# SHINGLES

## more than just a PAINFUL ERUPTION

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**ANCC Accredited NCPD Hours: 2 hrs**

**Target Audience: RN/APRN**

## NEED ASSESSMENT

Herpes zoster (HZ), or shingles, is a reactivation of the latent varicella-zoster virus, primarily affecting nerve tissue but often presenting with multisystem complications that demand a multidisciplinary approach to management. While the hallmark is a painful vesicular rash, complications can extend beyond the skin to include secondary bacterial infections, persistent neuropathic pain (postherpetic neuralgia), segmental motor deficits, stroke, ocular involvement such as keratitis, iridocyclitis, and secondary glaucoma, and visceral manifestations like pneumonia or hepatitis. The incidence and severity of HZ and its complications rise significantly with age, largely due to immunosenescence—the age-related decline in cell-mediated immunity—alongside increased comorbidities and evolving social-environmental factors. Moreover, individuals who are immunocompromised due to underlying conditions or immunosuppressive therapies are at heightened risk, regardless of age. The burden of HZ, particularly from postherpetic neuralgia, is substantial, impacting patients' quality of life, caregiver responsibilities, healthcare resource utilization, and workplace productivity. Despite advancements in antiviral therapies and preventive vaccines, preventing and managing HZ and its complications remain a considerable clinical challenge.

## OBJECTIVES

- Describe the general aspects of shingles.
- To understand the epidemiological trends,

incidence, and prevalence of herpes zoster.

- Identify the different risk factors for shingles.
- Describe the pathogenesis and clinical features of shingles.
- Discuss the clinical aspects of herpes zoster infection.
- Discuss the diagnosis and management strategies concerning shingles.
- Describe the Quality of life of people affected by shingles and discuss the preventive measures.

## GOAL

This article aims to provide a comprehensive overview of herpes zoster infection by examining its incidence, prevalence, associated risk factors, vulnerable populations, and potential complications. The aim is to enhance clinical awareness and inform effective prevention and management strategies.

## INTRODUCTION

Herpes zoster (HZ), commonly referred to as shingles, arises from the reactivation of the varicella zoster virus (VZV), which remains latent in ganglionic neurons following a primary varicella (chickenpox) infection, typically acquired during childhood. During latency, the virus remains dormant without producing viral particles or causing noticeable neuronal damage. Reactivation can occur through various mechanisms, particularly in immunocompromised individuals, older adults, or those with weakened cell-mediated immunity. Clinically, HZ presents as a painful, erythematous maculopapular rash that evolves into fluid-filled vesicles before crusting over. A hallmark diagnostic feature is its unilateral distribution confined to a single dermatome, distinguishing it from other dermatologic conditions.

While antiviral therapy can reduce symptom severity and duration, herpes zoster is associated with a wide spectrum of complications affecting multiple organ systems, including ophthalmic (e.g., keratitis, retinitis), neurological (e.g., myelitis, meningitis, cranial nerve palsies), vascular (e.g., stroke due to VZV vasculopathy), and visceral systems (e.g., pancreatitis, hepatitis, gastrointestinal ulcers). These complications not only impair quality of life but also contribute to increased healthcare utilization and financial burden. The most frequent and debilitating complication is postherpetic neuralgia (PHN)—a chronic, often severe neuropathic pain persisting for more than 90 days after rash onset—which occurs in approximately 20% of affected individuals, with an estimated 0.5 to 1 million cases annually. Despite ongoing research, the exact pathogenesis of PHN remains unclear, and it is often challenging to manage effectively.

Importantly, VZV is the only human herpesvirus for which effective vaccines are

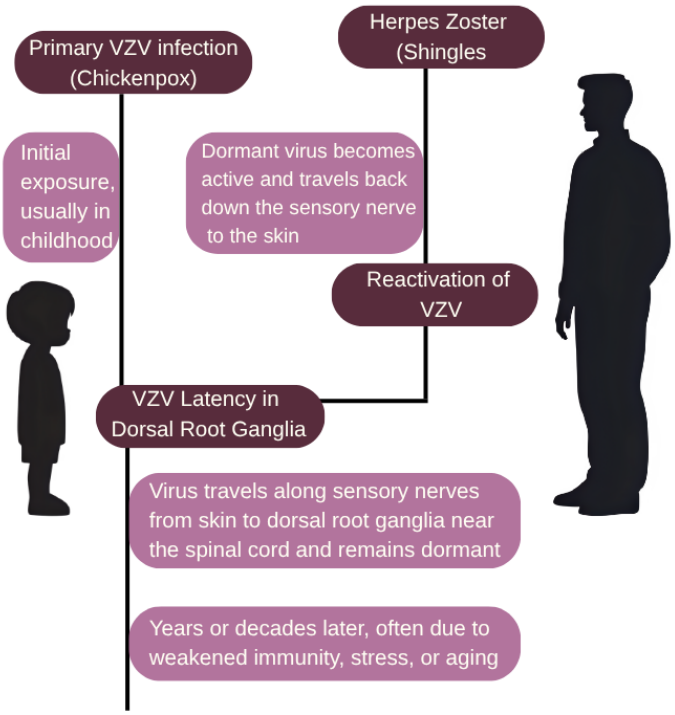
currently available. Two types of vaccines are used in clinical practice: one aimed at preventing primary varicella infection and another specifically developed to prevent herpes zoster and its complications. Although both natural infection and vaccination confer long-term immunity against varicella, this immunity does not completely protect against later reactivation of the virus as shingles. Therefore, continued efforts in prevention, early treatment, and complication management remain essential in reducing the overall disease burden of herpes zoster [1, Rank 5]

## GENERAL ASPECTS OF SHINGLES (HERPES ZOSTER)

Herpes zoster, or shingles, is a viral infection caused by reactivation of the **varicella-zoster virus (VZV)**, which lies dormant in sensory nerve ganglia after primary varicella (chickenpox). It presents as a **painful, unilateral vesicular rash** following a dermatomal distribution, often preceded by localized pain or tingling.

Shingles primarily affects **older adults and immunocompromised individuals**, with risk increasing with age. **Postherpetic neuralgia (PHN)** is the most common complication, leading to chronic pain that may persist for months.

Early antiviral therapy within 72 hours of rash onset can reduce symptom duration and complications. The **recombinant zoster vaccine (Shingrix)** is highly effective and recommended for adults aged 50 and older to prevent herpes zoster and PHN.



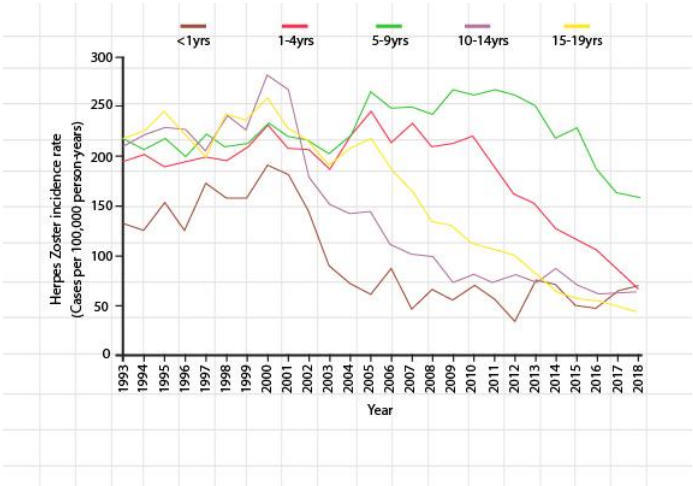

## PREVALENCE OF HERPES ZOSTER

### Varicella (Primary VZV Infection)

Varicella, or chickenpox, occurs globally and remains endemic in populations large enough to support continuous transmission, with outbreaks typically occurring every 2–3 years. Most epidemiological data originate from developed countries. In temperate climates, annual incidence ranges from 13 to 16 cases per 1,000 individuals, with the highest age-specific rates in children aged 1–9 years, often exceeding 100 cases per 1,000 children. As a result, over 90% of individuals in these regions are infected by adolescence, leaving fewer than 10% of adults susceptible. In contrast, tropical regions experience varicella infections at older

ages, with a higher proportion of adult cases, potentially due to climatic factors like heat and humidity that may reduce viral transmissibility. Varicella exhibits strong seasonality, peaking during winter and spring in temperate zones, and during cooler, drier seasons in tropical climates. Outbreaks are common in congregate settings such as schools, childcare centres, hospitals, refugee camps, and correctional facilities. Although typically self-limiting, varicella can lead to severe complications, such as bacterial superinfection, pneumonia, encephalitis, and haemorrhagic events—especially in adults, infants, and immunocompromised individuals. In developed nations, approximately 5 in 1,000 cases require hospitalization, and mortality occurs in 2–3 per 100,000 cases. Congenital varicella syndrome, marked by severe foetal anomalies, occurs in roughly 1% of pregnancies affected during the first two trimesters.

Widespread childhood varicella vaccination has dramatically altered its epidemiology. In the United States, where a two-dose childhood vaccination strategy was adopted, varicella incidence, hospitalizations, and mortality in children have declined by over 95%. Furthermore, herd immunity has contributed to decreased disease burden in unvaccinated populations, significantly reducing outbreaks and seasonal epidemics.




**Annual herpes zoster incidence rates, by age. Rates include both vaccinated and unvaccinated subjects. Dashed lines represent annual herpes zoster incidence rates during universal vaccination eligibility. For each age group, the dashed line begins when subjects eligible for universal vaccination (i.e. birth cohort 2000-2018) are old enough to be included in the group**

## Herpes Zoster (Reactivation of VZV)

Herpes zoster (HZ), or shingles, occurs when latent VZV reactivates, typically decades after the initial varicella infection. Its incidence and severity increase markedly with age, attributed to the progressive decline in VZV-specific cell-mediated immunity. The population-based incidence of zoster is approximately 3–4 cases per 1,000 person-years, increasing from about 1 per 1,000 in children under 10 to more than 10 per 1,000 in adults aged 60 and older. By age 85, over half of the population is estimated to have experienced at least one episode of zoster. Before the introduction of VZV vaccines, around 30% of adults developed shingles during their lifetime.

Postherpetic neuralgia (PHN), the most serious complication of zoster, affects roughly 15% of patients and becomes more prevalent with advancing age, particularly after 50 years. Additional high-risk groups include organ transplant recipients, individuals undergoing chemotherapy, patients with HIV or chronic illnesses, and the growing elderly population. Notably, race appears to influence susceptibility: Black adults in the U.S. and U.K. have a 25–50% lower incidence of zoster than white adults, suggesting a potential genetic protective factor.

Exposure to exogenous VZV (e.g., through contact with children who have varicella) may boost immunity and reduce the risk of reactivation. Despite the implementation of childhood varicella vaccination, studies from the United States reveal an upward trend in zoster incidence that began before the vaccine's introduction and has continued at a similar rate afterward, indicating other contributing factors beyond reduced natural boosting.

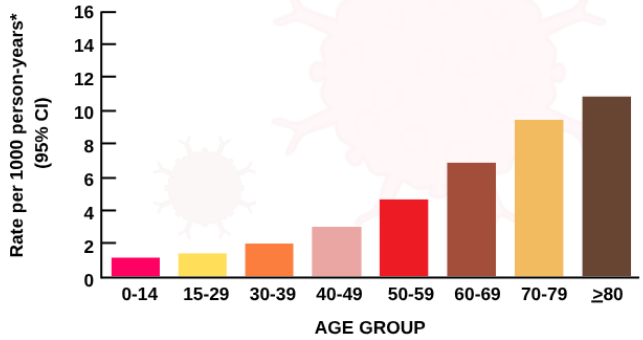
## Epidemiology of Herpes Zoster

Herpes zoster (HZ), or shingles, remains a significant public health concern, particularly in older adults and immunocompromised individuals. Among adults aged 65 and older, the annual incidence of herpes zoster is estimated to range between 10 to 14 cases per 1,000 individuals. In the general population, the lifetime risk of developing HZ is approximately 20–30%, with this figure rising to nearly 50% in those who live to age 85 or older. Based on current population demographics and incidence rates, an estimated 1 million new cases of herpes zoster occur annually in the United States alone.

While the incidence of recurrent HZ is not as well-documented as primary episodes, recurrence is known to be more common among immunocompromised individuals. For example, one study reported a recurrence rate of 5.7% among immunocompetent persons, with significantly higher rates observed in those with compromised immune systems.

Aging and diminished cell-mediated immunity are the most significant risk factors for herpes zoster, with the risk beginning to rise around ages 50–60 and continuing to increase with advancing age. Immunosuppression—whether due to underlying diseases or medical treatments—also substantially elevates the risk. High-risk populations include individuals with HIV infection, Hodgkin's and non-Hodgkin lymphoma, leukaemia, organ or bone marrow transplant recipients, and those with autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. The use of immunosuppressive agents, including tumour necrosis factor (TNF) inhibitors, further increases susceptibility. Additional epidemiological factors associated with increased HZ risk include white race, female sex, and physical trauma.

Herpes zoster is also transmissible, though less so than varicella. Patients with active vesicular lesions can spread the varicella zoster virus (VZV) through direct contact, airborne particles, or droplet nuclei to seronegative individuals, who may subsequently develop primary varicella (chickenpox) within 10 to 21 days of exposure. However, if the rash is entirely maculopapular or has fully crusted, the risk of transmission is minimal. Vulnerable populations include unvaccinated children, healthcare workers, and institutional staff who are seronegative—particularly if they are pregnant or immunocompromised—posing a concern in healthcare and long-term care settings. [29, Rank 3]




**Age-specific incidence rates (across both sexes) of herpes zoster from a healthcare claims database of more than 2.8 million individuals for the years 2000-2001, sex-adjusted to the 2000 United States population. Approximately 40% to 50% of the 1 million new cases of herpes zoster that occur each year develop in individuals who are 60 years of age or older. Source: Insinga RP, et al. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med. 2005; 20:748-753. 5**

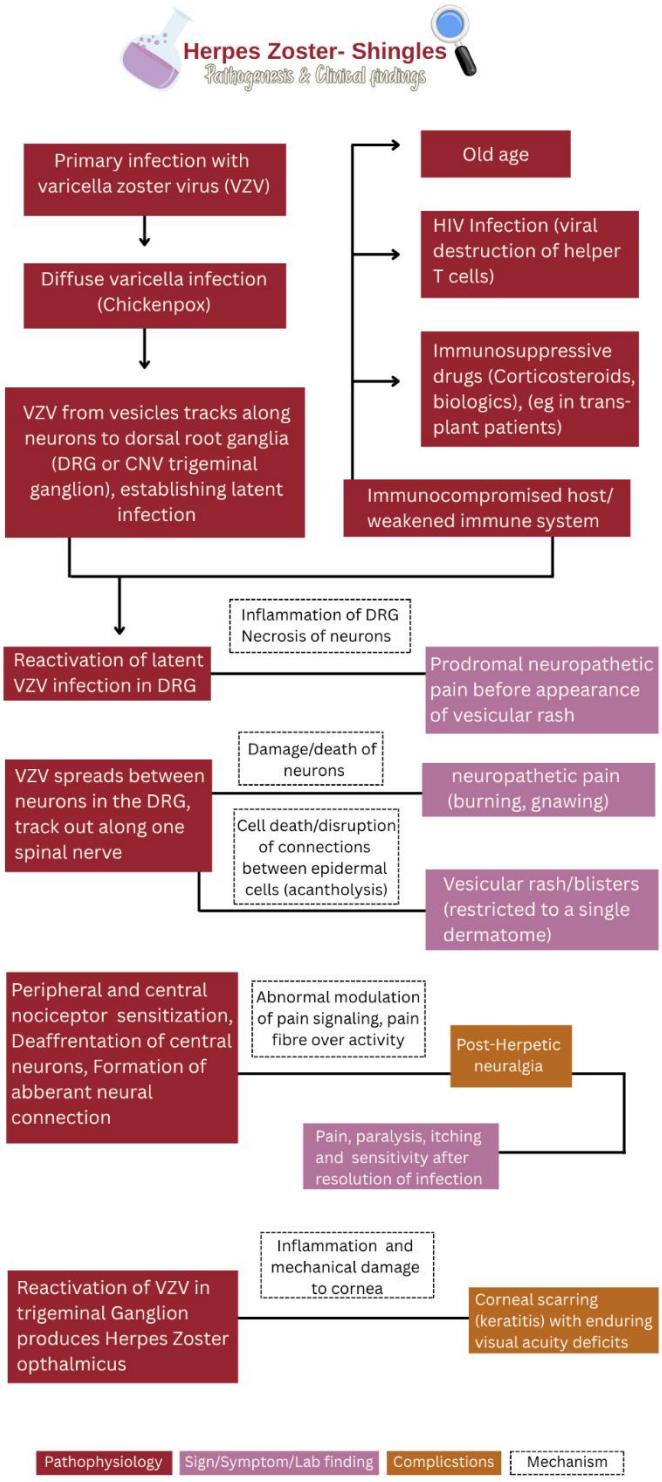
## PATHOGENESIS OF SHINGLES (HERPES ZOSTER)

Herpes zoster arises from the **reactivation of latent varicella-zoster virus (VZV)**, which remains dormant in the **sensory dorsal root or cranial nerve ganglia** following primary infection with varicella (chickenpox), typically in childhood. After the initial infection resolves, the virus enters a latent state within neuronal cells.

**Reactivation** occurs when **cell-mediated immunity declines**, most commonly due to **aging, immunosuppression, stress, or chronic illness**. Upon reactivation, the virus replicates and travels along the sensory nerves to the skin, resulting in **inflammation and characteristic unilateral vesicular eruptions** confined to the affected dermatome.

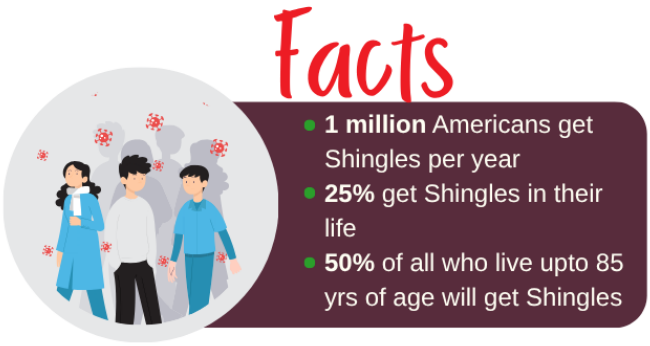
The inflammatory process affects both the **nerve and the surrounding tissues**, leading to acute pain and sensory disturbances. In some individuals, particularly older adults, this neuronal injury may result in **postherpetic neuralgia (PHN)**, a chronic pain condition that persists after resolution of the rash.

Thus, the pathogenesis of herpes zoster is driven by a **decline in VZV-specific cellular immunity**, allowing the latent virus to reactivate and cause localized neurocutaneous symptoms.




## Risk Factors for Shingles (Herpes Zoster)

Advancing age is the most universally acknowledged risk factor for the reactivation of varicella-zoster virus (VZV), primarily due to immunosenescence—a natural, age-related decline in cell-mediated immunity (CMI). This decline contributes significantly to the increased incidence of both herpes zoster (HZ) and its most common complication, postherpetic neuralgia (PHN), in older populations.




Beyond aging, several chronic medical conditions have been consistently linked to a heightened risk of HZ. These include diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease (including myocardial infarction, heart failure, and hypertension), chronic kidney disease, and cancer. These conditions may impair immune system functionality, particularly CMI, increasing vulnerability to VZV reactivation. Epidemiological evidence supports these associations. A recent prospective cohort study demonstrated an elevated incidence of HZ in individuals with diabetes, cardiovascular, and respiratory conditions. Similarly, a large retrospective cohort study reported that patients with diabetes, kidney failure, malignancies, and other chronic illnesses had a 1.8 to 8.4 times higher risk of developing shingles compared to individuals without such comorbidities. A U.S.-based case-control study

further confirmed a significantly greater risk of HZ among patients with diabetes, cardiovascular disease, or COPD, with 7.6% of the study population also identified as immunosuppressed.


Immunosuppression—whether due to underlying diseases such as HIV or autoimmune disorders, or due to treatments like chemotherapy, corticosteroids, or biologics (e.g., TNF inhibitors)—is a major risk factor for HZ across all age groups. In immunocompromised individuals, shingles tends to be more severe and may involve increased complications or recurrence.

Psychological stress, traumatic life events, and major depressive disorders have also been implicated as potential triggers for HZ, likely through their suppressive effects on immune function. In patients with depression, the onset of shingles and especially PHN can exacerbate mental health conditions, potentially increasing suicide risk, particularly in those already receiving multiple treatments.

Mechanical trauma to a nerve or dermatome region has also been observed as a risk factor for HZ, with some studies suggesting that localized nerve stimulation or injury may provoke viral reactivation. Additionally, some evidence suggests that females may be at slightly increased risk of HZ compared to males, though findings on sex-related susceptibility remain inconsistent across studies.

Importantly, individuals with chronic diseases not only have a higher relative risk of developing HZ, but they are also more likely to experience exacerbation of their underlying conditions following a shingles episode. This increases the frequency, severity, and healthcare burden of HZ-related complications in this vulnerable population.


## Asthma – AN Unrecognized Risk Factor for Herpes Zoster

Herpes zoster (zoster or shingles) is estimated to occur in up to 30% of all adults by age 80 with nearly 1 million cases a year in the United States. The decade of life with the largest number of cases is 50 to 59 years, causing significant loss of work and productivity. While the reasons for this increase in zoster rates are unknown, the introduction of the childhood varicella vaccination is unlikely to account for

the rising trends of zoster.

Despite the presumed immunosenescence with aging, it is still unclear why some people develop zoster while others do not. Almost all of the United States population aged ≥ 40 years have serologic evidence for previous varicella infection and therefore are at risk for zoster, but two-thirds of people will never develop zoster. Only 8 to 10% of zoster cases have known significant immune suppression potentially suggesting unrecognized risk factors.

Asthma represents one of the five most burdensome chronic diseases in the US affecting 7–17% of the US population. It increases the risk of serious and common microbial infections, which might be, in part, accounted for by suboptimal innate and adaptive immune functions. [17, Rank 5]

## CLINICAL ASPECTS OF HERPES ZOSTER (HZ)

Herpes zoster (HZ) has a profound clinical, psychological, and economic impact—one that increases with age and is closely linked to its potential complications. These complications can significantly reduce quality of life, heighten the risk of long-term disability, and impose substantial healthcare costs.

### Major Complication: Postherpetic Neuralgia (PHN)

The most common and debilitating complication of HZ is **postherpetic neuralgia (PHN)**, defined as pain that persists for more than 90 days following resolution of the acute zoster rash. PHN is associated with chronic neuropathic pain that is often severe, treatment-resistant, and significantly diminishes a patient's quality of life, especially in older adults.

### Other Local and Systemic Complications

- **Secondary Bacterial Infections:** Commonly occur in the affected dermatome and may exacerbate skin damage or delay healing.
- **Segmental Paresis:** Muscle weakness can manifest in the limbs, abdominal wall, diaphragm, or extraocular muscles, depending on the site of viral reactivation.
- **Ophthalmic Involvement (Herpes Zoster Ophthalmicus - HZO):** Occurs in 10–20% of HZ cases, resulting from reactivation of VZV in the ophthalmic branch of the trigeminal nerve. Among these, 20–70% of patients develop ocular complications such as:
  - **Blepharitis**
  - **Keratoconjunctivitis**
  - **Iritis**
  - **Scleritis**
  - **Acute retinal necrosis**

Neurological complications associated with HZO may include **ophthalmoplegia**, **optic neuritis**, and **ptosis**, though these occur less frequently than ocular complications.

## SEVERE AND DISSEMINATED HZ IN IMMUNOCOMPROMISED PATIENTS

In immunosuppressed individuals, HZ can disseminate beyond the initial dermatome, spreading hematogenously or neurally to involve visceral organs. This can result in severe complications, including **encephalitis**, and may be life-threatening.

**Vascular and Functional Complications**

- **Ischemic Events:** HZ—particularly ophthalmic involvement—has been associated with increased risk of **stroke** and **transient ischemic attacks (TIAs)**.
- **Functional Decline in the Elderly:** In older adults, HZ can cause a lasting reduction in independence, physical activity, and psychosocial functioning. Many patients are unable to return to their pre-disease lifestyle or activity level.

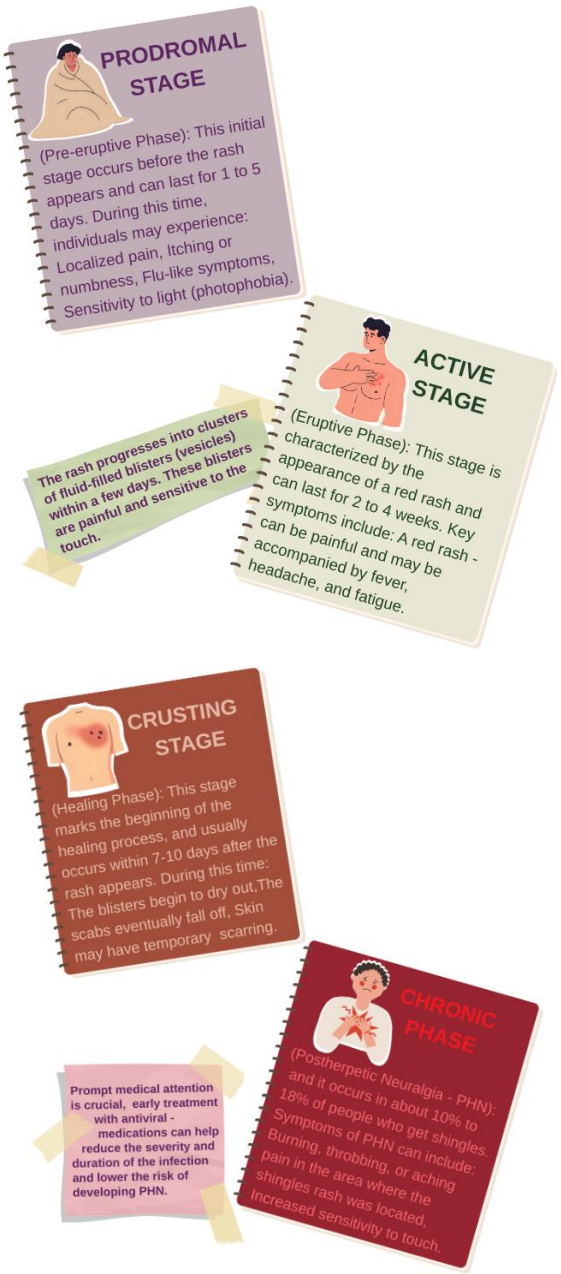
## PUBLIC HEALTH IMPLICATIONS AND PREVENTIVE STRATEGIES

HZ represents a significant public health concern due to its high prevalence and the frequent, sometimes devastating complications it can cause. Despite the availability of antiviral therapies, treatment options for HZ-related complications, especially PHN, remain limited in effectiveness.

Consequently, **prevention through vaccination** is essential, particularly in high-risk groups such as those with:

- **Diabetes mellitus**
- **Autoimmune diseases**
- **Renal insufficiency**
- **Malignancies**

Vaccination has been shown to significantly reduce the incidence of HZ, lessen the severity of disease when it occurs, and decrease the burden of PHN and other complications. As such, immunization represents a promising strategy to reduce the clinical, economic, and quality-of-life burden of HZ in aging and at-risk populations. [6, Rank 4]



## RECURRENCE OF VARICELLA ZOSTER VIRUS (VZV)

While VZV primarily reactivates as **herpes zoster (shingles)**, recurrent infections can manifest in a variety of severe and sometimes atypical presentations, including central nervous system (CNS) and visceral involvement. These forms of recurrence may occur with or without the classic dermatologic rash and are particularly challenging to diagnose and manage.

### Central Nervous System (CNS) Involvement

Reactivation of VZV can lead to serious **neurological complications** such as **encephalitis** and **meningitis**.

- **Clinical Presentation:** Patients typically present with **altered mental status**, **headache**, and **focal neurological deficits**. Notably, **seizures are uncommon**, and **up to one-third of patients may not exhibit a rash**, complicating timely diagnosis.
- **Outcomes:** Even with prompt antiviral treatment, **mortality rates range from 9% to 20%**, and survivors often suffer from **long-term sequelae**, including:
  - Cognitive slowing
  - Memory impairment
  - Emotional disturbances

### Visceral Involvement

Recurrent VZV can also involve internal organs, leading to **visceral zoster**, which may manifest as:

- **Pancreatitis**
- **Hepatitis**
- **Gastritis**

**Clinical suspicion** should be high in patients with recent or current cutaneous herpes zoster who present with **unexplained gastrointestinal or hepatic symptoms**. Diagnosis may be confirmed via:

- **PCR testing of blood**
- **Histological examination**
- **Tissue culture demonstrating VZV**

### Disseminated Herpes Zoster (HZ)

Defined by:

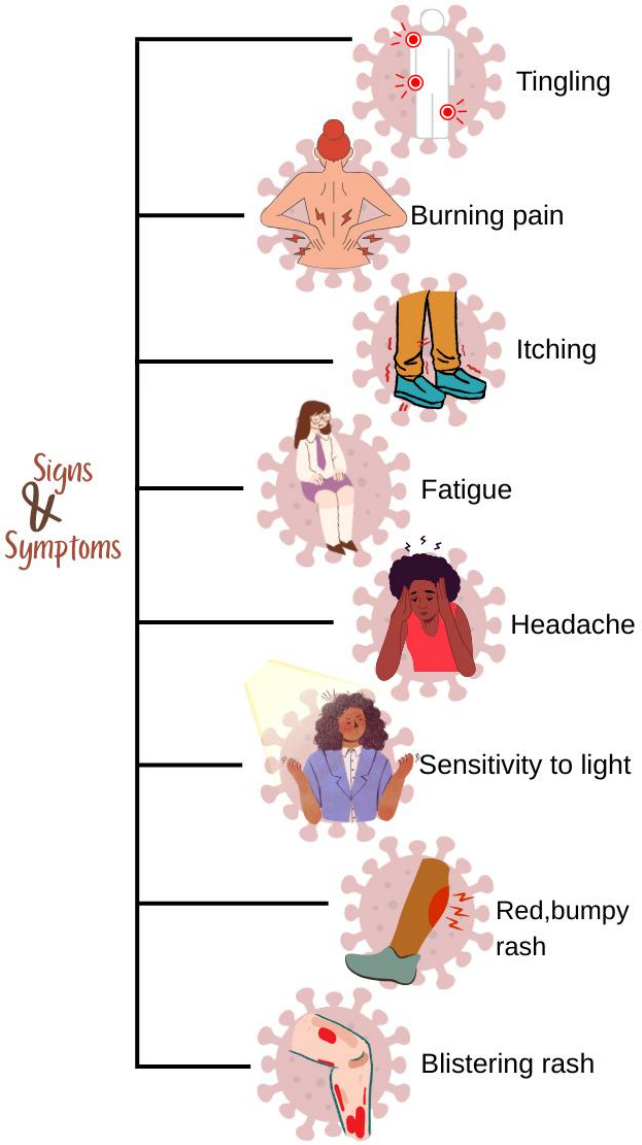
- The appearance of **20 or more vesicles** outside the primary and adjacent dermatomes
- Involvement of **three or more dermatomes**

Disseminated HZ, along with visceral zoster, occurs **more frequently in immunocompromised individuals**, including patients with malignancy, HIV/AIDS, or those undergoing immunosuppressive therapy. However, **case reports document rare occurrences in immunocompetent individuals**, highlighting the importance of clinical vigilance.

## CLINICAL IMPLICATIONS

Recurrent and disseminated VZV infections

are **medically significant** due to their potential for **high morbidity and mortality**. Given the possibility of **atypical presentations without rash**, especially in CNS and visceral involvement, a **high index of suspicion is essential** in both immunocompromised and immunocompetent hosts. Timely diagnosis and treatment can reduce complications but may not prevent long-term sequelae, further emphasizing the importance of **preventive vaccination** in high-risk populations.




## CLINICAL FEATURES OF SHINGLES

Classically, reactivation of VZV presents as a unilateral dermatomal rash (*i.e.*, does not cross the midline) which is initially maculopapular on an erythematous base, evolves into vesicular-pustular appearance, which after 7–10 days begins to crust over and heals within 2–4 weeks. It can either be limited to a single dermatome or occur over adjacent dermatomes, depending on the distribution of the sensory ganglia where reactivation occurs.

In older adults, the rash may have an atypical appearance and may be limited to a small patch within the dermatome or have a maculopapular appearance without evolving into vesicles. The onset of the rash is often preceded by neuropathic pain (aching, burning, lancinating) over the involved dermatome(s). This prodromal phase can result in a diagnostic dilemma for the physician as it may mimic other painful conditions in older adults, such as migraine headaches, trigeminal neuralgia, myocardial infarction, biliary or renal colic, appendicitis, lumbosacral pain, or muscle strain.

The presence of very sensitive skin could clue the physician that this is HZ. This prodromal phase may be associated with systemic symptoms of fever, fatigue, headache, malaise, and photophobia. [25, Rank 5]

A small percentage of people with HZ present as herpes zoster ophthalmicus (HZO), which occurs when the VZV reactivation involves the

ophthalmic branch of the trigeminal nerve. Since the cranial nerve V1 also innervates the skin over the nose, the presence of a cutaneous lesion at the tip of the nose, referred to as the Hutchinson sign, is highly predictive of ocular involvement.

Eye manifestations include periorbital cutaneous lesions, conjunctival infection and chemosis, keratitis, corneal ulceration, uveitis, scleritis, episcleritis, glaucoma, retinal necrosis, and optic neuritis. Keratitis remains the most commonly seen complication. Acute retinal necrosis (ARN), however, is associated with greater morbidity and occurs in both immunocompetent and immunocompromised hosts. This is a full-thickness, patchy, rapid necrosis of the retina presenting with periorbital pain, floaters, and almost always permanent peripheral vision loss. In the immunocompromised host, progressive outer retinal necrosis (PORN) occurs and, though similar to ARN, often presents as sudden onset of painless vision loss, floaters, and constricted visual fields with retinal detachment. This may be preceded by zoster ophthalmicus, retrobulbar neuritis, aseptic meningitis, and/or central retinal artery occlusion. PORN may present concurrently with VZV vasculopathy.

HZ may manifest as cranial neuritis, with an array of clinical presentations depending on the cranial nerve affected. HZ neuritis involving cranial nerves III, IV, and VI may present with ophthalmoplegia and/or ptosis; involvement of branches V2 and V3 of the trigeminal nerve may rarely present with osteonecrosis and spontaneous tooth loss. Ramsey-Hunt syndrome describes involvement of cranial nerve VII, which presents as an ipsilateral facial palsy with lesions in the external auditory meatus and tympanic membrane or on the ipsilateral anterior two-thirds of the tongue and hard palate.

Involvement of cranial nerve VIII may occur simultaneously, with symptoms of nausea, vomiting, hearing loss, tinnitus, vertigo, and nystagmus. HZ of cranial nerves XI, X, and IX presents as odynophagia, dysphagia, hoarseness, dysgeusia, hemilaryngeal or hemi-pharyngeal paresis. HZ involving the cervical or lumbar nerve roots may result in radiculopathy. Rarely, cervical zoster may result in diaphragmatic weakness and thoracic zoster can result in abdominal wall weakness and herniation.

VZV myelitis, which is characterized by paresis of the extremities, bowel and/or bladder incontinence, and sensory deficits, has two types of clinical presentation. In immunocompetent hosts, it is usually self-limited and occurs days to weeks after acute varicella or zoster. In the immunocompromised host, VZV myelitis is more likely to have a poor outcome associated with disability and even death [26, Rank 4]

## DIAGNOSIS OF VARICELLA

## ZOSTER VIRUS (VZV) INFECTION

The diagnosis of varicella (chickenpox) and herpes zoster (shingles) is most often made clinically based on their characteristic presentations. Varicella typically presents with a diffuse, generalized vesicular rash, while herpes zoster appears as a unilateral, dermatomal vesicular rash. However, clinical diagnosis can be challenging in atypical cases such as disseminated zoster, zoster with minimal or absent rash, or when herpes simplex virus mimics zoster (zosteriform HSV). Other diagnostic challenges include breakthrough varicella in vaccinated individuals, rashes caused by other infectious or non-infectious etiologies (e.g., enteroviruses, drug reactions, contact dermatitis), and VZV infection without rash, such as zoster sine herpete. In such presentations, especially when neurologic involvement (e.g., meningitis, stroke, myelitis) or visceral symptoms are present, laboratory confirmation becomes essential for accurate diagnosis, appropriate management, and infection control.

### Laboratory Diagnosis

Among laboratory methods, polymerase chain reaction (PCR) is the preferred diagnostic tool due to its high sensitivity and specificity. PCR can detect VZV DNA from vesicle swabs, fluid, or crusts, as well as from saliva or cerebrospinal fluid (CSF) in patients presenting with neurological symptoms. PCR is particularly valuable in identifying infection in patients without a rash. In addition to confirming VZV infection, PCR coupled with restriction enzyme digestion and sequencing can help identify antiviral resistance, particularly to acyclovir. Direct immunofluorescence assay (DFA) is another rapid diagnostic method used on vesicular lesions, although it is less sensitive than PCR.

### Serologic Testing

Serologic testing is generally not useful for acute diagnosis, as antibody responses take time to develop. Detection of anti-VZV IgM may suggest recent infection but is nonspecific. Serologic testing is more appropriate for determining prior immunity rather than diagnosing active disease.

## SPECIAL CONSIDERATIONS IN VACCINATED INDIVIDUALS

In vaccinated individuals who develop symptoms such as rash or meningitis, it is critical to confirm VZV infection with PCR and determine whether the virus is a wild-type or vaccine strain. In the United States, the Centers for Disease Control and Prevention (CDC) offers free testing for such cases, and the results are reported to the Food and Drug Administration (FDA) in the context of potential vaccine-related complications.

VZV DNA may occasionally be detected in the

saliva of severely stressed but otherwise asymptomatic individuals, suggesting subclinical reactivation. However, this phenomenon is rare in people under 60 years of age and is not typically associated with infectious virus. The presence of viral DNA does not always indicate active infection, as DNA can persist after viral clearance or result from silent reactivation. Importantly, there is little epidemiological evidence to support asymptomatic transmission of VZV, in contrast to herpes simplex virus (HSV), which is commonly spread in this manner.

Nonetheless, early detection of VZV DNA in symptomatic individuals before rash onset can help clinicians initiate antiviral therapy promptly. Timely treatment may prevent ganglionic damage and reduce the risk of developing postherpetic neuralgia (PHN), one of the most debilitating complications of herpes zoster. Therefore, while clinical evaluation remains central to diagnosis, laboratory testing—especially PCR—plays a vital role in confirming VZV infection in atypical, immunocompromised, or neurologically involved cases. [6, Rank 4]

## MANAGEMENT OPTIONS FOR HERPES ZOSTER

The management of Herpes Zoster (HZ) typically involves a combination of antiviral therapy and pain control measures to reduce the severity and duration of acute symptoms and to help prevent complications. Antiviral drugs such as acyclovir, valacyclovir, and famciclovir are most effective when initiated within 72 hours of rash onset. These agents have been shown to reduce the intensity and duration of acute pain, promote faster healing of the rash, and may lower the risk of developing postherpetic neuralgia (PHN). Among them, valacyclovir and famciclovir are preferred due to their more convenient dosing schedules and improved bioavailability compared to acyclovir.

Pain management in acute HZ often starts with paracetamol (acetaminophen), either alone or combined with a weak opioid such as codeine. For more severe or persistent pain, especially when neuropathic pain is present, additional medications such as tricyclic antidepressants (e.g., amitriptyline), gabapentin, or pregabalin may be used. In some cases, stronger opioids like oxycodone are necessary, although older adults are particularly susceptible to adverse effects from systemic medications. Despite these treatment options, PHN remains a challenging complication to manage. Systemic drugs for PHN generally provide only modest pain relief—typically reducing pain by 50% in about half of patients—and often come with significant side effects, particularly in the elderly.

Topical therapies may be better tolerated and offer targeted pain relief. Lidocaine 5% patches are commonly used for localized pain, and

high-concentration (8%) capsaicin patches may provide relief in select patients, though application can be painful and may require supervised administration. Overall, the goal of HZ management is to initiate antivirals early and tailor pain control strategies to balance efficacy with tolerability, especially in older or high-risk individuals.

## MULTIDISCIPLINARY PERSPECTIVES OF HERPES ZOSTER INFECTION

Herpes Zoster (HZ) often requires input from multiple medical disciplines, depending on the patient's health system and the severity or complications of the infection. While most cases are managed by general practitioners (GPs), complications frequently prompt specialist involvement. A survey revealed that GPs handled the majority of HZ cases, with only 18% referred to specialists, such as pain specialists, ophthalmologists, or dermatologists. Referral rates increased with patient age. Hospitalization was rare (1.3% overall), but among those hospitalized for HZ or postherpetic neuralgia (PHN), 92% were aged over 50. PHN developed in 7.4% of cases, and among these, 74% were referred to a specialist, while 2% required hospitalization. The financial burden of outpatient and inpatient care related to HZ complications is substantial.

Although GPs may not frequently encounter HZ, the infection typically affects their most vulnerable patients—often older adults with multiple chronic conditions—who are at increased risk of complications, adverse drug reactions, and functional decline. Due to this, clinical guidelines play an important role in supporting GP decision-making, especially since individual experience with HZ may be limited. Guidelines typically recommend initiating antiviral treatment within 72 hours of rash onset, though exceptions may be made for severe cases, ongoing viral activity (e.g., new lesions), or in Herpes Zoster Ophthalmicus (HZO). GPs are encouraged to refer patients with significant complications, such as PHN or HZO, to specialists for advanced management. Geriatricians play a key role in managing older patients with HZ, particularly those with complex needs. In some healthcare systems, they manage most elderly cases, while in others, they primarily treat complicated or hospitalized patients. Older individuals often experience more severe and prolonged pain, with a high burden of comorbidities—averaging five at age 65 and nearly seven by age 85. PHN can have systemic effects, including increased cardiovascular risk (elevated heart rate, blood pressure, and hypercoagulability), gastrointestinal dysfunction (delayed motility), respiratory complications, fluid retention, and immune suppression. Poorly controlled pain contributes to sleep disturbances, malnutrition, anxiety, impaired mobility, and cognitive issues

like disorientation and confusion, significantly lowering quality of life.

Infectious disease specialists are involved in managing severe HZ cases, recurrent infections, or those with neurological complications. They also guide prevention strategies, particularly for immunocompromised patients, including those undergoing organ transplantation. These specialists are often consulted on a case-by-case basis for prophylactic measures and typically manage only complicated or hospitalized cases of HZ.

Rheumatologists should remain vigilant, as patients with autoimmune inflammatory rheumatic diseases (AIRD) are at higher risk for HZ and related complications, especially when receiving immunosuppressive therapy. In the event of an HZ diagnosis, temporary discontinuation of immunosuppressive agents is often necessary to allow viral control.

Pain specialists and dermatologists contribute to managing refractory pain and dermatological manifestations. In cases of HZO, prompt ophthalmologic evaluation is essential, particularly in patients with ocular symptoms such as redness, pain, or blurred vision—even if these appear weeks after the initial HZ episode. Hutchinson's sign, involving lesions on the tip or side of the nose, is a strong predictor of ocular involvement (80% risk compared to 50% without the sign) and warrants thorough intraocular examination. Immunocompromised patients are at increased risk for serious ocular complications, including necrotizing retinitis, which can threaten vision.

## MANAGEMENT OF VARICELLA INFECTION

### In Children

Most varicella in healthy children is mild, self-limiting, and uncomplicated. Accordingly, and even though early antiviral therapy can reduce the duration of illness, treatment of uncomplicated varicella in children is usually confined to symptomatic relief. Acetaminophen (paracetamol) is the preferred antipyretic agent because of the association between aspirin and Reye syndrome (life-threatening sudden onset encephalopathy and liver dysfunction) and because of an epidemiological link between ibuprofen and an increased risk of invasive group A streptococcal disease in the context of varicella, although not necessarily a causal one. Topical anti-pruritic agents are of anecdotal benefit. Antiviral therapy is reserved for those with severe varicella or who are considered at greater risk of developing complications owing to age, compromised immunity or chronic diseases of the skin or lungs [8, Rank 4]

Severe varicella is characterized by extensive and prolonged viral replication, often associated with fever, continued development of new skin vesicles for >5 days, and/ or involvement of the lungs, liver and/or brain.

Severe varicella is a feared complication that was a major impetus towards vaccine development. Severe varicella has caused many deaths in individuals with congenital or acquired impairment of cellular immunity, even after the development of antiviral therapy. Children with impaired innate immunity, for example, those with natural killer cell abnormalities, are also at risk for severe varicella. Thus, strenuous measures should be taken to prevent VZV infection in this group, including post-exposure prophylaxis.

Acyclovir is a guanosine analogue that inhibits the synthesis of viral DNA and treatment with acyclovir reduces visceral dissemination of the virus. It is typically given for 7–10 days and can be switched to oral therapy 48 h after the last lesions appear or continued until all lesions are crusted. Oral acyclovir has poor bioavailability; thus, the related drugs valaciclovir and famciclovir, which have excellent absorption from the intestinal tract, produce high blood antiviral activity and have a long half-life, should be used for oral therapy instead. Valaciclovir and famciclovir are prodrugs, which are converted to active guanosine analogues *in vivo*.

## In Adults

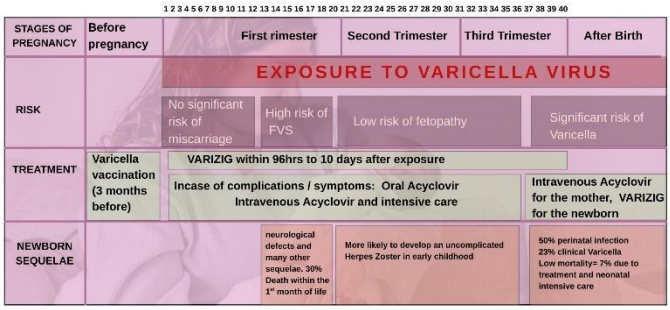
As both prodrugs need less frequent administration than acyclovir, patient compliance is improved and they are frequently used in children aged >2 years and in adults. Immunocompromised patients with severe VZV infections still receive intravenous acyclovir, which results in higher blood levels than oral therapy. Alternatively, intravenous foscarnet and cidofovir can be used. However, because of toxicity, these drugs should be only used in immunocompromised individuals with acyclovir-resistant VZV. Notably, intravenous antivirals, including acyclovir, can be nephrotoxic; both acyclovir and foscarnet require dose adjustment in patients with renal impairment. [9, Rank 4]

VZV infection in individuals aged >13 years is associated with an increased risk of severe or fatal outcome, and oral antiviral therapy is recommended, even in otherwise healthy adolescents and adults. In immunocompetent patients, oral acyclovir, or preferably famciclovir or valaciclovir need to be started within 24 h of the first skin lesions to shorten the duration of fever and rash; 5 days and 7 days of treatment have comparable efficacy.

## In Pregnant Women

Varicella in pregnant women is also problematic: pregnancy increases the risk of severe disease in the mother, and VZV can harm the unborn child and lead to congenital abnormalities (congenital varicella syndrome). Thus, pregnant women with varicella are usually treated with intravenous acyclovir, even though this is a category B drug and not licensed in pregnancy. The effect of treatment

on the development of congenital varicella syndrome is unknown. Maternal onset of varicella between 5 days before and 2 days after delivery is associated with a high risk of severe varicella in the newborn, who should receive prophylaxis with VZV-specific immunoglobulin. Newborns with congenital varicella syndrome should receive high-dose intravenous acyclovir every 8 h owing to increased clearance of the drug in this age group. Oral acyclovir is poorly absorbed and should be used cautiously, if at all. [10, Rank 4]




## PHARMACOLOGICAL MANAGEMENT OF SHINGLES

Pharmacological management of herpes zoster (shingles) focuses on antiviral therapy and pain control. Antiviral treatment is recommended for all patients with zoster, particularly those who are immunocompromised, aged ≥50 years, or present with facial or ocular involvement, severe rash, or complications. In immunocompetent individuals, oral antivirals such as acyclovir, valaciclovir, or famciclovir are commonly used. Among these, valaciclovir and famciclovir are preferred due to their higher oral bioavailability, simplified dosing schedules, and greater efficacy in reducing acute zoster pain. Brivudin, though less widely available, offers superior activity against VZV. Antiviral therapy is typically administered for 7–10 days and shortens the duration to new lesion cessation, lesion crusting, and resolution of acute pain. In hospitalized or immunocompromised patients, or those with neurological complications, intravenous acyclovir is used, significantly reducing the risk of visceral involvement and disseminated disease. For patients with acyclovir-resistant VZV, foscarnet is the treatment of choice.

Antiviral therapy should ideally begin within 72 hours of rash onset; however, initiation beyond this period remains beneficial if new lesion formation continues. While antivirals reduce acute pain, they have not reliably been shown to prevent postherpetic neuralgia (PHN), nor are they effective in treating established PHN. Prednisone can reduce acute pain and improve functional ability during the acute phase, but it does not decrease PHN risk and should be used cautiously, particularly in elderly patients with comorbidities such as hypertension, diabetes, or osteoporosis. If prednisone is prescribed, it should always be used in conjunction with antiviral therapy.

Pain management is individualized based on severity. Mild zoster pain can be managed with NSAIDs or acetaminophen. For localized pain, lidocaine patches offer relief but should be

applied only to intact skin, as they may cause irritation. More severe pain may require systemic agents such as opioids (e.g., oxycodone, tramadol), anticonvulsants (gabapentin, pregabalin), or tricyclic antidepressants (e.g., nortriptyline). In comparative studies, oxycodone has demonstrated greater efficacy than gabapentin. However, all systemic therapies must be titrated gradually, considering side effects like sedation, dizziness, ataxia, peripheral oedema (with gabapentin/pregabalin), or anticholinergic effects (with tricyclics). These adverse effects are especially problematic in older adults.

Specific complications require tailored management. Ramsay Hunt syndrome, characterized by facial palsy, vesicular ear rash, and taste loss, should be treated with oral antivirals and corticosteroids. Ocular involvement warrants urgent ophthalmologic evaluation, with additional therapies to manage intraocular pressure and prevent complications such as keratitis or iritis. Early antiviral treatment is linked with improved outcomes in herpes zoster ophthalmicus. Patients with zoster-associated vasculopathy benefit from intravenous acyclovir and corticosteroids.

Postherpetic neuralgia is a challenging complication to treat, with fewer than half of patients experiencing substantial pain relief. Management is symptomatic and includes topical lidocaine (often first-line), capsaicin cream or patches, gabapentin, pregabalin, and tricyclic antidepressants. However, topical capsaicin may cause burning and erythema, limiting its use. Combination therapy, such as gabapentin with nortriptyline, may offer enhanced relief but with increased risk of side effects. Opioids are generally considered third-line due to the potential for dependency and unclear long-term benefit. Referral to a pain specialist is often beneficial. Alternative therapies such as acupuncture, intrathecal corticosteroid injections, local anaesthetic blocks, or nerve blocks have yielded inconsistent results and are not routinely recommended. [13, Rank 5]

## THE IMPORTANCE OF CORTICOSTEROIDS AND ADJUVANT AGENTS IN HERPES ZOSTER TREATMENT

### Corticosteroids

Play a supportive role in the management of herpes zoster (HZ), primarily aimed at reducing acute pain and improving functional outcomes. Clinical trials have shown that while corticosteroids can alleviate acute zoster pain, the benefit is typically short-lived and does not extend to preventing postherpetic neuralgia (PHN). In one study, patients receiving both acyclovir and prednisone experienced significantly faster return to daily activities, improved sleep, and earlier cessation of analgesics. In that trial, prednisone was

administered in a tapering regimen: 60 mg/day for days 1–7, 30 mg/day for days 8–14, and 15 mg/day for days 15–21. Adverse effects of short-term corticosteroid use may include gastrointestinal symptoms (e.g., dyspepsia, nausea, vomiting), peripheral edema, and granulocytosis. Corticosteroids may also be considered in specific clinical scenarios such as VZV-induced facial paralysis or cranial polyneuritis to help preserve motor function, minimize nerve compression, and reduce pain. Importantly, corticosteroids should **never be used alone** and must be combined with antiviral therapy to avoid exacerbation of viral replication.

## Adjuvant agents

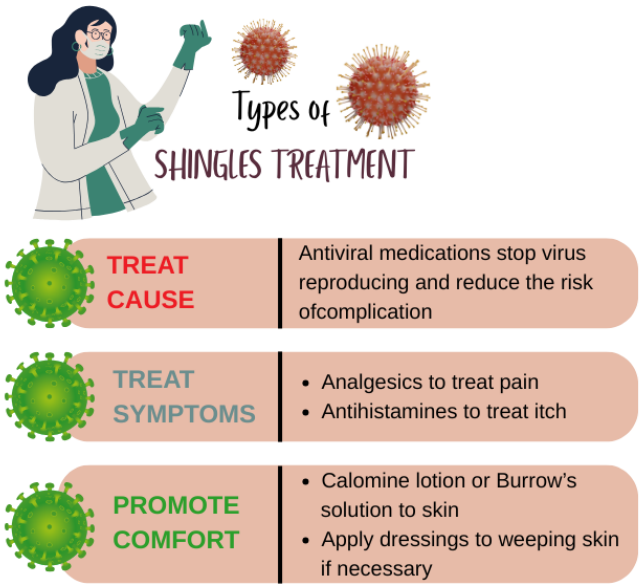
Often required for moderate-to-severe pain that is not adequately controlled by antiviral therapy combined with corticosteroids and/or standard oral analgesics. While these agents do not prevent PHN, they may provide additional relief during the acute phase. Gabapentin and pregabalin, both anticonvulsants, are commonly used. Although a single 900 mg dose of gabapentin has shown modest short-term pain reduction over a 6-hour period, neither drug has demonstrated consistent efficacy in preventing PHN or significantly relieving acute pain. Their side effects—such as sedation, dizziness, ataxia, and peripheral edema—necessitate cautious dosing, especially in elderly patients. Gabapentin is typically titrated to three times daily, while pregabalin is administered twice daily, beginning with a low bedtime dose to minimize adverse effects.

When pain remains uncontrolled despite these therapies, **anesthetic nerve blocks** may be considered. Referral to a pain specialist is generally required for these procedures. A randomized controlled trial comparing standard therapy (antivirals and analgesics) with and without a single epidural block using bupivacaine and methylprednisolone demonstrated that neural blockade can reduce acute zoster pain, though it does not prevent PHN.

## Opioids

May be used as a last resort for severe, refractory pain. When effective, they provide relief within hours to days, though a trial of at least four weeks may be required to assess full benefit. However, their use is often limited in older adults due to adverse effects such as sedation, constipation, and risk of falls. Caution is warranted in individuals with a history of substance use disorder, though the risk of developing addiction in opioid-naïve elderly patients is considered low. **Tramadol**, a centrally acting analgesic with weak mu-opioid agonist activity, may also provide short-term relief, but shares many of the same adverse effects as traditional opioids. Notably, tramadol carries a heightened risk of **seizures**, particularly in patients with a history of epilepsy

or when used with drugs that lower the seizure threshold. Additionally, it poses a **risk of serotonin syndrome** when combined with SSRIs or other serotonergic agents.




## INVASIVE AND NON-INVASIVE TREATMENTS IN HERPES INFECTIONS

For some older patients with **postherpetic neuralgia (PHN)**, conventional first-line treatments—including antivirals, gabapentin, tricyclic antidepressants, and topical agents—may not provide adequate pain relief. In such cases, additional **pharmacologic and non-pharmacologic interventions** should be considered, especially when pain persists despite optimal medical therapy.

### Non-Invasive Treatments

Non-invasive strategies are generally low-risk and may offer symptom relief, especially when used as adjuncts to pharmacotherapy. These include:

- **Cold application**
- **Transcutaneous electrical nerve stimulation (TENS)**
- **Percutaneous electrical nerve stimulation (PENS)**
- **Acupuncture**
- **Psychological therapies**, including cognitive behavioral therapy (CBT) and pain coping strategies

Although these modalities have demonstrated anecdotal benefit, **robust clinical trial data supporting their efficacy in PHN is limited**, and further research is warranted. Nevertheless, their minimal risk profile makes them reasonable options to trial in selected patients.

Some patients with PHN also experience **myofascial pain**, characterized by:

- **Taut muscle bands** within the affected dermatome
- **Trigger points**, which are hyperirritable spots in skeletal muscle that are painful on compression

In such cases, **PENS** may be particularly beneficial, targeting both neuropathic and myofascial pain components.

### Invasive Treatments

Invasive interventions should be considered for patients with refractory PHN who do not respond to standard or non-invasive therapies.

Referral to a **pain management center** is strongly advised before initiating these procedures.

Invasive treatment options include:

- **Neural blockade techniques**:
  - Sensory nerve blocks
  - Sympathetic nerve blocks
  - Plexus blocks
  - **Epidural or intrathecal injections** of local anaesthetics (e.g., lidocaine) and/or corticosteroids
- **Central nervous system (CNS) drug delivery systems**:
  - Implantable pumps delivering opioids or anaesthetics directly into the spinal cord area
- **Spinal cord stimulation (SCS)**:
  - Delivers electrical impulses to the spinal cord to modulate pain signals
  - Shown to reduce neuropathic pain in selected patients with intractable PHN
- **Neurosurgical procedures** (e.g., dorsal root entry zone lesions or other ablative techniques):
  - Considered in rare, extreme cases where all other modalities have failed

While these invasive procedures carry a higher risk, **they may offer meaningful relief** for patients with severe, debilitating PHN who have exhausted conservative options.

## COMMON COMPLICATIONS OF HERPES ZOSTER

### Post Herpetic Neuralgia (PHN)

Pain that is present for 90 days or more after HZ rash onset is known as PHN. PHN is the most common complication of HZ. Although the pain often resolves within a few weeks, it can last for several months or even years. It is a debilitating complication that is challenging to treat and is responsible for most of the HZ-related burden of disease.

Factors associated with the development of PHN include greater severity of acute pain, older age, greater rash severity, immunocompromised patients, and restricted activities of daily living before HZ. Prodromal pain, female sex, diabetes, and the presence of herpes zoster ophthalmicus (HZO) have also been reported to play a role

### Skin Complications

Dermatological complications that occur include disseminated HZ, usually associated with immune suppression and characterized by vesicles spreading beyond the distribution of the affected dermatome, with the potential to affect other organs (e.g., encephalitis), making the condition potentially lethal.

Others include hemorrhagic HZ, a rare condition also correlated with immune suppression, coagulopathy, thrombocytopenia and Ramsay Hunt syndrome, defined as peripheral facial nerve palsy accompanied by an erythematous vesicular rash in the ear (zoster oticus), resulting from involvement of the

geniculate ganglion by HZ reactivation. Chronic varicella zoster is defined as an atypical mucocutaneous wart-like or ulcerative VZV infection, persisting for at least 1 month, mainly occurring in patients who are HIV positive

Other complications, both in the primarily affected dermatome and elsewhere, may occur, although these are less common. Dermatomal complications include secondary bacterial infections, ophthalmic complications and various degrees of segmental paresis, which can affect extraocular muscles, limbs, abdominal wall or diaphragm, depending on the dermatome involved.

Viral reactivation in the first branch of the trigeminal nerve (i.e. the ophthalmic or V1 division) results in HZO. HZO accounts for about 10–20% of cases of HZ. The lifetime risk of developing HZO is approximately 1%. Ocular complications typical of HZO can occur even when there is no visible rash (i.e. zoster sine herpete). Polymerase chain reaction (PCR) analysis has shown that VZV may be present in the cornea and tears, even in the absence of ocular symptoms or skin rash. Hence, VZV reactivation in the ocular neuronal pathways is frequently misdiagnosed and, therefore, its incidence is underestimated [22, Rank 4]

## Other Complications

Between 20% and 70% of patients with HZO develop complications that can include blepharitis, keratoconjunctivitis, iritis, scleritis, and acute retinal necrosis. Neurological complications are less frequent than ocular complications and may include ophthalmoplegia, optic neuritis, and ptosis. Patients presenting with HZO should be treated with oral antiviral drugs, preferably within 72 h after rash onset; however, if new lesions are present, treatment may still be useful after this time

Treatment is usually for 7 days; there is no evidence that longer treatment is beneficial, except in older or immunocompromised patients in whom viral activity has been shown to be ongoing for up to 34 days. Despite antiviral treatment, chronic disease can persist in 30% of patients with HZO, increasing to 70% in patients over 80 years old. A prominent cause of persistent or chronic disease is vasculitis, perivasculitis, neuritis, and peri neuritis; the neuronal damage begins before the characteristic dermatomal rash appears and therefore before antiviral treatment is initiated

Disseminated zoster occurs mainly in immunocompromised patients and, in the case of visceral location, can lead to pneumonia, encephalitis (with associated cognitive impairment and sensory or motor deficits), and hepatitis with a 5–10% fatality rate, despite antiviral drug treatment. Primary VZV encephalitis is not necessarily associated with immunodeficiency. In a study, HZ encephalitis was identified as the second most frequent

cause of death (15%) after herpes simplex virus (HSV).

**Immunosuppressed Cases**

Patients with cancers and other diseases that alter immune function, such as autoimmune inflammatory rheumatic disease (AIRD: rheumatoid arthritis, systemic lupus erythematosus, granulomatosis with polyangiitis), and patients taking immunosuppressants or chemotherapy have a higher risk of HZ. It has been suggested that in patients with AIRD, the drugs used for treatment (e.g., steroids, antitumor necrosis factor α agents, and some disease-modifying drugs) add to the risk. When HZ is diagnosed, the possibility of stopping immunosuppressive drugs should be considered. Patients who are HIV positive with low CD4 counts also have a higher risk than the general population; the lower the count, the greater the risk.

HZ and its complications have been shown to hurt quality of life (QoL) and activities of daily living. Some patients, particularly older patients, lose their independence, and many patients require help from their families or paid caregivers. In particular, sleep and social activities are most severely affected. Although individuals can recover some of their loss of independence, they rarely recover to the same level as they had before the HZ episode. People who have had HZ or know people who have had HZ are more aware of the risks, associated pain, consequences, and impact on QoL of the disease. An individual's attitude towards HZ prevention is related to their knowledge of HZ and views on vaccination in general. [23, Rank 3]

## THE INCIDENCE OF HERPES ZOSTER INFECTION IN PATIENTS WITH DIABETES MELLITUS

Several studies showed that the incidence of herpes zoster infection is higher in patients with type 2 DM (T2DM). In a recent study, it was found that T2DM was independently associated with increased risk for herpes zoster infection. Importantly, it has been estimated that approximately 13% of cases of herpes zoster infection occur in patients with T2DM. Moreover, undiagnosed T2DM is frequent in patients with herpes zoster infection, suggesting that these patients should be evaluated for the presence of T2DM

Limited data suggest that type 1 DM (T1DM) is also a risk factor for herpes zoster infection. Interestingly, a recent study showed that T1DM might increase the risk for herpes zoster infection more than T2DM

In accordance with patients without DM, the incidence of herpes zoster increases with age and is also higher in women with DM than in men. Interestingly, DM appears to increase the risk for herpes zoster infection more in the elderly than in younger patients. Moreover, patients with micro- and macrovascular

complications of DM are also at higher risk for herpes zoster than patients without complications.

In addition, treatment with thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4), and insulin appears to increase the risk of herpes zoster, whereas metformin and sulphonylureas do not appear to affect this risk. [27, Rank 3]

## THE RELATION BETWEEN ASTHMA AND ZOSTER

Zoster occurs in children but much less often than in adults. VZV reactivation is more common in highly immunosuppressed children who are receiving therapy for cancer or rheumatological diseases. Asthma, a common illness in children, might also increase the rate of zoster. Asthma is an inflammatory disorder of the airways. A population-based case–control study in the USA showed a higher incidence of zoster in children with asthma than in those without asthma; inhaled or systemic corticosteroids were excluded as a cause for this difference. Subsequently, a similar analysis was carried out in a much larger adult study cohort, with similar results. Asthma might, therefore, be a contributing cause to VZV reactivation in both children and adults, suggesting that intact innate immunity or the absence of chronic inflammation from asthma may be involved in the maintenance of latency [15, Rank 4]

## THE RISK OF HERPES ZOSTER IN CHILDREN WITH CANCER

Herpes zoster is rare in healthy children, but immunocompromised persons have an increased risk of herpes zoster and severe diseases. Herpes zoster is characterized by a vesicular skin rash and is often preceded or accompanied by acute pain and itching. Several neurologic complications may develop afterwards, including postherpetic neuralgia, myelitis, cranial nerve palsies, and vasculopathy. Pain, itching, and complications can lead to the impairment in quality of life and even functional disabilities.

Herpes zoster is common in adults with lifetime risk ~10% to 30% but rare in healthy children. Increasing age is the most well-known major risk factor. Immunocompromised persons with impaired T-cell immunity are at an increased risk of herpes zoster, such as those with leukemia and lymphoma, recipients of hematopoietic stem cell transplantation, those receiving chemotherapy or immunosuppressants, and those with human immunodeficiency virus infection. In children with cancer, herpes zoster can lead to serious complications, including severe post herpetic neuralgia, visceral dissemination, acute or progressive outer retinal necrosis, and even death. The awareness of the symptoms and early treatment are important. [28, Rank 3]

## NEUROLOGICAL COMPLICATIONS OF ZOSTER

### Zoster Paresis

Manifestations of zoster paresis include arm or diaphragmatic weakness after cervical zoster, leg weakness after lumbar or sacral zoster and urinary retention after sacral zoster. MRI reveals involvement of both dorsal and ventral roots of spinal nerves. Rarely, cervical zoster paresis extends to the brachial plexus. The prognosis varies, but ~50% of patients recover completely

### Post Herpetic Neuralgia (PHN)

PHN, the most common complication of zoster, is defined as pain that persists for at least 3 months after rash onset.

Recently, certain strains of VZV were postulated to produce PHN by altering voltage-gated sodium channels, leading to altered excitability. Isolated and then cultured VZV strains from patients with PHN and those with zoster but without PHN were applied to neuroblastoma cells that express fast and slow sodium channels. Recent studies suggest that PHN might be partly attributable to the particular strain causing zoster.

Virological analyses of ganglia from patients with PHN are lacking. One study reported the detection of VZV DNA in peripheral blood mononuclear cells (PBMCs) for up to 8 years after zoster in 11 out of 51 patients with PHN but not in controls. A case report described a correlation between pain and VZV DNA detection in PBMCs in an immunocompetent elderly woman with PHN. After treatment with famciclovir (a guanosine analogue antiviral drug), pain resolved and the PBMCs no longer contained VZV DNA .

If PHN is caused by persistent VZV replication in neurons, antiviral treatment might decrease its severity. Treatment with oral antiviral agents reduces pain associated with acute zoster; however, this acute treatment has not reduced the incidence, severity or duration of chronic pain of immunocompetent patients with PHN. Acyclovir improved symptoms in 1 out of 10 patients with PHN, whereas valaciclovir improved symptoms in 8 out of 15 patients. Proof of a positive effect of antivirals on PHN would require a randomized controlled study of patients with PHN. Most studies, however, have not found antiviral therapy to be effective in the treatment of PHN and regulatory authorities do not recommend antivirals to treat this condition [4, Rank 3]

### VZV meningoencephalitis

Acute VZV infection may present as meningitis or meningoencephalitis with or without rash. Detection of VZV DNA and antibodies in cerebrospinal fluid has confirmed VZV as a cause of aseptic meningitis, meningo-radiculitis and cerebellitis.

### VZV vasculopathy

A serious complication of VZV reactivation is infection of the cerebral arteries (VZV vasculopathy), which causes ischaemic and haemorrhagic stroke. The incidence of VZV vasculopathy is unknown. In children, up to one-third of ischaemic arteriopathies are associated with varicella. In adults, the risk of stroke is increased by 30% within 1 year of zoster and by 4.5-fold after zoster in the ophthalmic branch of the trigeminal nerve.

However, no cases of vasculopathy or stroke were observed among patients with documented zoster followed up for >6 months after rash onset, although majority of them received antiviral therapy. Indeed, stroke following herpes zoster ophthalmicus (HZO) is of high clinical importance. VZV that reactivates in the trigeminal nerve can travel via the ophthalmic sensory nerves to the face and via afferent sensory fibres to the internal carotid artery and its intracranial branches. Thereafter, the virus establishes infection in the arterial wall, which leads to inflammation, arterial weakening, aneurysm formation, occlusion and stroke. Infected cerebral arteries contain multinucleated giant cells, and herpesvirus particles, as well as VZV DNA and VZV antigens.

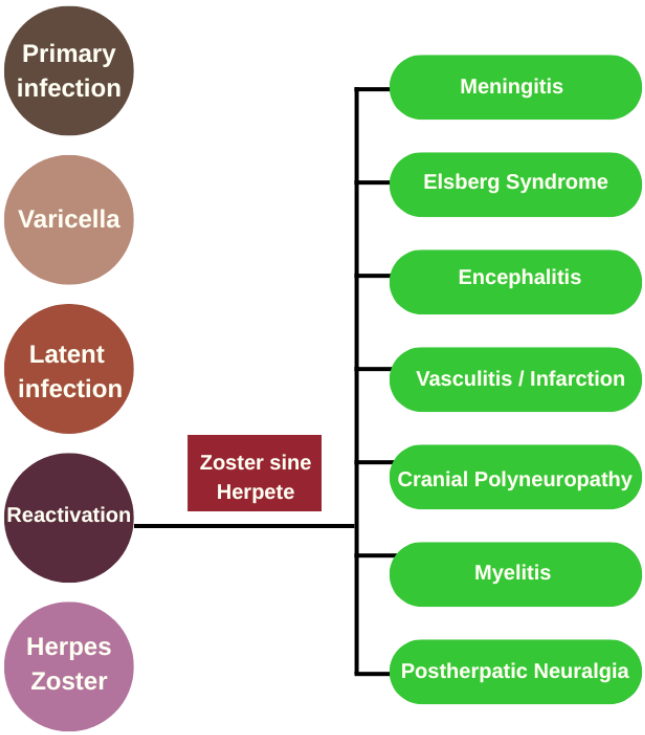
VZV vasculopathy presents with headache, mental status changes and focal neurological deficits. Large and small vessels are involved. Brain MRI frequently reveals lesions at grey-white matter junctions. In more than two-thirds of patients, angiography reveals focal arterial stenosis and occlusion, aneurysm or haemorrhage.

## VZV and giant cell arteritis

One of the most exciting recent developments is the detection of VZV antigen, VZV DNA and virus particles in the temporal arteries of patients with giant cell arteritis (inflammatory vasculopathy, most often involving the temporal arteries). Analysis of temporal artery biopsies from healthy individuals aged >50 years and from patients with arteritis revealed VZV antigen in the temporal arteries of 74% of patients with arteritis compared with 8% in normal temporal arteries. This discovery, if confirmed, suggests that antiviral treatment might confer additional benefit to corticosteroids in patients with giant cell arteritis.

## VZV-induced diseases of the eye

VZV can cause stromal keratitis with corneal anaesthesia, acute retinal necrosis and progressive outer retinal necrosis, particularly in immunocompromised individuals. Patients complain of eye pain and loss of vision. Retinal haemorrhages and whitening with bilateral macular involvement may occur. Zoster, aseptic meningitis, vasculitis or myelitis can precede retinal necrosis. As with neurological disease, VZV-associated ocular disorders can also occur without rash. [5, Rank 3]




## MANAGING THE COMPLICATIONS OF VARICELLA INFECTION

The most common severe complication of varicella is bacterial superinfection, particularly due to group A Streptococcus, for which varicella is a major risk factor. Superinfection typically presents as a recurrence of fever with or without localized signs of cellulitis, osteomyelitis, septic arthritis, or pneumonia. Notably, cellulitic areas associated with disproportionate pain, fatigue, and systemic symptoms—even in the absence of fever—should raise suspicion for necrotizing fasciitis, necessitating immediate initiation of broad-spectrum antibacterial therapy, resuscitative measures, analgesia, and urgent surgical consultation for possible debridement. Other serious but less common complications include cerebellar ataxia (typically self-limiting), ischemic stroke (due to post-varicella vasculopathy), and acquired protein S deficiency, which can result in purpura fulminans and venous thromboembolism. While the direct impact of antiviral therapy on specific complications is not well established, treatment with antivirals such as acyclovir is justified in cases where there is ongoing viral replication, evidenced by persistent new vesicle formation or continued VZV PCR positivity in blood or cerebrospinal fluid in symptomatic individuals. This pragmatic approach supports timely intervention to potentially limit the progression and severity of complications.

## THE IMPACT OF VARICELLA ZOSTER INFECTION ON QUALITY OF LIFE

In the early twentieth century, varicella and zoster seemed to be diseases of little consequence compared with other common infections such as influenza, measles and poliomyelitis, which frequently were fatal. There was little demand for treatment because both infections were usually mild and self-limiting. Life expectancy was shorter than it is today, which limited the number of zoster cases. Varicella illness lasted only a few days, and meant a few days off from school. School curricula permitted missing a few days without consequence and most families had one parent at home who could care for their sick children.

Then technological developments, new procedures, such as transplantation and drugs to treat cancer, improved medical care and increased life expectancy, but this also increased the number of people susceptible to severe VZV infection. For example, curing children with leukaemia became possible but, at the same time, damage to the immune system by chemotherapy and other curative drugs resulted in severe varicella and subsequent bacterial infections becoming threats. Now, healthy children and those with leukaemia can be protected from varicella by vaccination, the latter by herd immunity. The varicella vaccine also somewhat protects children from zoster.

Today, the varicella and zoster vaccines have dramatically improved the quality of life in the United States. Children rarely miss school due to varicella, and fewer working parents need to stay home to care for their sick children. As lifespans have increased, zoster vaccines have become increasingly important. Antiviral therapy and improved diagnostic methods have also decreased the damage VZV can inflict. Basic research has made a tremendous difference in controlling VZV infections and improving quality of life [14, Rank 4]

## PREVENTION OF HERPES ZOSTER INFECTION

Prevention of HZ and its complications by vaccination would improve the life of older people and also reduce the societal impact of HZ. A live-attenuated VZV vaccine against HZ, which has been licensed in a number of countries worldwide for administration to adults aged over 50 years, has been shown to reduce the incidence of HZ, PHN and other complications in immunocompetent adults. Vaccination recommendations should target at-risk groups, including older individuals, since age is a known risk factor. In addition, there is no way to predict which patients will develop HZ, when or how severe the disease will be. However, individuals need to be adequately informed about the disease and its complications to enable them to make a personal risk assessment, in consultation with their GP, before deciding to accept HZ vaccination. [18, Rank 5]

HZ vaccination reduces the burden of HZ-related interference with daily life activities in vaccinated subjects, particularly older people, who develop HZ. The vaccine attenuates the severity of HZ and PHN when they occur in individuals of all ages, and thus contributes to a reduction of disease burden. The vaccine has been shown to be effective for reducing the risk of HZO and other complications in those aged over 60 and if Herpes Zoster Ophthalmicus (HZO) occurs, despite vaccination, the risk of PHN is significantly lower.

Age at vaccination, duration of vaccine protection, and vaccine efficacy against PHN are all important variables for determining vaccine cost effectiveness. The results from

studies performed suggest that the optimal age for HZ vaccination is 65 or 70 years. Cost effectiveness decreases after this age because vaccine efficacy declines with age, and life expectancy is shorter. Cost effectiveness is also reduced for vaccination before this age due to uncertainties about the duration of vaccine protection. Therefore, in the light of current evidence, HZ vaccination offers significant clinical benefit to older adults and economic benefit to healthcare systems. [19, Rank 4]


## THE IMPORTANCE OF PATIENT AWARENESS REGARDING HERPES ZOSTER

The results from a survey carried out on the general public in United States showed that 75% of those questioned knew what shingles was but only 10% knew that a vaccine exists. Other surveys have shown knowledge that long-term pain may follow HZ is low, although those who had a close friend or relative who had suffered from HZ were more aware.

Two-thirds of healthcare workers considered HZ vaccination to be an important clinical priority but half reported that the vast majority remained unvaccinated. Half of patients questioned stated that they would have the HZ vaccine if it was recommended by their GP and a third would if it was recommended in the media. The main reasons for not getting vaccinated were that patients did not know that the vaccine existed, did not consider themselves to be at risk, and did not know the cost of vaccination. The HZ vaccine is mainly prescribed by GPs but when prescribed by a specialist, the patients generally said that they wanted to discuss it with their GP first. Therefore, GPs need to be informed about HZ and the efficacy and safety of the vaccine so that they can effectively recommend it and be able to help the patient evaluate the risks and benefits. [20, Rank 5]

## THE IMPACT OF VARICELLA VACCINATION ON DISEASE EPIDEMIOLOGY

Re-exposure to circulating VZV, a phenomenon known as exogenous boosting, could prevent reactivation of VZV. Vaccination of children against varicella could have two effects on the epidemiology of HZ. The first is that there will be fewer adults

carrying dormant wild type VZV as vaccinated children grow older, thus reducing the incidence of HZ. The second is that, in the shorter term, adults with dormant VZV will have less contact with children with varicella and therefore less opportunity for exogenous boosting. Since exogenous boosting is thought to inhibit VZV reactivation, this could result in a temporary increased incidence of HZ and could reduce the age of HZ onset. [21, Rank 2]

## CONCLUSION

HZ is a common disease with the highest burden in older adults who frequently have at least one chronic disease. HZ and its complications represent a significant burden on the patients, caregivers, the healthcare economy and employers. Acute disease treatment does not significantly prevent the most common long-term complication, PHN. Treatments for PHN that provide higher levels of pain relief with fewer adverse effects are needed. Less common, but often serious, ophthalmic locations (HZO) and related complications can have permanent detrimental effects.

Future goals include developing new vaccines for specific groups, such as immunocompromised individuals, and developing an evidence base on which type of immunocompromised individuals can be safely and effectively vaccinated with a live-attenuated vaccine. Prevention and attenuation of HZ and its complications are now feasible for most patients and a rational and economically acceptable integrated vaccination policy is a desirable goal. Improved knowledge about HZ and its complications for the public and physicians is needed so that individuals can make informed decisions about HZ vaccination. [30, Rank 5]

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