# Efficacy of varicella (VZV) vaccination: an update for the clinician

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***Abstract:*** Varicella-zoster virus (VZV) infection causes two distinct clinical conditions. Primary varicella infection results in chickenpox, a contagious rash illness typically seen among children. VZV can reactivate years after the initial infection to cause herpes zoster (HZ) and lead to post-herpetic neuralgia, a common complication resulting in persistent pain that may last for years after the zoster rash resolves. A person's risk of having longer lasting and more severe pain associated with HZ increases with age. Since the introduction of VZV vaccines, the rates of infection, hospitalizations, and mortality have declined. In this review, we discuss in detail current VZV vaccines available for the prevention of VZV and HZ infections. Varilrix (GSK Biologicals, UK), Varivax (Merck, USA) and the combined measles, mumps, rubella, and varicella (MMRV) vaccine contain the live attenuated Oka strain of VZV for routine varicella vaccination. While Zostavax is the only HZ vaccine currently approved for use in the United States and the European Union [EMEA, 2011], a subunit vaccine candidate called HZ/su has recently shown improved efficacy for zoster prevention in two clinical trial phase III studies. VariZIG, a post-exposure prophylactic, uses zoster immune globulin to prevent VZV infection in those who have recently been in contact with VZV but lack evidence of varicella immunity and are contraindicated to receive the varicella vaccine. Further, we discuss the skin tropic and neurotropic factor VZV ORF7 gene and its involvement in varicella infection, reactivation and latency in ganglia. Ultimately, these studies can contribute to the development of a neuroattenuated vaccine candidate against varicella or a vector for delivery of other virus antigens.

***Keywords:*** Chickenpox, Shingles, Vaccine, Varicella-zoster virus, VZV, Varilrix, Varivax

## Varicella-zoster virus

Varicella-zoster virus (VZV) is a double-stranded DNA virus and a member of the *herpesviridae* family [Arvin, 2013]. Human beings are the only known hosts of this virus. VZV has an envelope with viral glycoproteins inserted in the membrane. Within the envelope, a tegument layer consisting of viral regulatory proteins surrounds an icosahedral nucleocapsid core that contains the linear double-stranded DNA genome [Arvin, 2013]. The VZV genome (125 kb) encodes 71 open reading frames (ORFs), approximately 44 of which are genes essential for viral replication and pathogenesis [Cohen, 2010; Zhang *et al.* 2010]. Primary infection with VZV results in the diffuse vesicular rash of varicella, or chickenpox. The incubation period usually ranges between 7–23 days, during which the virus spreads to the tonsils and other local lymphoid tissues, from where infected T-cells can transport the virus *via* the bloodstream to the skin [Ku *et al.* 2004]. The major route of transmission is airborne; however, transmissions *via* aerosols or direct contact with the blister fluid have also been reported [Zerboni *et al.* 2014]. Acute varicella infection is generally a mild disease and self-limiting compared with the more severe presentations found in adults and immunocompromised patients. VZV has the capacity to persist in the body after primary infection as a latent infection in sensory nerve ganglia. Reactivation of VZV causes herpes zoster (HZ), also known as zoster or shingles [Mahalingam *et al.* 1991; Zerboni *et al.* 2014]. When viral replication is reactivated, VZV reaches the skin *via* anterograde axonal transport to produce the symptoms of HZ [Gershon and Gershon, 2010], characterized by pain and rashes involving one to three dermatomes [Ozaki *et al.* 1996]. Anyone

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who has been infected with VZV is at risk of developing HZ, although this is more prevalent in the elderly and immunocompromised individuals. Persons over the age of 50 years are at a higher risk for VZV reactivation and the incidence of HZ after age 60 is 8 to 10-fold higher than in those under 60 years old [Harnisch, 1984]. The decline of VZV-specific cell-mediated immunity (CMI) is the principal factor in the disruption of the dynamic containment process responsible for VZV latency within the sensory ganglion. VZV-specific CMI may limit reactivation of latent VZV in sensory neurons and prevent the development of HZ by inhibiting the spread of VZV infection from these neurons. VZV-specific $CD4^+$ and $CD8^+$ T-cells are both involved, but $CD4^+$ T-cells appear predominant [Malavige *et al.* 2008; Steain *et al.* 2014]. Older adults and people with compromised or suppressed immune systems are more likely to have complications from HZ [Harpaz *et al.* 2008], including postherpetic neuralgia (PHN), ophthalmicus, bacterial superinfections, local muscle weakness, and scarring. The most common complication of HZ is PHN, a persistent, debilitating nerve pain in areas where the HZ skin lesions appear. This pain can last for months or even years after the episode of HZ, directly interfering with a patient's quality of life. A person's risk of developing PHN increases with age. In the central nervous system, manifestations of varicella range from aseptic meningitis to encephalitis. Encephalitis is an infrequent complication of varicella, but may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Some studies suggest that exposure to varicella boosts a person's immunity to VZV and reduces the risk for VZV reactivation [Jumaan *et al.* 2005; Leung *et al.* 2011; Yih *et al.* 2005]. In the United States, HZ rates are increasing among adults. This increase has been gradual over a long period of time. Despite concerns that routine childhood varicella vaccination could lead to an increase in HZ due to reduced opportunities for exposure to VZV [Brisson *et al.* 2002; Ferguson *et al.* 1996; Reynolds *et al.* 2008], the current two-dose varicella vaccination program has lowered varicella incidence, outbreaks and hospitalizations in the US [Bialek *et al.* 2013; Leung *et al.* 2015b; Seward *et al.* 2002].

## Vaccines

Varicella is one of the leading causes of vaccine-preventable deaths in children [CDC, 1999]. Routine childhood immunization has markedly reduced the incidence of varicella in the US [Marin *et al.* 2007, 2008; Schmid and Jumaan, 2010; Seward *et al.* 2008]. The varicella vaccination may provide protection against 85% of cases of chickenpox and 95% of cases of severe secondary infection [Vazquez *et al.* 2001]. Prior to 1995, nearly four million cases of chickenpox occurred each year in the US, resulting in 11,000 hospital admissions and 100 deaths [Galil *et al.* 2002]. However, the introduction of a universal vaccination in many countries such as Japan [Takahashi *et al.* 1974], Korea [Sadzot-Delvaux *et al.* 2008], and the US [Marin *et al.* 2007] has led to a dramatic reduction in the varicella incidence, its associated complications, hospitalizations, and fatality rate [Holmes, 1996]. There are two live, attenuated VZV-containing vaccines available for the prevention of varicella. Varivax (Merck, USA), is a single-antigen varicella vaccine introduced in 1995 for use among healthy individuals 12 months of age and older [CDC, 1996]. A combination measles, mumps, rubella, and varicella vaccine (MMRV) was licensed in the US in 2005 for healthy children aged 12 months to 12 years [Marin *et al.* 2010]. The zoster vaccine, Zostavax, from the Shingles Prevention Study is a live, attenuated virus vaccine used in the prevention of HZ and PHN in individuals 50 years of age and older [Harpaz *et al.* 2008; Lu *et al.* 2009; Oxman *et al.* 2005; Oxman and Levin, 2008]. In two recent randomized phase III trials, the HZ/su HZ vaccine candidate (GSK Biologicals, UK) showed improved, lasting efficacy in adults 50 years of age and older [Lal *et al.* 2015a, 2015b]. VariZIG is a zoster immune globulin (ZIG) recommended for immunocompromised patients, pregnant women, preterm infants, and neonates whose mothers have signs and symptoms of varicella around the time of delivery [Brunell *et al.* 1969; CDC, 2013]. Our group previously identified the unique VZV ORF7 to be both a skin tropic and neurotropic factor for efficient primary VZV infection. Currently, ORF7 is the only known gene required for viral spread in human neurons and its role could lead to the potential development of a neuroattenuated vaccine against HZ or a vector for delivery of other antigens [Zhang *et al.* 2008, 2010].

## Varicella vaccines

### *Varivax and Varilrix*

Varivax (Merck, USA) is a live, attenuated varicella vaccine, derived from the Oka strain of VZV [Takahashi *et al.* 1974]. The vaccine was licensed

for general use in Japan and Korea in 1988 [Sadzot-Delvaux *et al.* 2008; Takahashi *et al.* 1974] and licensed in the US in 1995 for persons 12 months of age and older. Varivax is administered by subcutaneous injection. Two routine doses of Varivax are recommended for children; the first dose at 12–15 months old and second dose at 4–6 years old. The second dose catch-up vaccination can be given three months after the first dose for children younger than 13 years of age. For adolescents and adults 13 years old and above, two doses should be administered 4–8 weeks apart [Marin *et al.* 2007]. The virus was attenuated by sequential passages in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells [Takahashi *et al.* 1974]. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages. This reconstituted vaccine contains small amounts of sucrose, processed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, potassium chloride, trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine is reconstituted with sterile water and contains no preservatives [Marin *et al.* 2007]. Another equally effective varicella vaccine is Varilrix (GSK Biologicals, UK). Both vaccines contain live attenuated VZV, which can reactivate and cause HZ [Brunell and Argaw, 2000; Cimolai *et al.* 2014; Civen *et al.* 2009; Gilden *et al.* 1983; Schmid and Jumaan, 2010]. However, children vaccinated against varicella appear to have a lower risk of HZ than people who were infected with wild-type VZV [Sadzot-Delvaux *et al.* 2008; Schmid and Jumaan, 2010]. This is because vaccinated children are less likely to become infected with wild-type VZV, and the risk of Oka/Merck strain VZV reactivation is lower than the risk of wild-type VZV reactivation. In a study of children with leukemia, those who received varicella vaccination had a 67% lower risk of developing HZ as compared with those who had natural infection with wild-type VZV [Hardy *et al.* 1991]. Healthy children vaccinated against varicella demonstrated a reduced risk of HZ than children infected with wild-type VZV [Weinmann *et al.* 2013]. In addition, studies have proven that the varicella vaccine is both well tolerated and efficacious, as 97% of children display detectable antibody titers 7–10 years after vaccination [Johnson *et al.* 1997; Seward *et al.*, 2008]. Vaccine efficacy is estimated to be 70–90% effective against varicella infection, and 90–100% effective against moderate and severe disease [Krause and Klinman, 1995]. Among healthy adolescents and adults 13 years of age and older, an average of 78% developed antibodies against VZV after one dose, and 99% developed antibodies after a second dose given 4–8 weeks later. Antibodies persisted for at least one year in 97% of vaccinated individuals who received the second dose 4–8 weeks after the first dose [Krause and Klinman, 1995]. In those with breakthrough varicella infection, most did not present with a fever [Krause and Klinman, 1995]. Recent investigations have identified the presence of asthma, use of steroids, and vaccination at an age younger than 15 months as risk factors for breakthrough varicella. Classification of varicella infection as breakthrough could be a result of several factors, including interference of vaccine virus replication by circulating antibodies, errors in storage or handling causing an impotent vaccine, and inaccurate record keeping. Interference from a live viral vaccine administered before the varicella vaccine could also reduce vaccine effectiveness [Marin *et al.* 2007]. A study of children in two health maintenance organizations during 1995–1999 found that children who received varicella vaccination $<30$ days after the measles-mumps-rubella (MMR) vaccination had a three-fold increased risk of breakthrough varicella as compared with those who received the varicella vaccine before, simultaneously with, or $>30$ days after the MMR vaccine [Lapphra and Scheifele, 2009].

### *Measles–mumps–rubella–varicella vaccine*

In September 2005, the US Food and Drug Administration (FDA) licensed a combined live, attenuated MMRV vaccine (ProQuad, Merck, USA) for use in persons 12 months through 12 years of age. A 0.5 ml dose for subcutaneous or intramuscular injection is administered at 12–15 months of age and a second dose, if needed, is usually administered at 4–6 years of age [Marin *et al.* 2010]. A study showed support of the implementation of a two-dose MMRV vaccination to ensure optimal protection [Prymula *et al.* 2014]. The vaccine viruses in the MMRV vaccine are identical and of equal titer to those in the original MMR vaccine [Marin *et al.* 2010]. The titer of Oka/Merck however, is higher in the MMRV vaccine than in a single-antigen varicella vaccine such as Varivax or Varilrix, with a minimum of 9772 plaque-forming units (PFUs) *versus* 1350 PFUs, respectively. Each 0.5 ml dose contains small quantities of sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium

phosphate monobasic, potassium chloride, potassium phosphate dibasic, residual components of MRC-5 cells (DNA and protein), neomycin, bovine calf serum, and other buffer and media ingredients. The vaccine is reconstituted with sterile water and contains no preservatives [Marin *et al.* 2010]. The efficacies and immunogenicities of the varicella and MMRV vaccines are comparable [Kuter *et al.* 2006; Leung *et al.* 2015a; Shinefield *et al.* 2005a, 2005b; Vesikari *et al.* 2012]. In meganalysis studies, the MMRV vaccine demonstrated well tolerated safety profiles, except for a higher incidence of fever (relative risks 1.12–1.60) and a measles/rubella-like rash (relative risks 1.44–1.45) in MMRV groups [Leung *et al.* 2015a; Ma *et al.* 2015a]. Some children who received the MMRV vaccine may have an increased risk of fever and febrile seizure 6–12 days after the first vaccine dose when the peak in replication of the live attenuated measles virus occurs [Barlow *et al.* 2001; Ma *et al.* 2015b; MacDonald *et al.* 2014]. This risk period has been defined variably in clinical and epidemiologic studies as 8–14 days, 7–12 days, or 5–12 days [Barlow *et al.* 2001; Jacobsen *et al.* 2009; Vestergaard *et al.* 2004]. However, febrile seizures are not common and have not been associated with any long-term problems [Klein *et al.* 2010; Rowhani-Rahbar *et al.* 2013]. The risk for febrile seizures in children during measles illness is in fact higher than the risk after either MMRV or MMR vaccination [Perry and Halsey, 2004]. In the 12–47 month age group, the Centers for Disease Control and Prevention recommends that the first dose be administered by separate injections of MMR vaccine and varicella vaccine, except in the case of patient preference for the MMRV vaccine or provider assessment of potential adverse events. For the second dose of MMRV vaccine in the 15 months to 12 years age group and for the first dose at age 48 months and older, the MMRV vaccine is generally preferred over separate injections of its equivalent component vaccines [Marin *et al.* 2010]. The use of the MMRV vaccine simplifies immunization delivery by providing protection against more diseases with one less injection. This improves timely vaccination coverage and reduces healthcare costs for additional health visits [Knuf *et al.* 2008; Marin *et al.* 2010]. However, administering the MMR and varicella vaccines separately avoids the increased risk for a febrile seizure after the first dose of MMRV vaccine [Barlow *et al.* 2001; Ma *et al.* 2015a; MacDonald *et al.* 2014]. Given the balance of risks, benefits and the importance of individual preferences, decisions should be made by caregivers and parents on a case-by-case basis.

## Herpes zoster vaccines

### *Zostavax*

Zostavax (Merck, USA) is the only shingles vaccine currently used in persons 60 years of age and older who have no contraindications [CDC, 2011a; Oxman *et al.* 2005]. It is a lyophilized preparation containing at least a 14-fold greater titer of the same live attenuated Oka/Merck strain of VZV used in the varicella and MMRV vaccines. Zostavax is administered subcutaneously and each dose contains a minimum of 19,400 PFUs of VZV active ingredient, compared with the varicella vaccine which contains 1350 PFUs [CDC, 2011a; Oxman *et al.* 2005]. For people with a severe allergic reaction to particular vaccine components, other clinically relevant ingredients include hydrolyzed porcine gelatin, neomycin and residual DNA and protein from the MRC-5 human cell line. The vaccine is reconstituted with sterile water and contains no preservatives [CDC, 2011b; Oxman *et al.* 2005]. The US FDA approved Zostavax for persons aged 50 years and older based on a study showing that the vaccine decreased the risk of developing HZ by 69.8% (95% CI, 54.1–80.6%) in the age group of 50–59 years old over a mean follow-up time of 1.3 years [Merck and Co., 2011; Schmader *et al.* 2012a]. However, the Advisory Committee on Immunization Practices (ACIP) recommends its use in adults aged 60 years and older [CDC, 2011b]. This is partially due to vaccine supply shortages from Merck and Co, Inc. [CDC, 2007] and the need for more data on short- and long-term vaccine efficacy, safety, and immunogenicity. As mentioned previously, the zoster vaccine administered to adults aged 50–59 years reduced the risk of developing HZ over a mean follow-up period of 1.3 years [Schmader *et al.* 2012a]. In the subset of patients aged 60–69 years from the Shingles Prevention Study (SPS), the vaccine group had an efficacy of 51.3% (CI 44.2–57.6%) for prevention of HZ and 66.5% fewer PHN complications in recipients that developed HZ (CI 47.5–79.2%). In adults aged 70 years and older, efficacy decreased to 37.6% for HZ prevention and 66.8% fewer PHN complications over a three year period [Oxman *et al.* 2005] (Table 1). Zostavax efficacy against HZ and PHN decreased with age and is contraindicated for immunocompromised persons [Langan *et al.* 2013; Oxman *et al.* 2005]. Moreover, the Short-Term Persistence Sub-Study (STPS) showed declining vaccine efficacies after 5 years post-vaccination for HZ burden of illness (BOI)

**Table 1.** Zostavax shingles vaccine and HZ/su vaccine candidate.

| | Zostavax (SPS) | (GSK clinical trial III) |
|---|---|---|
| Vaccine type | Live, attenuated VZV Oka strain | Nonlive, recombinant subunit glycoprotein E + adjuvant AS01 |
| Recommendations | ⩾60 years immunocompetent adults | ⩾50 years immunocompetent adults |
| Administration | 1 subcutaneous injection | 2 intramuscular injections (2 months apart) |
| Vaccine efficacy for HZ incidence (95% CI) | **Overall:** 51.3%* (44.2–57.6)<br>**50–59 years:** 69.8% (54.1–80.6)<br>**60–69 years:** 63.9% (55.5–70.9)<br>⩾**70 years:** 37.6% (25.0–48.1) | **Overall:** 97.2%* (93.7–99.0)<br>**50–59 years:** 96.6% (89.6–99.3)<br>**60–69 years:** 97.4% (90.1–99.7)<br>⩾**70 years:** 97.9% (87.9–100.0) |
| Immunity duration | Age-dependent | Age-independent |
| FDA approval | Yes | Not yet |

*Percentage reduction in vaccine, compared with placebo.
CI, confidence interval; FDA, US Food and Drug Administration; GSK, GlaxoSmithKline; HZ, herpes zoster; HZ/Su, HZ-adjuvanted subunit vaccines ZOSTER-006 and ZOSTER-022; SPS, Shingles Prevention Study; VZV, varicella-zoster virus.

(61.1–50.1%), incidence of PHN (66.5–60.1%), and the incidence of HZ (51.3–39.6%) [Schmader *et al.* 2012b].Vaccine persistence declined further in year 8 post-vaccination in the Long-Term Persistence Study (LTPS) [Morrison *et al.* 2015]. Although initial zoster vaccine efficacy was significant, Zostavax has a clinically relevant declining efficacy in reducing HZ incidence in post-vaccination years 3–11. [Cook and Flaherty, 2015; Morrison *et al.* 2015; Oxman *et al.* 2005; Oxman and Levin, 2008; Schmader *et al.* 2012b].

### *HZ/su Vaccine*

Recent results from studies on the HZ-adjuvanted subunit vaccine, HZ/su vaccine (ZOE-50, GSK Biologicals, UK), show its promise as a candidate for the prevention of HZ in adults aged 50 years and older [Lal *et al.* 2015a; Leroux-Roels *et al.* 2012]. ZOE-50 is a randomized, placebo-controlled, observer-blind, phase III study. The HZ/su candidate vaccine is nonlive and combines glycoprotein E (gE), a VZV envelop protein, with an adjuvant system, AS01B, that enhances the immunological response to gE. Glycoprotein E plays a critical role in VZV replication and is the main target of VZV-specific $CD4^+$ T-cell responses [Arvin and Abendroth, 2007; Moffat *et al.* 2007]. The VZV gE subunit consists of a truncated molecule lacking the anchor and carboxy-terminal tail domains, which is transfected into Chinese hamster ovary (CHO) cells (CHO-gE-2-9) [Haumont *et al.* 1996]. The AS01 adjuvant system contains QS-21 Stimulon (Agenus, Massachusetts, US), MPL (3-O-desacyl-4'-monophosphoryl lipid A) and liposomes [Lal *et al.* 2013; Leroux-Roels *et al.* 2012]. MPL and saponin QS-21 boost immune responses by activating Toll-like receptor 4 (TLR-4) and increasing antigen uptake and retention by dendritic cells [Coffman *et al.* 2010]. The HZ/su vaccine combines 50 μg recombinant VZV gE antigen with AS01B adjuvant (50 μg MPL and 50 μg QS-21), and is administered *via* two doses intramuscularly into the left deltoid area. Participants ($n$ = 15,411) were stratified into age groups 50–59, 60–69, and ⩾70 years. The primary efficacy end point of ZOE-50 exhibited an overall vaccine efficacy of 97.2% in reducing the risk of HZ (95% CI, 93.7–99.0%) for all age groups from 50–70 years and over. Vaccine efficacy was calculated as one minus the ratio of the incidence of HZ in the HZ/su vaccine group to the incidence of HZ in the placebo group, multiplied by 100. During a mean follow up of 3.2 years, HZ incidence rates were 0.3 and 9.1 per 1000 person-years in the vaccine group and placebo group, respectively [Lal *et al.* 2015a]. There were solicited or unsolicited reports of grade 3 symptoms in 17% of vaccine recipients and in 3.2% of placebo recipients [Lal *et al.* 2015a]. The safety profile of HZ/su vaccine was tolerable and no severe adverse events were reported [Leroux-Roels *et al.* 2012]. Further safety and immunogenicity assessments up to six years post-vaccination in healthy older adults confirm that gE-specific cellular and humoral immune responses persisted [Chlibek *et al.* 2015] and that the two-dose regimen of HZ/su exhibits an acceptable safety profile for healthy young (10–30 years old) and older (50–69 years old) Japanese adults [Lal *et al.* 2013]. Unlike Zostavax, HZ/su is a recombinant adjuvanted vaccine and induces higher immunogenicity than a live attenuated VZV vaccine. The ZOE-50 study shows

that HZ/su provides age-independent protection against HZ and that vaccine efficacy does not wane in older individuals. In comparison, Zostavax tends to lose efficacy as patients age and over time post-vaccination [Cook and Flaherty, 2015; Morrison *et al.* 2015; Oxman *et al.* 2005; Oxman and Levin, 2008; Schmader *et al.* 2012b]. Previous studies have found that higher VZV cell mediated immunity (CMI) at HZ onset, as indicated by high vaccine-induced $CD4^+$ T-cell responder frequency, was associated with reduced HZ severity and lower PHN incidence [Weinberg *et al.* 2009]. Two doses of the HZ/su vaccine induced stronger gE- and VZV-specific $CD4^+$ T-cell and antibody responses than two doses of a live, attenuated Oka strain VZV vaccine. The addition of a second dose of the Oka strain VZV vaccine did not further boost immune responses elicited by the initial dose of HZ/su injection [Leroux-Roels *et al.* 2012]. The Zostavax vaccine is recommended for adults aged ⩾60 years; however, it is contraindicated for immunocompromised persons. The HZ/su vaccine efficacy is also being evaluated in adults aged ⩾70 years (ZOE-70) [Lal *et al.* 2015a] and immunocompromised patients, including solid and hematological cancer patients, hematopoietic stem cell and renal transplant recipients and HIV-infected people [GSK, 2015]. Further evaluations of the HZ/su vaccine is necessary to ensure persistent efficacy in the prevention of PHN, HZ-associated morbidity, mortality, and hospitalizations. Long-term studies on vaccine safety and immunogenicity are also necessary in order for federal agencies to approve its future use in the general population.

## Current research and applications

### *ORF7*

During latency, VZV is found in ganglia but the mechanisms involved in the establishment of latency and varicella reactivation are still unknown. The current varicella vaccines are highly attenuated in the skin and may reactivate to damage sensory neurons [Ku *et al.* 2004; Mahalingam *et al.* 1991; Silver and Zhu, 2014]. VZV genome (125 kb) encodes 71 ORFs, including factors required for efficient invasion of and egress from specific tissues during the course of natural infection. Using a comprehensive library of whole-VZV genome deletion mutants, our laboratory identified ORF7 to be both a skin tropic and neurotropic factor [Selariu *et al.* 2012; Zhang *et al.* 2010]. The VZV ORF7 deletion mutant inhibited viral spread in human nervous tissue *ex vivo* and in an *in vivo* mouse model. Unlike the commonly used vaccine viral strain Oka, the ORF7 mutant is a pure and genetically defined strain lacking the ability to infect human skin and nervous tissue *in vivo*, thus meeting crucial safety and genetic stability criteria for a promising next-generation chickenpox vaccine. Using bacterial artificial chromosome engineering to generate recombinant ORF7 mutants is useful in studying viral replication, latency and pathogenesis [Selariu *et al.* 2012; Zhang *et al.* 2010]. While current varicella vaccines have been shown to significantly reduce the incidence rates of VZV infections, studies examining the impact of varicella vaccination have found conflicting results regarding trends in HZ incidence [Johnson *et al.* 2015; Jumaan *et al.* 2005; Yih *et al.* 2005]. Therefore, further understanding of VZV neurotropism and the role of ORF7 in neuropathogenesis could contribute to the development of a neuroattenuated vaccine against chickenpox or a vector for delivery of other antigens to inhibit VZV reactivation.

### *Varicella zoster immune globulin (VariZIG)*

In March 2013, VariZIG (Cangene Corporation, Winnipeg, Canada) was licensed by the US FDA for postexposure prophylaxis of varicella for persons at high risk for severe disease who lack evidence of immunity to varicella and for whom the varicella vaccine is contraindicated [CDC, 2006]. VariZIG is a purified immune globulin preparation made from human plasma containing high levels of anti-VZV immunoglobulin G (IgG). It is the only varicella ZIG preparation currently available in the US [CDC, 2006] and is administered intramuscularly at a recommended dose of 125 IU/10 kg of body weight, up to a maximum dose of 625 IU. Studies have indicated that clinical varicella was prevented in susceptible, healthy children by administration of ZIG (prepared from patients recovering from HZ) within 72 hours of household exposure [Brunell *et al.* 1969]. ZIG also lowered attack rates and modified disease severity among susceptible immunocompromised children when administered within 72 hours after exposure [Brunell *et al.* 1972; Mona Marin *et al.* 2013]. VariZIG is now approved for administration as soon as possible following VZV exposure, ideally within 96 hours for greatest effectiveness [CDC, 2013]. The CDC recommends administration of VariZIG as soon as possible after exposure to the VZV and within 10 days. The ACIP also recommends receiving VariZIG by extending

the period of eligibility for previously recommended premature infants exposed to VZV during the neonatal period. Because the immune systems of premature infants may be compromised, they are considered to be at high risk for severe varicella [Marin *et al.* 2007]. The decision to administer VariZIG depends on three factors: (1) whether the patient lacks evidence of immunity to varicella, (2) whether the exposure is likely to result in infection, and (3) whether the patient is at a greater risk for varicella complications than the general population. For high-risk patients who have additional exposure to VZV for more than three weeks after initial VariZIG administration, another dose of VariZIG should be considered [CDC, 2013]. For pregnant women who lack evidence of immunity to varicella and are at an increased risk for developing a varicella infection if exposed to a contagious individual, the possibility of receiving VariZIG was discussed [Bapat and Koren, 2013].

## Summary

Currently, the commonly used varicella vaccines (Varilrix/Varivax and MMRV) and zoster vaccine (Zostavax) contain the live attenuated Oka strain of VZV as the vaccine active ingredient. Since the introduction of the Oka strain varicella vaccine, varicella incidence [Galil *et al.* 2002; Guris *et al.* 2008; Seward *et al.* 2008], morbidity, mortality [Marin *et al.* 2011; Nguyen *et al.* 2005] and hospitalization rates [Davis *et al.* 2004; Shah *et al.* 2010; Zhou *et al.* 2005] have been reduced significantly.

Although the Oka vaccine virus is highly attenuated in the skin, it may reactivate to damage sensory neurons [Ku *et al.* 2004; Mahalingam *et al.* 1991; Silver and Zhu, 2014]. Vaccination of adults with the Oka varicella vaccine produces both antibody and CMI responses [Hayward *et al.* 1992], and the vaccines maintain high antibody levels as a result of endogenous reactivation of the Oka vaccine virus [Krause and Klinman, 2000]. Following naturally acquired VZV infection, VZV-specific antibody and CMI responses continue to be re-boosted not only by reactivation of latent virus, but also exogenous re-exposure to VZV. Without the occasional exogenous VZV re-exposure, VZV-specific immune responses decline and VZV reactivation could lead to clinical manifestations of HZ [Hope-Simpson, 1965; Luyten *et al.* 2014]. Although more evidence is needed to support the exogenous-boosting hypothesis [Ogunjimi *et al.* 2013], future studies on its long-term effect on HZ incidence may shed more light.

While current varicella vaccines have been shown to significantly reduce the incidence rates of VZV infections, studies examining the impact of varicella vaccination have found conflicting results regarding trends in HZ incidence [Johnson *et al.* 2015; Jumaan *et al.* 2005; Yih *et al.* 2005]. In a recent comprehensive review on the incidence of HZ, Kawai and colleagues examined 130 studies conducted in 26 countries during the pre- and post-varicella eras [Kawai *et al.* 2014]. Some studies reported no change in HZ incidence rates in the post vaccination era, while others reported an increase in HZ before the introduction of the varicella vaccine that continued into the post-vaccination era. There is no clear evidence however that these trends are the result of the varicella vaccine, as similar trends can be seen in countries in the absence of a national varicella vaccination program. We may have to wait a longer period of time to determine whether the varicella vaccination has an impact on HZ incidence.

For those who lack evidence of immunity to varicella after VZV exposure, VariZIG can be administered to reduce the risk of developing varicella infection. Unlike Zostavax, the new AS01-adjuvanted zoster vaccine, HZ/su, consists of gE and appears to be a promising candidate with an age-independent efficacy for HZ prevention maintained across age groups, from 50–70 years and over. The US FDA, however, has not yet approved this vaccine and further assessment is needed to ensure its efficacy in preventing HZ in the general population.

Meanwhile, genetic analysis of VZV ORFs offers insights into viral invasion of and egress from specific tissues during the course of natural infection. ORF7 is currently the only identified skin tropic and neurotropic factor in the VZV genome. A greater understanding of VZV ORF7 skin tropism and neurotropism could contribute to the development of a neuroattenuated vaccine against chickenpox and a vaccine vector for delivery of other antigens. Chickenpox and shingles are public health concerns because of their potential for serious complications, such as PHN, that worsen with age and have a negative impact on quality of life and cost of care. This raises the need for future studies to understand the impact of the varicella vaccine on HZ incidence and the

development of zoster vaccines that provides long-term efficacy, safety, and protection for adults of all ages, especially persons in immunocompromised conditions.

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## References

Arvin, A. and Abendroth, A. (2007) VZV: immunobiology and host response. In: Arvin, A., Campadelli-Fiume, G., Mocarski, E., Moore, P., Roizman, B., Whitley, R. *et al.* (eds), *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press, pp. 1–13.

Arvin, A., Fields, D., Knipe, D. and Howley, P. (2013) *Virology* 6: 2015–2057.

Bapat, P. and Koren, G. (2013) The role of VariZIG in pregnancy. *Expert Rev Vaccines* 12: 1243–1248.

Barlow, W., Davis, R., Glasser, J., Rhodes, P., Thompson, R., Mullooly, J. *et al.* (2001) The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 345: 656–661.

Bialek, S., Perella, D., Zhang, J., Mascola, L., Viner, K., Jackson, C. *et al.* (2013) Impact of a routine two-dose varicella vaccination program on varicella epidemiology. *Pediatrics* 132: e1134–e1140.

Brisson, M., Gay, N., Edmunds, W. and Andrews, N. (2002) Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine* 20: 2500–2507.

Brunell, P. and Argaw, T. (2000) Chickenpox attributable to a vaccine virus contracted from a vaccinee with zoster. *Pediatrics* 106: e28.

Brunell, P., Granat, M. and Gershon, A. (1972) The antigens of varicella-zoster virus. *J Immunol* 108: 731–737.

Brunell, P., Ross, A., Miller, L. and Kuo, B. (1969) Prevention of varicella by zoster immune globulin. *N Engl J Med* 280: 1191–1194.

CDC (1996) Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep* 45: 451–436.

CDC (1999) Prevention of varicella: update recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 48: 1–5.

CDC (2006) A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. *MMWR Morb Mortal Wkly Rep* 55: 209–210.

CDC (2007) Notice to readers: update on supply of vaccines containing varicella-zoster. *JAMA* 298: 736.

CDC (2011a) Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 60: 1–45.

CDC (2011b) Update on herpes zoster vaccine: licensure for persons aged 50 through 59 years. *MMWR Morb Mortal Wkly Rep* 60: 1528.

CDC (2013) Updated recommendations for use of VariZIG United States, 2013. *MMWR Morb Mortal Wkly Rep* 62: 574–576.

Chlibek, R., Pauksens, K., Rombo, L., van Rijckevorsel, G., Richardus, J., Plassmann, G. *et al.* (2015) Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. *Vaccine* 34: 863–868.

Cimolai, N., Krajden, M. and Petric, M. (2014) Herpes zoster eruption associated with vaccine-strain varicella-zoster virus: a case report. *BC Med J* 56: 135–136.

Civen, R., Chaves, S., Jumaan, A., Wu, H., Mascola, L., Gargiullo, P. *et al.* (2009) The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. *Pediatr Infect Dis J* 28: 954–959.

Coffman, R., Sher, A. and Seder, R. (2010) Vaccine adjuvants: putting innate immunity to work. *Immunity* 33: 492–503.

Cohen, J. (2010) The varicella-zoster virus genome. *Curr Top Microbiol Immunol* 342: 1–14.

Cook, S. and Flaherty, D. (2015) Review of the persistence of herpes zoster vaccine efficacy in clinical trials. *Clin Ther* 37: 2388–2397.

Davis, M., Patel, M. and Gebremariam, A. (2004) Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. *Pediatrics* 114: 786–792.

EMEA (2011) Zostavax European Public Assessment Report. Available at: http://www.ema.

europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000674/human_med_001185.jsp&mid=WC0b01ac058001d124

Ferguson, N., Anderson, R. and Garnett, G. (1996) Mass vaccination to control chickenpox: the influence of zoster. *Proc Natl Acad Sci USA* 93: 7231–7235.

Galil, K., Brown, C., Lin, F. and Seward, J. (2002) Hospitalizations for varicella in the United States, 1988 to 1999. *Pediatric Infect Dis J* 21: 931–935.

Gershon, A. and Gershon, M. (2010) Perspectives on vaccines against varicella-zoster virus infections. *Curr Top Microbiol Immunol* 342: 359–372.

Gilden, D., Vafai, A., Shtram, Y., Becker, Y., Devlin, M. and Wellish, M. (1983) Varicella-zoster virus DNA in human sensory ganglia. *Nature* 306: 478–480.

GSK (2015) GSK Candidate Vaccine for the Prevention of Shingles Demonstrates Overall Efficacy of 97.2% Which Does Not Diminish in the Age Groups Studied. London: GSK.

Guris, D., Jumaan, A., Mascola, L., Watson, B., Zhang, J., Chaves, S. *et al.* (2008) Changing varicella epidemiology in active surveillance sites-United States, 1995–2005. *J Infect Dis* 197(Suppl. 2): s71–s75.

Hardy, I., Gershon, A., Steinberg, S. and LaRussa, P. (1991) 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* 325: 1545–1550.

Harnisch, J. (1984) Zoster in the elderly: clinical, immunologic and therapeutic considerations. *J Am Geriatr Soc* 32: 789–793.

Harpaz, R., Ortega-Sanchez, I. and Seward, J. (2008) Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 57: 1–30.

Haumont, M., Jacquet, A., Massaer, M., Deleersnyder, V., Mazzu, P., Bollen, A. *et al.* (1996) Purification, characterization and immunogenicity of recombinant varicella-zoster virus glycoprotein gE secreted by Chinese hamster ovary cells. *Virus Res* 40: 199–204.

Hayward, A., Villanueba, E., Cosyns, M. and Levin, M. (1992) Varicella-zoster virus (VZV)-specific cytotoxicity after immunization of nonimmune adults with Oka strain attenuated VZV vaccine. *J Infect Dis* 166: 260–264.

Holmes, S. (1996) Review of recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, on varicella vaccine. *J Infect Dis* 174(Suppl. 3): s342–s344.

Hope-Simpson, R. (1965) The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* 58: 9–20.

Jacobsen, S., Ackerson, B., Sy, L., Tran, T., Jones, T., Yao, J. *et al.* (2009) Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* 27: 4656–4661.

Johnson, B., Palmer, L., Gatwood, J., Lenhart, G., Kawai, K. and Acosta, C. (2015) Annual incidence rates of herpes zoster among an immunocompetent population in the United States. *BMC Infect Dis* 15: 502.

Johnson, C., Stancin, T., Fattlar, D., Rome, L. and Kumar, M. (1997) A long-term prospective study of varicella vaccine in healthy children. *Pediatrics* 100: 761–766.

Jumaan, A., Yu, O., Jackson, L., Bohlke, K., Galil, K. and Seward, J. (2005) Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. *J Infect Dis* 191: 2002–2007.

Kawai, K., Gebremeskel, B. and Acosta, C. (2014) Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 4: e004833. DOI: 10.1136/bmjopen-2014-004833.

Klein, N., Fireman, B., Yih, W., Lewis, E., Kulldorff, M., Ray, P. *et al.* (2010) Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics* 126: e1–e8.

Knuf, M., Faber, J., Barth, I. and Habermehl, P. (2008) A combination vaccine against measles, mumps, rubella and varicella. *Drugs Today (Barc)* 44: 279–292.

Krause, P. and Klinman, D. (1995) Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. *J Pediatr* 127: 518–525.

Krause, P. and Klinman, D. (2000) Varicella vaccination: evidence for frequent reactivation of the vaccine strain in healthy children. *Nat Med* 6: 451–454.

Ku, C., Zerboni, L., Zerboni, L., Ito. H., Graham, B., Wallace, M. and Arvin, A. (2004) Varicella-zoster virus transfer to skin by T cells and modulation of viral replication by epidermal cell interferon-alpha. *J Exp Med* 200: 917–925.

Kuter, B., Brown, M., Hartzel, J., Williams, W., EvesiKaren, A., Black, S. *et al.* (2006) Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). *Hum Vaccine* 2: 205–214.

Lal, H., Cunningham, A., Godeaux, O., Chlibek, R., Diez-Domingo, J., Hwang, S. *et al.* (2015a) Efficacy

of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 372: 2087–2096.

Lal, H., Cunningham, A. and Heineman, T. (2015b) Adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 373: 1576–1577.

Lal, H., Zahaf, T. and Heineman, T. (2013) Safety and immunogenicity of an AS01-adjuvanted varicella zoster virus subunit candidate vaccine (HZ/su): a phase-I, open-label study in Japanese adults. *Hum Vaccine Immunother* 9: 1425–1429.

Langan, S., Smeeth, L., Margolis, D. and Thomas, S. (2013) Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med* 10: e1001420. DOI: 10.1371/journal.pmed.1001420.

Lapphra, K. and Scheifele, D. (2009) Does vaccination with the varicella vaccine within four weeks after the measles, mumps and rubella vaccine reduce protection? *Paediatr Child Health* 14: 501.

Leroux-Roels, I., Leroux-Roels, G., Clement, F., Vandepapeliere, P., Vassilev, V., Ledent, E. *et al.* (2012) A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. *J Infect Dis* 206: 1280–1290.

Leung, J., Harpaz, R., Molinari, N., Jumaan, A. and Zhou, F. (2011) Herpes zoster incidence among insured persons in the United States, 1993–2006: evaluation of impact of varicella vaccination. *Clin Infect Dis* 52: 332–340.

Leung, J., Hirai, H. and Tsoi, K. (2015a) Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: a meta-analysis of randomized controlled trials. *Expert Rev Vaccines* 14: 1149–1157.

Leung, J., Lopez, A., Blostein, J., Thayer, N., Zipprich, J., Clayton, A. *et al.* (2015b) Impact of the US two- dose varicella vaccination program on the epidemiology of varicella outbreaks: data from nine states, 2005–2012. *Pediatr Infect Dis J* 34: 1105–1109.

Lu, P., Euler, G., Jumaan, A. and Harpaz, R. (2009) 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* 27: 882–887.

Luyten, J., Ogunjimi, B. and Beutels, P. (2014) Varicella-zoster virus vaccination under the exogenous boosting hypothesis: two ethical perspectives. *Vaccine* 32: 7175–7178.

Ma, S., Li, X., Xiong, Y., Yao, A. and Chen, Q. (2015a) Combination measles-mumps-rubella-varicella vaccine in healthy children: a systematic review and meta-analysis of immunogenicity and safety. *Medicine (Baltimore)* 94: e1721. DOI: 10.1097/MD.0000000000001721.

Ma, S., Xiong, Y., Jiang, L. and Chen, Q. (2015b) Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: a systematic review and meta-analysis. *Vaccine* 33: 3636–3649.

MacDonald, S., Dover, D., Simmonds, K. and Svenson, L. (2014) Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study. *CMAJ* 186: 824–829.

Mahalingam, R., Smith, D., Wellish, M., Wolf, W., Dueland, A., Cohrs, R. *et al.* (1991) Simian varicella virus DNA in dorsal root ganglia. *Proc Natl Acad Sci USA* 88: 2750–2752.

Malavige, G., Jones, L., Black, A. and Ogg, G. (2008) 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* 152: 522–531.

Marin, M., Broder, K., Temte, J., Snider, D. and Seward, J. and Centers for Disease Control and Prevention. (2010) Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 59: 1–12.

Marin, M., Guris, D., Chaves, S., Schmid, S. and Seward, J. and Advisory Committee on Immunization Practices, Centers for Disease Control and *Prevention* (CDC) (2007) Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 56: 1–40.

Marin, M., Meissner, H. and Seward, J. (2008) Varicella prevention in the United States: a review of successes and challenges. *Pediatrics* 122: e744–e751.

Marin, M., Zhang, J. and Seward, J. (2011) Near elimination of varicella deaths in the US after implementation of the vaccination program. *Pediatrics* 128: 214–220.

Merck and Co. (2011) Available at: https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf

Moffat, J., Ku, C., Zerboni, L., Sommer, M. and Arvin, A. (2007) VZV: pathogenesis and the disease consequences of primary infection. In: Arvin, A., Campadelli-Fiume, G., Mocarski, E., Moore, P., Roizman, B., Whitley, R. *et al.* (eds), *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press, pp. 1–14.

Mona Marin, S., Bialek, S. and Jane, F. (2013) Updated recommendations for use of VariZIG — United States. *CDC 24/7* 62: 574–576.

Morrison, V., Johnson, G., Schmader, K., Levin, M., Zhang, J., Looney, D. *et al.* (2015) Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 60: 900–909.

Nguyen, H., Jumaan, A. and Seward, J. (2005) Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N Engl J Med* 352: 450–458.

Ogunjimi, B., Van Damme, P. and Beutels, P. (2013) Herpes zoster risk reduction through exposure to chickenpox patients: a systematic multidisciplinary review. *PloS One* 8: e66485. DOI: 10.1371/journal.pone.0066485.

Oxman, M. and Levin, M. (2008) Vaccination against herpes zoster and postherpetic neuralgia. *J Infect Dis* 197(Suppl. 2): s228–s236.

Oxman, M., Levin, M., Johnson, G., Schmader, K., Straus, S. *et al.* (2005) A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 352: 2271–2284.

Ozaki, T., Kajita, Y., Namazue, J. and Yamanishi, K. (1996) Isolation of varicella-zoster virus from vesicles in children with varicella. *J Med Virol* 48: 326–328.

Perry, R. and Halsey, N. (2004) The clinical significance of measles: a review. *J Infect Dis* 189(Suppl. 1): s4–s16.

Prymula, R., Bergsaker, M., Esposito, S., Gothefors, L., Man, S., Snegova, N. *et al.* (2014) Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. *Lancet* 383: 1313–1324.

Reynolds, M., Chaves, S., Harpaz, R., Lopez, A. and Seward, J. (2008) The impact of the varicella vaccination program on herpes zoster epidemiology in the United States: a review. *J Infect Dis* 197(Suppl. 2): s224–s227.

Rowhani-Rahbar, A., Fireman, B., Lewis, E., Nordin, J., Naleway, A. *et al.* (2013) Effect of age on the risk of fever and seizures following immunization with measles-containing vaccines in children. *J Am Med Assoc Pediatr* 167: 1111–1117.

Sadzot-Delvaux, C., Rentier, B., Wutzler, P., Asano, Y., Suga, S., Yoshikawa, T. *et al.* (2008) Varicella vaccination in Japan, South Korea, and Europe. *J Infect Dis* 197(Suppl. 2): s185–s190.

Schmader, K., Levin, M., Gnann, J., McNeil, S., Vesikari, T., Betts, R. *et al.* (2012a) Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50–59 years. *Clin Infect Dis* 54: 922–928.

Schmader, K., Oxman, M., Levin, M., Johnson, G., Zhang, J., Betts, R. *et al.* (2012b) Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clin Infect Dis* 55: 1320–1328.

Schmid, D. and Jumaan, A. (2010) Impact of varicella vaccine on varicella-zoster virus dynamics. *Clin Microbiol Rev* 23: 202–217.

Selariu, A., Cheng, T., Tang, Q., Silver, B., Yang, L., Liu, C. *et al.* (2012) ORF7 of varicella-zoster virus is a neurotropic factor. *J Virol* 86: 8614–8624.

Seward, J., Marin, M. and Vázquez, M. (2008) Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis* 197(Suppl. 2): S82–S89.

Seward, J., Watson, B., Peterson, C., Mascola, L., Pelosi, J., Zhang, J. *et al.* (2002) Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *J Am Med Assoc* 287: 606–611.

Shah, S., Wood, S., Luan, X. and Ratner, A. (2010) Decline in varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against varicella. *Pediatr Infect Dis J* 29: 199–204.

Shinefield, H., Black, S., Digilio, L., Reisinger, K., Blatter, M., Gress, J. *et al.* (2005a) Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *Pediatr Infect Dis J* 24: 665–669.

Shinefield, H., Black, S., Williams, W., Marchant, C., Reisinger, K., Stewart, T. *et al.* (2005b) Dose-response study of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *Pediatr Infect Dis J* 24: 670–675.

Silver, B. and Zhu, H. (2014) Varicella zoster virus vaccines: potential complications and possible improvements. *Virol Sin* 29: 265–273.

Steain, M., Sutherland, J., Rodriguez, M., Cunningham, A., Slobedman, B. and Abendroth, A. (2014) Analysis of T-cell responses during active varicella-zoster virus reactivation in human ganglia. *J Virol* 88: 2704–2716.

Takahashi, M., Okuno, Y., Asano, Y. and Yazaki, T. (1974) Live vaccine used to prevent the spread of varicella in children in hospital. *Lancet* 2: 1288–1290.

Vazquez, M., LaRussa, P., Gershon, A., Steinberg, S., Freudigman, K. and Shapiro, E. (2001) The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med* 344: 955–960.

Vesikari, T., Becker, T., Gajdos, V., Fiquet, A., Thomas, S., Richard, P. *et al.* (2012) Immunogenicity

and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad(®)) in infants from 9 months of age. *Vaccine* 30: 3082–3089.

Vestergaard, M., Hviid, A., Madsen, K., Wohlfahrt, J., Thorsen, P., Schendel, D. *et al.* (2004) MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. *J Am Med Assoc* 292: 351–357.

Weinberg, A., Zhang, J., Oxman, M., Johnson, G., Hayward, A., Caulfield, M. *et al.* (2009) Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. *J Infect Dis* 200: 1068–1077.

Weinmann, S., Chun, C., Schmid, D., Roberts, M., Vandermeer, M., Riedlinger, K. *et al.* (2013) Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005–2009. *J Infect Dis* 208: 1859–1868.

Yih, W., Brooks, D., Lett, S., Jumaan, A., Zhang, Z., Clements, K. *et al.* (2005) The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998–2003. *BMC Public Health* 5: 68.

Zerboni, L., Sen, N., Oliver, S. and Arvin, A. (2014) Molecular mechanisms of varicella zoster virus pathogenesis. *Nat Rev Microbiol* 12: 197–210.

Zhang, Z., Huang, Y. and Zhu, H. (2008) A highly efficient protocol of generating and analyzing VZV ORF deletion mutants based on a newly developed luciferase VZV BAC system. *J Virol Methods* 148: 197–204.

Zhang, Z., Selariu, A., Warden, C., Huang, G., Huang, Y., Zaccheus, O. *et al.* (2010) Genome-wide mutagenesis reveals that ORF7 is a novel VZV skin-tropic factor. *PLoS Pathog* 6: e1000971. DOI: 10.1371/journal.ppat.1000971.

Zhou, F., Harpaz, R., Jumaan, A., Winston, C. and Shefer, A. (2005) Impact of varicella vaccination on health care utilization. *J Am Med Assoc* 294: 797–802.