Varicella (chickenpox) is a highly contagious airborne disease caused by primary infection with the varicella zoster virus (VZV). Following the resolution of chickenpox, the virus can remain dormant in the dorsal sensory and cranial ganglion for decades. Shingles (herpes zoster [HZ]) is a neurocutaneous disease caused by reactivation of latent VZV and may progress to postherpetic neuralgia (PHN), which is characterized by dermatomal pain persisting for more than 120 days after the onset of HZ rash, or “well-established PHN”, which persist for more than 180 days. Vaccination with an attenuated form of VZV activates specific T-cell production, thereby avoiding viral reactivation and development of HZ. It has been demonstrated to reduce the occurrence by approximately 50–70%, the duration of pain of HZ, and the frequency of subsequent PHN in individuals aged ≥50 years in clinical studies. However, it has not proved efficacious in preventing repeat episodes of HZ and reducing the severity of PHN, nor has its long-term efficacy been demonstrated. The most frequent adverse reactions reported for HZ vaccination were injection site pain and/or swelling and headache. In addition, it should not be administrated to children, pregnant women, and immunocompromised persons or those allergic to neomycin or any component of the vaccine. (Korean J Pain 2013; 26: 242-248)

Key Words: chickenpox, herpes zoster, herpes zoster vaccine, human herpesvirus 3, postherpetic neuralgia.
owing to the introduction of vaccination. Additionally, over 1 million cases of HZ are reported in the USA annually, with an estimated lifetime attack rate of 30% [2].

This article reviews the pathogenesis of varicella, HZ, and postherpetic neuralgia (PHN), the varicella and HZ vaccines, and as well as known outcomes and future studies related to varicella and HZ vaccinations.

### THE PATHOGENESIS OF VARICELLA, HZ, AND PHN

1. Varicella zoster virus

   A virus is a submicroscopic (20–300 nanometer in diameter), metabolically inert, infectious agent that replicates only within the cells of living hosts, mainly bacteria, plants, and animals. It is composed of an RNA and DNA core, and a protein coat, and in more complex types, a surrounding envelop as well.

   According to the International Committee on Taxonomy of Viruses (ICTV) in 2012, thus far, there are 7 orders, 96 families, 2,200 genera, 2,618 species, and over 3,000 types yet unclassified. The order Herpesvirales comprises 3 families: Alloherpesviridae, Herpesviridae, and Malacoherpesviridae. The family Herpesviridae has at least 3 subfamilies: Alpha-, Beta-, and Gamma-herpesvirinae. The subfamily human Alphaherpesvirinae includes Varicellaviruses and Simplexvirus genera. The species, HSV (HSV-1 and HSV-2) and VZV (HSV-3), persist in the sensory neurons for the life of the host and cause latent infection [3,4].

   VZV, like adenoviruses and poxviruses, is a member of group 1 of the 7 groups categorized according to the Baltimore classification, because it is a dsDNA virus that does not use reverse transcriptase [5].

   VZV is the smallest of the human herpes viruses and the most genetically stable. The virus exhibits multiple cell tropisms, infecting peripheral blood mononuclear cells (PBMCs) and skin cells before establishing latency in sensory neurons. Such tropisms are essential for primary infection, which manifests itself as chickenpox (varicella), as well as for its subsequent reactivation causing HZ (shingles) (Table 1). The highly cell-associated nature of the virus, coupled with its narrow host range, has resulted in the lack of an animal model that mimics the human disease, thereby greatly hindering the study of VZV pathogenesis. Despite this, extensive studies both in vitro and in small animal models have provided interesting insights into the molecular events that govern VZV-associated diseases. In addition, VZV is the first human herpes virus for which a live attenuated vaccine has been developed (Fig. 1A) [4,6].

2. Varicella (chickenpox)

   Unique amongst the human herpes viruses, VZV is spread by inhalation of aerosolized virus particles. Spread of VZV by inhalation is facilitated by the fact that VZV is biologically stable in the external environment. Following exposure, VZV infects respiratory mucous membranes and spreads to the regional lymph nodes where it undergoes the first phase of replication. This is followed by a cell-associated viraemia during which the virus infects PBMCs. The presence of viral DNA has been detected by polymerase chain reaction and in situ hybridization methods in PBMCs from immunocompetent patients with varicella both before and 24–72 h after the appearance of rash. The estimated number of VZV-infected PBMCs from these individuals varies depending on the experimental technique, but ranges from 0.001% to 0.01% [4].

   VZV is capable of infecting mature and immature dendritic monocytes. Infected immature dendritic cells of the respiratory mucosa transport the virus to the T-cell-rich draining lymph nodes. This results in T-cell infection and subsequent dissemination of the virus to reticuloendothelial cells in the liver, spleen, and other organs. As progeny virions exit from reticuloendothelial cells, a secondary cell-

| Table 1. Comparison Between Chickenpox and Shingles |
|-----------------------------------------------------|
| **Varicella**                                      | **Herpes zoster**                        |
| Transmission                                      | Through respiratory secretions, vesicular fluid | By reactivation of latent VZV |
| Signs and symptoms                                | Malaise, fever, rash                      | Neuralgia, dermatomal rash      |
| Distribution of rash                               | Trunk initially, progressing to face, extremities, mucosa or a combination | Primarily thoracic; remainder cranial, cervical, or lumbar |
| Character of rash                                  | Non-grouped, itchy vesicles               | Grouped, markedly erythematous, painful vesicles |
Fig. 1. The pathogenesis of varicella, herpes zoster, and postherpetic neuralgia. (A) Varicella zoster virus (VZV) structure and taxonomy. (B) Varicella (chickenpox) pathogenesis-infection of VZV is initiated through inhalation and exposure of the mucous membranes of the respiratory tract to the virus. Initially, replication occurs in the regional lymph nodes followed by cell-associated viraemia during which the virus infects peripheral blood monocyte cells (PBMCs). Progeny virus is then disseminated to reticuloendothelial cells in the liver, spleen, and other organs. Virion release from reticuloendothelial cells initiates by a second phase of cell-associated viraemia, spreading VZV to the skin. During the resolution of varicella, VZV establishes latency in the trigeminal and dorsal root ganglia where, in most cases, it remains latent throughout the life of its host (Fig. 1B) [4].

The first antibodies, produced after primary VZV infection, identify the viral envelope glycoproteins: gp66 and gp116, and the nucleocapsid protein p155. Antibodies to these immunodominant viral proteins persist for years after varicella resolution; therefore, their presence is an excellent marker of prior VZV infection. Subclinical VZV reinfection is also associated with transient increases in the levels of these same polypeptide-specific antibodies. The immunoglobulin response to HZ appears more rapidly than that of chickenpox or reinfection and is the broadest complement of viral proteins including the distinctive VZV polypeptide p32 [7].

A single attack of varicella usually confers lifelong protection against exogenous reinfection with VZV and subsequent clinical disease. However, it has been long recognized that clinical and subclinical reinfection (manifested by a rise in antibody titer after close contact exposure) can occur, despite the presence of detectable serum VZV antibodies at the time of exposure. This is particularly common in adults who have had varicella but alter have close household contact with active varicella. However, more frequently, clinical reinfection develops in immunocompromised individuals and in cases of occupational exposure. Replication of reinfecting strains and subsequent antigen presentation within local lymphoid tissue is important for boosting cell-mediated immunity responses and consequently, for protecting of latently infected individuals from viral reactivation [8–10].

3. Herpes zoster (shingles)

In approximately 25% of infected individuals, usually
during adulthood, VZV reactivation results in herpes zoster (shingles). The reactivated virus multiplies and spreads within the ganglion causing neuronal necrosis and intense inflammation— a process that often results in severe neuralgia. VZV then spreads outwardly down the sensory nerve causing intense neuritis. Finally VZV progeny are released from sensory nerve endings in the skin producing the characteristic clusters of zoster vesicles. Typically, this results in a unilateral vesicular rash within a single cutaneous dermatome in the thoracic region. This is often complicated by pain, known as postherpetic neuralgia (PHN), which persists after the rash has healed (Fig. 1C) [4].

The onset of HZ and PHN can be divided into 3 phases: acute herpetic neuralgia, subacute herpetic neuralgia, and postherpetic neuralgia. The period of acute herpetic neuralgia spans approximately 1 month from the onset of prodromal symptoms, which usually precede the appearance of a rash by 3 to 7 days, until the rash has healed. The rash progresses from vesicles to pustules that finally crusts, and is resolved with, or without, a patchwork of hypo- or hyperpigmented scarring. Since PHN is defined as dermatomal pain that persists for more than 120 days after the onset of the HZ rash, the period of subacute herpetic neuralgia extends from 1 to 4 months before PHN. In addition, well-established PHN is characterized by pain persisting for more than 180 days after rash onset and is less likely to subside, reflecting its recalcitrant nature (Fig. 1C). Risk factors associated with an increased incidence of HZ include advanced age, disease states, and immunosuppressive therapy (Table 2). Common risk factors for developing PHN are advanced age, severe prodromal pain, acute herpetic neuralgia, and rash (Table 3) [11].

**Table 2. Factors Associated With an Increased Incidence of Herpes Zoster**

| Increased age | Human immunodeficiency virus infection |
|--------------|----------------------------------------|
| Disease states | Lymphoproliferative disorders |
| Immunosuppressive therapy | After organ transplantation |
| | Chemotherapy |
| | Steroid treatment |
| | Caucasian rather than African-American |
| | Psychological stress |
| | Physical trauma |

**Table 3. Risk Factors for Postherpetic Neuralgia**

| Very common | Less common |
|-------------|-------------|
| Older age | Female gender |
| Severity of rash | Greater sensory abnormalities in the affected dermatomes |
| Proximal pain | Polyneuropathy |
| Severity of acute pain | Psychosocial variables |
| Prodromal pain | Ophthalmic distribution |

**DIFFERENCES BETWEEN THE VARICELLA AND HERPES ZOSTER VACCINES**

1. **Varicella vaccine**

Two live, attenuated VZV−containing vaccines are available in the USA for preventing of varicella. The Oka/Merck strain of live, attenuated VZV vaccine was developed in 1974 by serial passage of wild−type VZV (Oka−P) first through human embryonic fibroblasts, followed by guinea pig embryo fibroblasts, and propagation in human diploid cell cultures to yield the Oka−V strain. The strain has been marketed by Merck (Merck & Co., Inc., Whitehouse Station, New Jersey) under the trade name Varivax® since 1995 for healthy children aged ≥ 12 months [12].

Each sterile, 0.5 ml subcutaneous dose of Varivax® contains a minimum of 1,350 plaque−forming units (PFU, a functional measurement of the number of virus particles) of Oka/Merck VZV after reconstitution and can be stored at room temperature for a maximum of 30 min. Each dose also contains sucrose, hydrolyzed gelatin, sodium chloride, monosodium L−glutamate, sodium phosphate dibasic, potassium phosphate monobasic, and potassium chloride. Additionally, residual components of human lung diploid fibroblast (MRC−5) cells including protein and DNA along with trace quantities of sodium phosphate monobasic, ethylene diamine tetraacetic acid (EDTA), neomycin, and fetal bovine serum are also present in the product; however, it does not contain any preservative (Table 4). A combination measles, mumps, rubella, and varicella vaccine constituting the vaccine—ProQuad® (Merck & Co., Inc., Whitehouse Station, New Jersey) has also been licensed in the USA since 2005 for use among healthy children aged 12 months−12 years.

Immunooassay of VZV immunoglobulin G by enzyme immunoassorbent assay is used as a surrogate marker for previous primary infection or successful immunization.
Table 4. Comparison Between Varicella and Herpes Vaccination

|                     | Varicella vaccine | Herpes zoster vaccine |
|---------------------|-------------------|-----------------------|
| **Active ingredient:** |                   |                       |
| Oka/Merck strain of live, attenuated varicella-zoster virus | 1,350 PFU | 19,400 PFU |
| **Inactive ingredient** |                   |                       |
| (0.5 vs. 0.65 ml) | 25 mg of sucrose | 31.16 mg of sucrose |
| 12.5 mg hydrolyzed gelatin | 15.58 mg of hydrolyzed porcine gelatin |
| 3.2 mg of sodium chloride | 3.99 mg of sodium chloride |
| 0.5 mg of monosodium L-glutamate | 0.62 mg of monosodium L-glutamate |
| 0.45 mg of sodium phosphate dibasic | 0.57 mg of sodium phosphate dibasic |
| 0.08 mg of potassium phosphate monobasic | 0.10 mg of potassium phosphate monobasic |
| 0.08 mg of potassium phosphate monobasic of MRC-5 cells including DNA, protein, and trace quantities of sodium phosphate monobasic, EDTA, neomycin and fetal bovine serum | 0.10 mg of potassium phosphate monobasic of MRC-5 cells including DNA, protein, and trace quantities of neomycin and bovine calf serum |
| **Age** | 12–15 months old | ≥ 50 years of age |

PFU: plaque-forming units.

Fig. 2. Future outcome studies on varicella and herpes zoster (HZ) vaccination are needed. The first varicella vaccine recipients were 12 months old in 1995 and recently reached the age of 19 years. Information regarding an increased incidence of HZ due to reactivation of latent VZV will be available when these individuals reach 50 and 80 years of age in 2044 and 2074, respectively. HZ vaccination began in 2006 and 2011 in individuals aged ≥ 60 and ≥ 50 years, respectively. Long-term efficacy can be evaluated when these individuals reach the age of 80 years in 2026 and 2041, respectively.

Patients who have had natural primary infection do not require vaccination against varicella [12].

The incidence of varicella and varicella-related hospitalization and deaths has been reduced by almost 80% from 1995 to 2000 owing to introduction of varicella vaccination [2]. However, vaccination may increase the incidence of HZ followed by PHN because of risk of VZV reactivation compared to a natural HZ attack rate of 30%. Children who received the varicella vaccination during the first year of life in 1995 would reach the age of 50 years in 2044: thus, it remains to be determined if HZ morbidity costs exceed the savings from reductions in varicella-related disease [13–17] (Fig. 2).

2. Herpes zoster vaccine

Vaccination with an attenuated form of VZV activates specific T-cell production, thereby avoiding viral reactivation. The HZ vaccine was first introduced in 2006 after “the Shingles Prevention Study (SPS)” found that vaccination reduced morbidity from HZ and PHN by 51.3% and 39%, respectively in adults aged ≥ 60 years [18]. The study showed that the efficacy of HZ vaccination differed by age groups: 64% in subjects aged 60–9 years, 41% in subjects aged 70–9 years, and 18% in individuals aged ≥ 80 years. The use of the HZ vaccine reduced the overall burden of HZ illness by 61.1% and that of postherpetic neuralgia by 66.5%.

In 2011, following the Zostavax® efficacy and safety trial (ZEST), the USA Food and Drug Administration approved the vaccine for use in individuals aged ≥ 50 years [19]. Zostavax® (Merck & Co., Inc., Whitehouse Station, New Jersey) has been demonstrated to reduce the occurrence by approximately 70% in individuals aged ≥ 50
years. However, it has not proved efficacious in preventing episodes of HZ and reducing the severity of PHN, nor has its long-term efficacy been demonstrated. Additionally, it is not approved for the treatment of HZ or PHN nor indicated for the prevention of primary varicella infection. The HZ vaccine is administered subcutaneously as a single 0.65 ml dose in the deltoid region of the upper arm; intravenous or intramuscular delivery is not indicated. It is stored frozen and should be reconstituted immediately upon removal from the freezer. The reconstituted vaccine should be refrozen and must be discarded if not used within 30 min. Each dose contains a minimum of 19,400 PFU of the Oka/Merck strain of VZV, 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 0.62 mg of monosodium L-glutamate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA, protein, and trace quantities of neomycin and bovine calf serum, and no preservatives (Table 4).

HZ vaccination is contraindicated in individuals (1) with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; (2) who are immunosuppressed or immunodeficient, including those with a history of primary or acquired immunodeficiency states, such as, leukemia, lymphoma, other malignant neoplasms affecting the bone marrow or lymphatic system, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy; and (3) pregnant women and children.

The most frequent adverse reactions reported for the vaccination are injection site pain and/or swelling and headache.

**KNOWN AND FUTURE OUTCOMES OF STUDIES RELATED TO VARICELLA AND HERPES ZOSTER VACCINATIONS**

The risk of infection with varicella is the highest between the ages of 1 and 19 years. Varicella vaccination was first introduced in infants aged 12–15 or 18 months in 1995 and has been approved for use in order to reduce the incidence of varicella by up to 80%, based on the incidence of varicella in these individuals, as they reached the age 19 in 2013 [2]. However, varicella vaccination may increase the future incidence of HZ because of the risk of latent VZV reactivation. This issue about the increased risk of HZ in later years should be clarified when these individuals reach the age of 50 years in 2044 and further confirmed in 2074 when they reach the age of 80 years (Fig. 2).

The incidence of HZ increases continuously with age and exhibits a sharp increase after the age of 50 years. Additionally, the incidence of PHN after HZ is directly related to age [20,21]. The HZ vaccine was introduced in 2006 and initially administered to individuals aged ≥ 60 years. However, the vaccine has only been administered for 7 years and its long term efficacy has not been well established. Therefore, revaccination may be needed in the future. HZ vaccination was also administered to individuals aged ≥ 50 years since 2011. As the individuals in the 2 initial age groups reach the 80-year benchmark in 2026 and 2041, more information regarding this issue will be collected in those years (Fig. 2).

**CONCLUSIONS**

Herpes Zoster (shingles) is a neurocutaneous disease caused by the reactivation of VZV. An approved vaccine is effective in preventing HZ and subsequent PHN with minimal adverse effects, as determined by short-term studies [22]. In contrast, varicella vaccination may increase the incidence of HZ and subsequent PHN due to VZV reactivation.

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