

Herpes zoster, also known as zoster, or shingles, is caused by the reactivation of varicella-zoster virus (VZV). The term “herpes zoster” was first used by encyclopedist Celsus in c. 25 BCE to c. 50 AD. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by James von Bokay, when children who never had varicella (chickenpox) developed varicella after contact with a person with herpes zoster (shingles). In 1954, Thomas Weller used cell culture to isolate VZV from vesicular fluid of patients with varicella or zoster. However, it was not until 1965 that Edgar Hope-Simpson hypothesized that herpes zoster was due to the reactivation of latent VZV. The first vaccine to reduce the risk of herpes zoster was licensed in the United States in 2006.

## Varicella-Zoster Virus (VZV)

VZV is a DNA virus and is a member of the herpesvirus family. Like other herpesviruses, VZV persists in the body as a latent infection after the primary (first) infection; VZV persists in sensory nerve ganglia. Primary infection with VZV results in varicella (chickenpox). Latent infection can reactivate resulting in herpes zoster (or shingles).

The virus has a short survival time in the environment.

## Pathogenesis

Herpes zoster is the result of reactivation of latent VZV infection. During the primary (first) infection (i.e. varicella), VZV travels to the sensory ganglia where it resides permanently. In this latent form, replication is suppressed by the host immune system and VZV is noninfectious but can reactivate to form intact virions in the involved sensory neurons. Reactivated virions travel to epithelial cells resulting in a rash within the dermatome innervated by the sensory nerve. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with increased risk of developing herpes zoster disease include aging, immunosuppression, intrauterine exposure to VZV, and having had varicella at younger than age 18 months.

## Clinical Features

A vesicular eruption of zoster generally occurs unilaterally in the distribution of a sensory nerve or dermatome and does not cross the mid-line. Zoster can occur in any dermatome but occurs most often in the trunk or face. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. Zoster rash are initially red macules and papules but progresses to form clusters of vesicular lesions before crusting over. The rash lasts for 7–10 days with healing in 2–4 weeks.

### Herpes Zoster

- Caused by reactivation of varicella-zoster virus (VZV)
- Observed relationship between varicella and herpes zoster in 1888
- Hypothesis formed in 1965 that herpes zoster was due to reactivation of latent VZV
- First vaccine to reduce risk of herpes zoster licensed in the U.S. in 2006

### Varicella-Zoster Virus (VZV)

- DNA virus
- Member of herpesvirus family
- Persists as latent infection

### Zoster Pathogenesis

- Result of reactivation of latent VZV infection
- Immunologic mechanism for VZV latency not well understood
- Risk factors: Aging, immunosuppression, intrauterine exposure to VZV, history of varicella at younger than age 18 months

### Zoster Clinical Features

- Variable and usually less severe in children and younger adults
- Vesicular eruption occurring most often in the trunk or face
- Rash lasts for 7–10 days with healing in 2–4 weeks
- Immunocompromised persons experience more systemic symptoms

## Zoster Complications

- Postherpetic neuralgia (PHN) most common
- Ophthalmic involvement, bacterial superinfection, cranial and peripheral nerve palsies, and visceral involvement

In healthy persons there are few systemic symptoms. In immunocompromised persons, zoster may disseminate, causing generalized skin lesions and central nervous system, pulmonary, and hepatic involvement.

## Complications

The most common and debilitating complication from zoster is postherpetic neuralgia (PHN). PHN is pain that persists in the area of the initial rash occurrence after the lesions have resolved. Treatment of persons with PHN is complex, with varying degrees of success in controlling the chronic pain. PHN can last for weeks or months and occasionally may last a year or longer after the resolution of the rash. In addition to PHN, other complications from zoster include ophthalmic involvement, bacterial superinfection, cranial and peripheral nerve palsies, and visceral involvement, all of which often result in severe sequelae.

## Laboratory Testing

The diagnosis of zoster is usually made clinically. In some cases where disease is atypical, such as in persons with altered immunocompetence, laboratory testing can be performed, although a positive result does not differentiate zoster from varicella. Polymerase chain reaction (PCR) to detect VZV DNA is the most useful test for confirming cases of zoster. The ideal samples for PCR testing are swabs of unroofed vesicular lesions and scabs from crusted lesions. Direct fluorescent antibody (DFA) and Tzanck smear are not recommended due to limited sensitivity. Serologic methods have limited use for laboratory confirmation of herpes zoster. Although not widely available, there is a serologic test, VZV IgG avidity test, which may be used to distinguish primary infection from reactivation or reinfection.

## Zoster Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person
  - Direct contact with vesicular fluid or inhalation of aerosols
- Temporal pattern
  - No temporal pattern
- Communicability
  - From rash onset until lesions crust
  - 1/5 as infectious as varicella

## Epidemiology

### Occurrence

Zoster occurs worldwide. In the United States, about 1 in 3 people will develop zoster in their lifetime. Although zoster can occur at any age, the incidence increases with advancing age due to waning immunity. Approximately 50% of persons who live to age 85 years will have experienced zoster.

### Reservoir

VZV, which is the same virus that causes both varicella and zoster, is an exclusively human pathogen. No animal or insect source or vector is known to exist.

### Transmission

VZV transmission occurs person-to-person by direct contact with vesicular fluid or inhalation of aerosols from vesicular fluid of skin lesions of persons with acute varicella or zoster.

Transmission may also occur from infected respiratory tract secretions of patients with varicella that might also be aerosolized. Skin lesions are considered the major source of transmissible VZV. Transmission of VZV would cause varicella, not zoster, in a VZV-naïve person.

## Temporal Pattern

Zoster has no seasonal variation and occurs throughout the year.

## Communicability

A person with localized zoster is contagious beginning from rash onset until their lesions crust. Persons are less likely to transmit if their lesions are completely covered. Zoster is about 1/5 as infectious as varicella.

## Secular Trends in the United States

An estimated 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 32%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster. Rates of zoster are decreasing in the United States in children younger than age 18 years and in older adults.

Among adults age 60 years or older in 2017, 34.9% had ever received a herpes zoster vaccine.

### Zoster Secular Trends in the United States

- Estimated 1 million zoster episodes occur annually in U.S.
- Lifetime risk 32%
- Increasing age and cellular immunosuppression most important risk factors

## Zoster Vaccines

RZV (Shingrix) vaccine is a recombinant subunit vaccine and is currently the only zoster vaccine licensed and available for use in the United States. ZVL (Zostavax) vaccine, a live, attenuated zoster vaccine, was also available for use in the United States from 2006 until 2020, when its production for U.S. distribution was discontinued.

### Zoster Vaccines

- RZV (Shingrix)

## Characteristics

RZV vaccine contains recombinant glycoprotein E in combination with a novel adjuvant (AS01<sub>B</sub>). The lyophilized antigen component is reconstituted with the adjuvant suspension component. RZV vaccine is administered by intramuscular injection. Each dose of RZV vaccine contains DOPC and AS01<sub>B</sub> as adjuvants. It contains no antibiotic or preservative.

### Zoster Vaccine Characteristics

- Contains novel adjuvant
- Administered by intramuscular injection

## Zoster Vaccination Schedule

- 2-dose series at 0, 2–6 months in persons age 50 years or older

## Zoster Vaccine Use

- Immunocompetent persons age 50 years or older indicated for vaccination, including:
  - Persons who have previously received ZVL or varicella vaccine
  - Persons with a previous history of shingles

## Zoster Vaccine Efficacy

- Phase III multicenter clinical trial efficacy:
  - 96.6% for participants age 50 through 59 years
  - 97.4% for participants age 60 through 69 years
  - 91.3% for participants age 70 years or older

## Vaccination Schedule and Use

RZV vaccine is licensed for use in persons age 50 years or older. RZV vaccine is recommended for immunocompetent adults age 50 years or older, including those who have previously received ZVL or varicella vaccine. Persons with a previous history of shingles may also be vaccinated. Adults 50 years or older do not need to be screened for history of varicella infection prior to vaccination. RZV vaccine is administered as 2-dose series. Dose 2 is administered between 2 and 6 months after dose 1. If more than 6 months have elapsed between doses, the RZV vaccine series does not need to be restarted. However, a second dose given less than 4 weeks after the first dose should be repeated.

Because estimates of efficacy against both herpes zoster and PHN are higher for RZV than for ZVL, and because ZVL efficacy wanes substantially during the 4 years following receipt when compared to RZV, the Advisory Committee on Immunization Practices (ACIP) issued a preferential recommendation for RZV over ZVL in 2017, when both vaccines were in use.

Persons who have received ZVL vaccine should be revaccinated with a 2-dose series of RZV vaccine. Intervals shorter than 5 years between administration of ZVL vaccine and RZV vaccine have not been studied; however there are no data or theoretical concerns suggesting that RZV vaccine administered sooner than 5 years after ZVL would be less safe or effective. Because ZVL vaccine has been shown to be less efficacious when administered at age 70 years or older, providers might consider the age at which ZVL vaccine was administered when considering the interval between the two vaccines. Based on expert opinion, RZV vaccine should not be given less than 2 months after receipt of ZVL vaccine.

RZV vaccine may be administered concomitantly (at different anatomic sites) with other adult vaccines, including PPSV23 (Pneumovax 23) and annual seasonal influenza vaccine. Evaluation of coadministration with most other adult vaccines is ongoing, but there is currently no evidence of efficacy or safety concerns.

## Immunogenicity and Vaccine Efficacy

Efficacy of RZV was evaluated in a two-part, phase III multicenter clinical trial enrolling more than 30,000 participants. Efficacy for prevention of herpes zoster after more than 3 years was 96.6% for participants age 50 through 59 years, 97.4% for participants age 60 through 69 years, and 91.3% for participants age 70 years or older. Efficacy for prevention of PHN was 91.2% for participants age 50 years or older and 88.8% for participants age 70 years or older in a pooled analysis.

## Postexposure Prophylaxis

Exposure to a person with either varicella or herpes zoster does not cause zoster in the exposed susceptible person, but rather varicella. Zoster vaccine has no role in the postexposure management of varicella or zoster and should not be used for that purpose. Persons without evidence of immunity who are exposed to varicella or herpes zoster are recommended to receive varicella vaccine within 3 days, and possibly up to 5 days, after exposure. For persons exposed to varicella or herpes zoster who cannot receive varicella vaccine, varicella-zoster immune globulin (VariZIG) can prevent varicella from developing or lessen the severity of the disease.

## Varicella Immunity

Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:
  - Preschool-aged children (age 12 months or older): 1 dose
  - School-aged children, adolescents, and adults: 2 doses
- Laboratory evidence of immunity: commercial assays can be used to assess disease-induced immunity, but they lack adequate sensitivity to reliably detect vaccine-induced immunity (i.e., they may yield false negative results).
- Laboratory confirmation of disease.
- Birth in the United States before 1980 (except for health care personnel, pregnant women, and immunocompromised persons for whom birth in the United States before 1980 should not be considered evidence of immunity). Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A health care provider diagnosis or verification of varicella disease: verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended, and one of the following should be sought: a) an epidemiologic link to a typical varicella case, or b) evidence of laboratory confirmation if laboratory testing was performed at the time of acute disease. When such documentation is lacking, a person should not be considered as having a valid history of disease, because other diseases may mimic mild or atypical varicella.
- History of herpes zoster based on health care provider diagnosis or verification of disease history.

## Zoster Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
- Precaution
  - Moderate or severe acute illness
  - Pregnancy

## Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Persons with chronic medical conditions should receive RZV vaccine unless a contraindication or precaution exists.

Although RZV vaccine is approved for all persons age 50 years or older, immunocompromised persons, including those on moderate- to high- doses of immunosuppressive therapy, were excluded from efficacy studies. Therefore, ACIP has not yet made recommendations regarding use of RZV vaccine in those persons. However, ACIP recommends RZV vaccine for persons taking low-dose immunosuppressive therapy (e.g., less than 20 mg/day of prednisone or equivalent, or using inhaled or topical steroids), or who are anticipating immunosuppression or have recovered from an immunocompromising illness.

Adults age 50 years or older with a history of herpes zoster should receive RZV vaccine. If a patient is experiencing an acute episode of herpes zoster, vaccination should be delayed until the acute stage of the illness has resolved and symptoms abate.

## Vaccination in Pregnancy

There are no available data to establish whether RZV vaccine is safe in pregnant or lactating women, and there is currently no ACIP recommendation for use of RZV vaccine in these populations. Consider delaying vaccination until after delivery and lactation.

## Vaccine Safety

The most common solicited adverse reactions from two placebo-controlled clinical studies involving 29,305 subjects were injection-site pain (78%), myalgia (45%), and fatigue (45%). Serious adverse events were examined in eight studies; overall, rates of serious adverse events were similar in vaccine and placebo groups. Injection-site and systemic grade 3 (i.e., side effects that are severe or medically significant but not immediately life-threatening) solicited adverse events were surveyed in eight studies. Among 9,963 subjects, 16.5% of vaccine recipients, compared with 3.1% of placebo recipients, reported any grade 3 adverse event. Grade 3 injection-site reactions (pain, redness, and swelling) were reported by 9.4% of vaccine recipients and 0.3% of placebo recipients.

## Zoster Vaccine Safety

- Injection site pain
  - 78%
- Myalgia
  - 45%
- Fatigue
  - 45%

Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms) were reported by 10.8% of vaccine recipients and 2.4% of placebo recipients. Grade 3 local reactions were reported with equal frequency following doses 1 and 2, but Grade 3 systemic reactions were reported more frequently after dose 2. Data informing whether a person will experience a more severe reaction after the second dose, if they had a moderate or severe reaction after the first dose, are lacking.

Before vaccination, providers should counsel recipients about expected systemic and local reactogenicity. Recipients should be encouraged to complete the series even if they experienced a grade 1 to 3 reaction after the first dose.

RZV vaccine does not cause varicella as it is a recombinant vaccine and does not contain live virus.

In a postmarketing observational study, an increased risk of Guillain-Barré syndrome (GBS) was observed during the 42 days following vaccination with Shingrix in adults 65 years of age and older. Based on this evaluation, FDA has determined that there is an association of GBS with Shingrix, but that available evidence is insufficient to establish a causal relationship. FDA has concluded that revision to the Warnings and Precautions section of the Prescribing Information for Shingrix to include a warning about GBS is warranted. FDA has determined that the benefits of vaccination with Shingrix continue to outweigh its risks.

The vaccination recommendations for Shingrix remain the same. CDC and collaborators will continue safety monitoring of Shingrix in the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

## Vaccine Storage and Handling

Before reconstitution, both lyophilized antigen component vials and adjuvant suspension component vials should be stored refrigerated between 2°C and 8°C (36°F and 46°F) and protected from light. After reconstitution, use immediately or store refrigerated between 2°C and 8°C (36°F and 46°F). Discard if not used within 6 hours of reconstitution or if frozen. Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's *Vaccine Storage and Handling Toolkit*, [www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf](http://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf).







