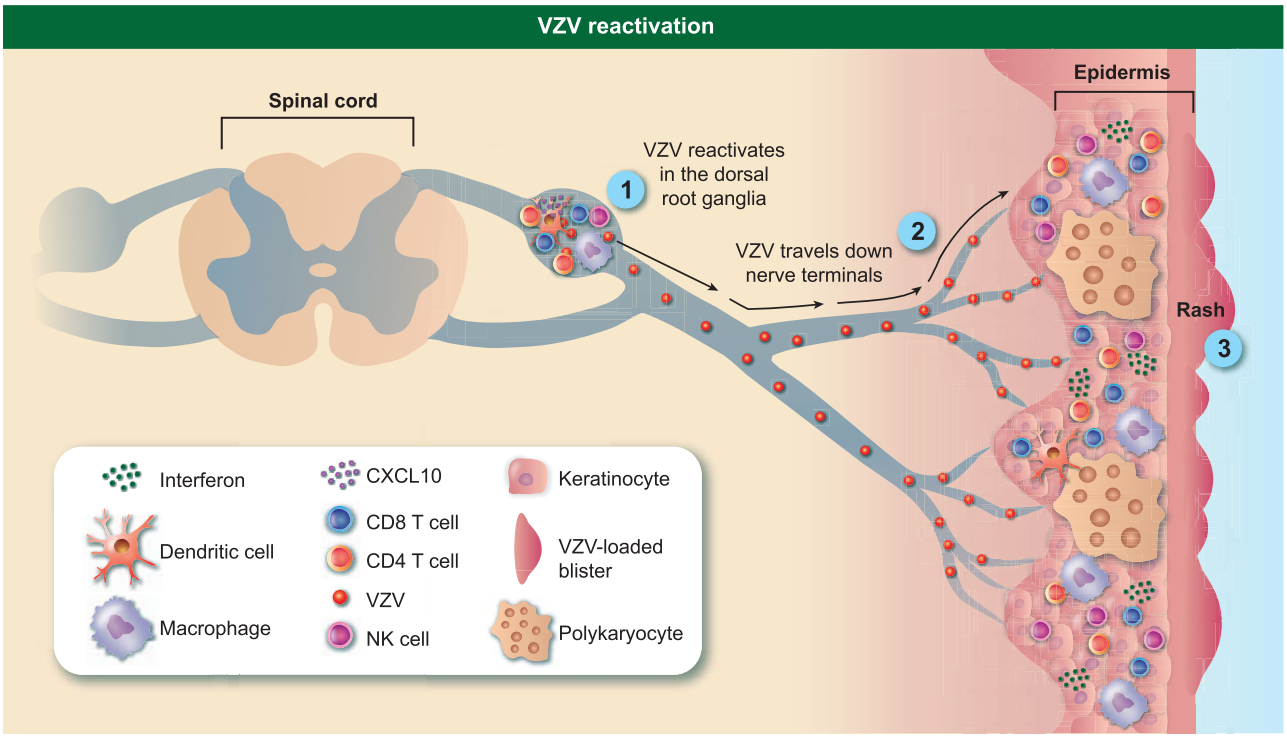

Fig. 1. Varicella zoster virus (VZV) immune response during reactivation. When immune responses weaken, VZV reactivates by travelling anterograde towards nerve endings, replicates in keratinocytes and epithelial cells causing the formation of polykaryocytes, leading ultimately to a dermatomal rash. The local immune response in the ganglia is characterized by the infiltration of CD8, CD4, natural killer (NK) cells, macrophages and B cells. The immune response in the skin is characterized by CD4, CD8, NK cells and macrophages along with increased expression of interferon (IFN)-γ, tumour necrosis factor (TNF)-α and interleukin (IL)-6.

CXCR3 to induce migration of memory T cells and NK cells [86]. Up-regulation of major histocompatibility complex (MHC)-I and MHC-II molecules during reactivation has also been observed, suggesting a second mechanism for T cell retention and activation in the sensory ganglia [85]. Skin biopsies collected during reactivation show the presence of CD4, CD8, NK cells and macrophages, along with increased expression of IFN-γ, TNF-α and IL-6, compared to skin biopsies from healthy controls [87] (Fig. 1).

As with primary infection, HZ generally resolves with no complications; however, 26% of patients experience additional complications that are, on rare occasions, fatal [88]. The most common complication is post-herpetic neuralgia (PHN, 19% of HZ cases), defined as chronic pain in the affected dermatomes lasting many months after resolution of the rash due presumably to damaged nerve ending [88]. Another serious complication is herpes zoster ophthalmicus (1–10% of HZ cases), where reactivation from the first division of the trigeminal nerve leads to chronic ocular inflammation that could lead ultimately to blindness [88,89]. Additional rare complications include vasculopathy (which can occur with or without rash) where the virus infects the cerebral arteries and causes ischaemic infarctions in the brain or spinal cord, leading to stroke, aneurysm and cerebral haemorrhaging [90]. In immunocompromised individuals, VZV reactivation may also result in myelopathy, where the virus infects the spinal cord or spinal arteries [91].

Treatment for most of these complications include anti-viral therapy; however, the efficacy of anti-viral drugs initiated later than 72 h after the appearance of the rash is uncertain [92]. Corticosteroids have also been shown to reduce morbidity, although their efficacy is short-lived and does not reduce the risk of PHN [93]. Other treatments for PHN include anti-depressants and anti-epileptic drugs such as gabapentin [94,95], opiate analgesic drugs and topical anaesthetic drugs such as lidocaine and capsaicin [96]. VZV vasculopathy and myelitis are treated with intravenous acyclovir [90]. Unfortunately, a large proportion of patients do not respond to these treatments, or have only moderate relief of pain or adverse side effects to the drugs [97].

Vaccines against herpes zoster

Live attenuated Zostavax®

The Food and Drug Administration (FDA) approved Zostavax® for the prevention in zoster in people aged 60 years and older in May 2006 [98]. This vaccine contains 19 400 plaque-forming units (PFU)/dose compared to the

varicella vaccine Varivax®, which contains ~1350 PFU/dose of live attenuated virus [71]. Zostavax® was approved after the completion of the Shingles Prevention Study (SPS), a double-blind, placebo-controlled study that involved 38 546 people over the age of 60 years [99]. Results from the SPS showed that Zostavax® reduced the incidence of disease by 51% and lowered the incidence of PHN and associated pain by 66·5% in subjects aged at least 60 years [99]. Efficacy of this vaccine against HZ decreases with increasing age, with only 18% efficacy in individuals aged more than 80 years [99]. The FDA lowered the age requirement to 50 years in 2011 due to the increased efficacy in adults aged 50–59 (70%) [100,101]. Long-term efficacy of this vaccine was shown to drop to 21·1% for HZ and 35·4% for the PHN during the course of 7–10 years [102]. A booster dose of Zostavax® 10 years after the first dose has been shown to enhance protection against HZ in people over the age of 70 years [81]. Therefore, like Varivax®, boosters may be recommended for this population.

Zostavax® vaccination induces a significant increase in VZV cell-mediated responses compared to placebo recipients 6 weeks after vaccination; however, as described for efficacy, vaccine-induced increases in T cell responses correlates negatively with the age of the recipient [103]. Moreover, vaccine-induced cell-mediated immunity declined dramatically 1 year post-vaccination, and at the end of a 3-year follow up T cell immunity had returned to almost pre-vaccination levels [99]. A recent study showed that Zostavax® vaccination increases CD4 T cell responses to ORFs 40, 67, 9, 59, 12, 62 and 18 1 month after vaccination. However, after 6 months only CD4 T cells responses to ORFs 40, 59, 63 and 67 remained higher than pre-vaccination levels [104]. Interestingly, T cell responses to VZV Oka vaccine strain cross-recognize HSV-1 and HSV-2 antigens, which may indicate that the Zostavax® vaccine also provides some degree of protection against HSV [105]. Zostavax® vaccination increases a humoral immune response to VZV, albeit to a lesser extent compared to levels achieved after VZV reactivation in the absence of vaccination [65]. Zostavax® can boost the antibody titre of individuals who had previously had HZ, and the magnitude of this boost is correlated negatively with time since HZ [106].

Adverse reactions to Zostavax® include mainly pain and inflammation at the site of infection [107]. Concomitant vaccine administration of zoster and influenza vaccine or pneumococcal vaccines does not affect their immunogenicities adversely [108,109]. Although Zostavax® vaccine has been proved to be safe for HIV-infected people with 15% CD4 T cells or a CD4 T cell count of 200 cells/μl, it is contraindicated for people who are: (1) taking steroids (40 mg per day for more than 7 days or 20 mg per day for more than 14 days), (2) receiving biologicals such as anti-TNF (in the past 12 months) or (3) currently undergoing or underwent radiation or chemotherapy in the past 6 months [110–112]. The Center for Disease Control (CDC) also recommends that newly vaccinated people avoid contact with individuals at high risk for varicella complications such immune-compromised patients. Infectious viral DNA has been found in saliva from Zostavax® vaccinated individuals for up to 4 weeks post-vaccination [113].

Inactivated adjuvanted subunit vaccine

Another potential strategy to develop a more efficacious vaccine is to generate a subunit vaccine that expresses immunogenic VZV proteins. Subunit vaccines can provoke a strong immune response while being safe for individuals for whom live attenuated vaccines are contraindicated. Two doses of a subunit vaccine (HZ/su) developed by GlaxoSmithKline using adjuvanted recombinant glycoprotein E (ORF68) has shown great immunogenicity and efficacy in older individuals regardless of their age. A Phase III study with HZ/su was completed recently, with a total of 15 411 participants in which 8926 participants received the vaccine and 4466 served as the placebo group. In a 3·2-year follow up study, the vaccine showed overall 97·2% efficacy rate among all three age groups tested (50–59, 60–69 and ≥ 70 years) [114]. However, 81·5% of HZ/su recipients in the Phase III study experienced pain at the site of injection and 66% of recipients had mild to moderate systemic reactions (grade 3 severity in 11·4% of the subjects) such as myalgia (most common), fatigue and headache [114]. Glycoprotein E was selected for this subunit vaccine because it is the most abundant viral glycoprotein, and also elicits specific CD4 T cell responses [115,116]. The adjuvant being used is ASO1, which is a liposome-based adjuvant system containing 3-O-desacyl-4′-monophosphoryl and saponin QS-21, which activates the Toll-like receptor (TLR)-4 pathway and stimulates both antibody and T helper type 1 (Th1) responses [117]. Two doses of HZ/su elicited a stronger anti-VZV gE, anti-VZV lysate antibody and anti-VZV lysate CD4 T cell response than two doses of Zostavax® in adults aged 50–70 years during a 12-month follow-up period [118]. CD4-specific T cells and antibody levels to HZ/su dropped by almost half after 42 months [118]. Three doses of the HZ/su vaccine were shown to be safe and immunogenic in haematopoietic cell transplants patients for up to 1 year and HIV patients for up to 18 months [119,120].

Heat-inactivated vaccines

A heat-inactivated Varivax® (V212) vaccine may be beneficial to bone marrow transplant recipients and recipients of haematopoietic-cell transplants [121,122]. Randomized, double-blind, placebo-controlled Phase III studies are being conducted currently to test the safety and efficacy of V212 in participants with solid tumours and haematological malignancies during a 5-year period. Study completion date is expected to the end of February 2017. The pros and

Table 1. Pros and cons for Zostervax®, herpes zoster/subunit vaccine (HZ/su) and V212 vaccines

Vaccine	Pros	Cons
Live, attenuated vaccine Zostavax®	• Boosts both cellular and humoral immune responses	• Contraindicated for people with weakened immune systems • Potential for shedding and therefore transmission to people with weakened immune system • Vaccine needs to stay frozen in order to remain potent • Immunity and efficacy wane with increasing age and with time since vaccination
Subunit vaccine HZ/su	• Only contains one viral protein, making it safe for immune-deficient people and pregnant women	• Requires 2 doses • High incidence of adverse events due to the potency of the adjuvant
Heat-inactivated V212	• Safe for immune-deficient people and pregnant women • Does not require refrigeration	• Stimulates a weaker immune response than live vaccines • Requires 4 doses, making compliance an issue

cons for the Zostervax®, HZ/su and V212 vaccines are described in Table 1.

Animal models of VZV studies

Our understanding of VZV pathogenesis remains incomplete. Gaps in our knowledge include: how VZV traffics to the skin and ganglia; when VZV establishes latency; viral transcription profile in the ganglia during acute infection and latency; and host and viral factors that play a role in reactivation. These questions could potentially be addressed by having a robust animal model of VZV infection. However, experimental inoculations of several animal models with VZV have failed to recapitulate all the essential features of VZV infection due to the strict human specificity of VZV. Specifically, infection of rodent models and non-human primates leads to the establishment of latency without viraemia or rash [60,61]. Similarly, infection of non-human primates results in abortive infection [123].

Due to the limitations of rodent models, an alternative model has been developed using the non-human primate homologue of VZV, simian varicella virus (SVV). The structure and size of the SVV genome is related closely to that of VZV [124,125]. Immunization of monkeys with VZV can protect against SVV challenge indicative of antigenic similarities [126]. Intrabronchial infection of rhesus macaques with SVV reproduces the cardinal features of VZV infection in humans, including viraemia, replication in lungs, development of cellular and humoral immunity and the establishment of latency in the sensory ganglia with limited transcriptional profile [64,127–136].

Using this model, we showed that CD4 T cells play a critical role in controlling acute infection [135] as well as the establishment of latency [136]. We also characterized the specificity of the T cell response to SVV during acute infection and latency using IFN-γ enzyme-linked immunospot (ELISPOT) following stimulation with overlapping peptide libraries that covered the entire SVV genome [137]. Our data show a robust and broad T cell response during acute infection with CD8 T cell responses directed mainly against immediate early and early viral proteins, while CD4 T cell responses were directed against SVV late genes. During latent infection, T cell responses were reduced significantly in magnitude and breadth compared to those observed during acute infection [137]. Interestingly, T cell responses against ORF4, ORF11, ORF19, ORF31 and ORF 37 were maintained into latency, albeit at lower levels, whereas T cell responses to ORF10, ORF20, ORF29, ORF31, ORF62, ORF63 and ORF68 showed a significant decrease of about 83% between primary and latent infection [137]. These observations may explain the success of the subunit vaccine HZ/su, which contains adjuvanted ORF68 protein and can potentially aid in the development of a multivalent subunit vaccine.

Studies using this model have also shed light on VZV trafficking to the ganglia. African green macaques (AGMs) infected with SVV expressing enhanced green fluorescent protein show that SVV primarily infects memory T cells and demonstrated the presence of SVV infected memory T cells in the ganglia, supporting a role for T cells in transporting SVV into the ganglia [138]. This study also showed the infiltration of memory CD8 T cells (most abundant), CD4 T cells, as well as dendritic cells and macrophages into the ganglia during acute SVV infection of AGMs [139]. However, given the severity of SVV infection in AGMs and the differences between AGMs and human immune systems, these studies should be validated further in the rhesus macaque model. As described for VZV, SVV can be reactive in macaques that undergo radiation combined with immune suppressive treatments [134]. As described for VZV in humans, CD4 and CD8 T cells infiltrate the ganglia during SVV reactivation, which correlates with CXCL10 expression [140].

Conclusions

The need for a more effective vaccine against VZV is imperative, due to the increased frequency of older

individuals. In fact, the number of individuals over the age of 65 is projected to double or triple by 2050 in most of the developed and developing world. Given the important role of T cell immunity in preventing reactivation, we need to develop novel vaccine strategies that specifically boost T cell immunity. Unfortunately, although several studies have demonstrated T cell responses to specific ORFs, no study to date has examined the immunogenicity of the entire VZV proteome and how it changes with age. Consequently, we do not yet have a complete understanding of which T cell responses decline most significantly with age and should be boosted. We also do not know which T cell responses are protective or how many VZV-specific T cells are required for protection against reactivation. We should be cautiously optimistic about the early success of the HZ/su vaccine. A similar strategy was employed to develop a vaccine against HSV-1 and HSV-2 using gD, which is also the most abundant protein in HSV. However, despite great success in animal models, this subunit vaccine failed in clinical trials [141,142]. Therefore, using subunit vaccines that contain more than just one gene may be more successful at inducing a longer and more protective immune response. Studies have shown that only 6·7% of individuals over the age of 60 have received the current vaccine available for HZ in the United States [143]. Therefore, it is especially important to educate people and talk to physicians about this disease and the importance of being vaccinated.

Disclosure

Authors have no competing interests to disclose.

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