

Herpes zoster

ZOSTER VACCINE FOR AUSTRALIAN ADULTS: INFORMATION FOR IMMUNISATION PROVIDERS

Disease and epidemiology

- Herpes zoster or 'shingles' is a localised, painful, vesicular skin rash resulting from reactivation of the same virus (the varicella-zoster virus) that causes chickenpox earlier in life. Shingles can affect any part of the body but the rash classically takes the shape of a belt or band in the thoracic or lumbar region.
- Although usually self-limiting, shingles can lead to post-herpetic neuralgia (PHN), a chronic neuropathic pain syndrome, and other complications.
- About 20–30% of people will have shingles in their lifetime, most after the age of 50 years. Older people (particularly those aged over 70 years) are also more likely to have shingles complicated by PHN.

Who should be vaccinated

- There is one zoster vaccine that is registered for use in people aged 50 years and over as a single dose. It is recommended for adults aged 60 years and over who are not immunocompromised.
- From November 2016, zoster vaccine will be funded under the National Immunisation Program for persons aged 70 years, with catch-up for those aged 71–79 years also funded until October 2021.

Who should *not* be vaccinated

- People who are immunocompromised, pregnant women, and those who have previously had anaphylaxis to any VZV-containing vaccine or its components should *not* receive the zoster vaccine.

Vaccine

- The vaccine contains live attenuated varicella-zoster virus. The amount of virus in the zoster vaccine is approximately 14 times greater than in varicella (chickenpox) vaccines.
- Vaccination of people aged 70–79 years is estimated to prevent about 41% of the cases of shingles and two-thirds of post-herpetic neuralgia cases in that population. In vaccinated people in whom an episode of shingles occurs, the pain, severity and duration is reduced by 50%.
- Protection from vaccination tends to decline with older age at vaccination and the time since vaccination. However, a booster dose is not currently recommended.
- Medical therapy (such as analgesics and antivirals) should still be considered for treatment of shingles, regardless of the patient's immunisation status.
- The vaccine is safe and well tolerated among individuals aged 50 years and over in clinical trials and post-licensure studies. Mild reactions at the injection site, such as pain, swelling and redness, are likely to occur in approximately 50% of vaccine recipients.

The disease

Herpes zoster (also known just as ‘zoster’ or ‘shingles’) is a localised, usually painful, blistering skin rash that occurs more frequently among older adults and in people who are immunocompromised. Shingles is caused by varicella-zoster virus (VZV). Primary (or initial) infection with VZV causes varicella (chickenpox). Once the primary infection resolves, VZV remains dormant in the dorsal root or trigeminal ganglia and can then reactivate, usually much later in life, to cause shingles. Anyone who has had varicella in the past may develop shingles. In most cases, the episode of shingles occurs for no apparent reason.

Clinical features

In the majority of patients, shingles presents as an acute, self-limiting, vesicular rash which is often painful and lasts approximately 10–15 days. The rash is usually unilateral (i.e. does not cross the midline) and has a dermatomal distribution, most commonly affecting thoracic or lumbar dermatomes. In 80% of shingles cases there is a prodromal phase of 48–72 hours before the appearance of the rash with symptoms of itching, tingling or severe pain in the affected dermatome and sometimes headache, photophobia and malaise.

The clinical characteristics of shingles are dependent on the location of the lesions, the immune status and age of the patient, and whether they have received adequate and timely therapeutic medication.

Complications

The most common complication of shingles is persistent chronic neuropathic pain known as post-herpetic neuralgia (PHN). Although there is no international consensus on the definition of PHN, most experts agree that true chronic neuropathic pain is pain that persists beyond 90 days from the onset of rash.^{1,2}

PHN can have a substantial impact on quality of life in those affected and can be refractory to treatment. Risk factors for the development of PHN include advanced age, severe prodromal pain, and severe pain or rash in the acute phase of shingles.^{3,4} The majority of PHN cases occur in patients over 50 years of age.⁴⁻⁷ The proportion of shingles patients who develop PHN increases with age (from approximately 1 in 10 cases in those aged 50–59 years to 1 in 4 cases in those aged over 80 years).^{5,6,8}

Other complications of shingles include:

- skin pigmentation changes and scarring
- secondary bacterial infection of the rash
- eye involvement, called herpes zoster ophthalmicus (in about 10–20% of shingles patients¹)
- cutaneous hypersensitivity or allodynia (in 5–10% of shingles patients⁹)
- neurological complications (commonly nerve palsies)
- pneumonia
- meningitis.

Disseminated disease, which can include generalised spread of skin lesions and, in some cases, organ system involvement, occurs rarely and is more likely in people who are immunocompromised.

Diagnosis

Shingles is usually diagnosed on the basis of clinical assessment, particularly once the rash appears. However, conditions such as HSV infection, eczema herpeticum, impetigo, contact dermatitis and others can be mistaken for shingles. Laboratory confirmation can be obtained by taking a sample from the base of the skin lesions and performing a nucleic acid detection test (such as PCR) or direct-fluorescent antibody test (DFA).¹⁰ Other techniques, such as viral culture, are less sensitive and take longer to complete.

Treatment

The aim of treatment for shingles is to accelerate the healing of the zoster rash, reduce the duration and severity of pain, and decrease the risk of complications. However, aggressive treatment early in the acute phase of shingles using antivirals and analgesics has not been conclusively shown to reduce the likelihood of PHN.^{2,3,10,11} Antiviral therapy should be initiated within 72 hours for optimal benefit but may still be beneficial if started after this time, particularly if new lesions are still forming or the patient is immunocompromised.^{1,10}

There are uncertainties about how to determine which combination of therapies for shingles and PHN is best, and there are few clinical trials that compare treatments or study their use in combination.¹² Also PHN risk varies between studies due to differences in the PHN definition used. Even with optimum early antiviral therapy for shingles, approximately 20% of adults over 50 years of age who develop PHN will still have persistent neuropathy after 6 months. The zoster vaccine has not been studied as a ‘treatment’ for shingles or PHN, and should not be administered for that purpose.

Disease transmission

VZV is usually present in the skin lesions of shingles rash until the lesions dry and crust over. Direct contact with skin vesicles can transmit VZV to cause chickenpox in susceptible people, including those who have not previously had chickenpox or who have never received chickenpox (varicella) vaccine. However, the rate of infection in susceptible people after exposure to a person with shingles (about 15% of susceptible household contacts will be infected) is much less than after exposure to a person with chickenpox (61–100% of susceptible contacts will be infected).^{13–15} A person with shingles who has susceptible household contacts should cover their rash until after the lesions have crusted and should avoid contact with people who are immunocompromised.

Epidemiology

Previous primary infection with VZV is an essential prerequisite for the development of shingles. In a national serosurvey conducted in 2007, more than 95% of the adult population in Australia had antibodies to VZV by the age of 30, indicating that they had been previously infected with the virus.¹⁶ Therefore, almost the entire adult population are at risk of shingles.¹⁷

Most cases of shingles (over 70%) occur in adults aged over 50 years. The cumulative lifetime risk of shingles is estimated to be approximately 20–30% across the population, and about half of people who live to 85 will develop shingles.^{4,10,18} Approximately 121,000–150,000 new cases of shingles occur annually in the general population in Australia, which translates to an overall incidence rate of about 7 per 1,000 population and accounts for around 0.1% of all general practitioner visits annually.^{7,17} The rate of shingles rises with age from 6.5 per 1,000 population in persons aged 50–59 years to over 14 per 1,000 population in those over 70 years of age.^{7,8,19}

A decline in cell-mediated immunity appears to be the most important risk factor influencing the development of shingles. Although antibodies to VZV generally persist through life, cellular immunity to the virus declines with age.^{20,21} Cell-mediated immunity to VZV may be maintained by both episodic ‘exogenous boosting’, from exposure to circulating VZV from chickenpox cases in the community, and/or by ‘endogenous boosting’, the response from either sub-clinical reactivation of VZV or an episode of shingles.¹³ However, the precise relationship between natural exposure to VZV and immunity against reactivation of the latent virus is unclear. While some epidemiological studies suggest an association between proxy measures of VZV exposure

(such as living and working with young children) and decreased risk of shingles in adults, other such studies counter this.^{22,23}

Immunosuppressive conditions and treatments that alter cell-mediated immunity increase the likelihood of developing shingles. For example, shingles is up to 15 times more likely to occur in people who are immunocompromised due to HIV infection, and occurs in up to 30% of patients following haematopoietic stem cell transplantation.^{13,24} Higher rates of shingles are also seen in those who had chickenpox in the first year of life and in those who had congenital varicella infection.

Second or subsequent episodes of shingles are rare; the reported lifetime risk of recurrence in people who have experienced a previous shingles episode is estimated at 1–5%. Rates of recurrence are greater in people who are immunocompromised.

The incidence of shingles is lower in children vaccinated against varicella than in unvaccinated children.^{25–27} Studies to determine the rate of shingles in populations vaccinated against varicella as they enter the age groups with historically high shingles incidence will be important over future decades. Until now, when shingles has occurred in people previously vaccinated with the varicella vaccine, genotyping of the virus has found the rash is usually due to the wild-type VZV (not the vaccine strain), indicating a history of previously undiagnosed varicella infection.¹³ Shingles caused by the reactivation of the varicella vaccine strain has been reported to occur, but appears quite rare.

Who should be vaccinated?

Unless otherwise contraindicated, *The Australian Immunisation Handbook* recommends a single dose of zoster vaccine for all adults 60 years and older who have not previously received a dose.²⁸

Vaccination of adults aged 70–79 years

From November 2016, a single dose of zoster vaccine will be funded on the National Immunisation Program (NIP) for all adults at 70 years of age. A single catch-up dose will also be funded for adults aged 71–79 years for a 5-year period until October 2021.

Routine vaccination of persons aged 70–79 years is expected to provide the greatest population-based benefits against shingles and its complications. This is based on the vaccine efficacy demonstrated in this age group and their increased risk of shingles and PHN compared to those 50–69 years of age.

Vaccination of adults aged 80 years and over

Although disease burden is also high in people aged 80 years and over, vaccine efficacy is lower in this age group. This is one reason why routine vaccination would not occur for those over 80 years of age. However, individual benefit may still be obtained from vaccination (see [Vaccine efficacy or effectiveness](#)).

Vaccination of adults aged 60–69 years

Adults aged 60–69 years can also receive a single dose of zoster vaccine, unless they have previously received a dose or there is a contraindication. Vaccination is not funded under the NIP for this age group.

Although the incidence of zoster and PHN is lower in persons in this age group compared with older ages, vaccine efficacy has been demonstrated in this age group. However, it appears that vaccine efficacy wanes with time, becoming negligible within 5–10 years. However, a recommendation for revaccination has not yet been made. (See also [Vaccine efficacy or effectiveness](#).)

Vaccination of adults aged 50–59 years

Routine use of zoster vaccine in persons aged 50–59 years is not recommended; however, individuals who wish to protect themselves may consider receiving the vaccine. Vaccination is not funded for this age group under the NIP.

Although zoster vaccine has been demonstrated to be efficacious and well tolerated in this age group,^{29,30} vaccine efficacy appears to wane with time and the risk of PHN is greater in those aged 60 years and over. The need for revaccination has not yet been established. (See also [Vaccine efficacy or effectiveness](#).)

Vaccination of people with a negative clinical history of chickenpox

Although an adult may report not having had chickenpox, it is unlikely that they will actually be seronegative for VZV.¹⁷ In people who are seronegative, the vaccine is likely to be well tolerated and immunogenic, although the incidence of injection site reactions may be slightly higher.³¹ It is *not* necessary to provide laboratory evidence of a history of chickenpox in adults over 50 years of age before administering zoster vaccine. However, serologic testing prior to zoster vaccination is recommended for people with asymptomatic HIV infection or those who anticipate significant immunocompromise in the future.

Vaccination of people with a history of shingles

Shingles may recur (see [Epidemiology](#)) but the likelihood of experiencing a repeat episode is difficult to predict.^{3,13} In addition, a clinical history of previous shingles may be

inaccurately recalled by a patient or the illness may have been mistakenly diagnosed (see [Diagnosis](#)). Based on these factors, it is suggested that people with a clinical history of shingles can be vaccinated with the zoster vaccine.

However, the efficacy of zoster vaccine to prevent repeated episodes of shingles has not been examined closely in clinical studies. In a retrospective cohort study in the USA, zoster vaccine did not significantly affect the already low risk of shingles recurrence in adults with a recent initial shingles episode.³²

The optimal time for administration of vaccine following an episode of shingles is uncertain. It is suggested that the vaccine could be given at least 1–3 years after an episode of shingles.²⁸ One study comparing the VZV-specific immune responses to herpes zoster and zoster vaccine found that both cell-mediated immunity and antibody levels after an episode of shingles in unvaccinated people were comparable to immunity conferred by vaccination, for up to 3 years. Therefore, vaccination might be delayed up to 3 years in an immunocompetent person with a recent history of shingles.³³ The safety profile of zoster vaccine (Zostavax[®]) in adults with a documented history of shingles is similar to that in those with no known history of shingles.^{34,35}

Vaccination of people with underlying chronic illnesses

Although people with certain underlying illnesses were excluded from clinical trials, pre-existing morbidities, such as hypertension and arthritis, were frequent among the study participants. Therefore, unless there are contraindications or precautions due to their condition or medical treatment, people with chronic medical conditions such as arthritis, hypertension, chronic renal failure, diabetes and other similar conditions can safely receive zoster vaccine.

Groups for whom zoster vaccination is *not* recommended

Zoster vaccination is not recommended for use in people under 50 years of age and is not registered in Australia for use in this age group.

Zostavax[®] is not indicated for therapeutic use during an acute shingles episode or for the treatment of PHN. In addition, the licensed varicella vaccines (Varilrix[®] and Varivax[®]) are *not* indicated for the primary purpose of preventing shingles in older people (who are likely to have already had varicella) and Zostavax[®] is *not* indicated to provide primary protection against varicella infection.

Zoster vaccination of people who have previously received varicella vaccine is not recommended at this time.

Vaccine

Zostavax[®] (Seqirus/Merck Sharp & Dohme) was registered in Australia in 2006 but there was no or very limited supply of the vaccine from 2007 until early 2014. It is the only zoster vaccine currently registered in Australia.

Zostavax[®] is a live attenuated viral vaccine. It is formulated from the same VZV vaccine strain (Oka-derived) as both currently licensed varicella (chickenpox) vaccines (Varilrix[®] and Varivax[®]) but is of a higher potency, containing, on average, at least 14 times more plaque forming units of vaccine virus per dose. This higher viral potency is required to yield a satisfactory boost in the immune response in older adults.³⁶ (See also [Vaccine efficacy or effectiveness.](#))

Administration

A single 0.65 mL dose of Zostavax[®] is required, to be given by subcutaneous injection only.

Vaccine efficacy or effectiveness

In the Shingles Prevention Study (SPS), 38,546 immunocompetent adults aged 60 years and over received either Zostavax[®] or a placebo.³⁷

In this study, Zostavax[®] was efficacious against incidence of shingles, PHN and the burden of illness (BOI) associated with shingles. (The BOI was a composite measure used in the clinical trial to describe the total pain, severity and duration of shingles.)³⁷ Overall, efficacy against shingles was 51.3%, against PHN was 66.5% and against BOI was 61.1% over a median of 3.1 years of follow-up.³⁷ In a separate study in adults 50–59 years of age, vaccine efficacy against incidence of shingles was higher (69.8%).²⁹ Thus, the vaccine reduces the likelihood that an individual will experience shingles or PHN, and may reduce the severity of a shingles episode if it occurs.

In the SPS, Zostavax[®] was more efficacious in reducing the incidence of shingles in people aged 60–69 years than in those aged over 70 years. However, efficacy in reducing the incidence of PHN and the burden of illness of shingles was similar across both age groups.³⁷ Furthermore, in people aged over 80 years, vaccine efficacy was lower and not statistically significant.¹³ The clinical benefit of the vaccine is likely to be less in those over 80 years of age, although the number of participants in this age group was low in the SPS.

Approximately 65% of the participants in the SPS received antiviral and pain medication within 72 hours of the onset of the rash (regardless of whether they were in the vaccine or placebo group), suggesting that the overall effect of the vaccine was in addition to any benefit that may have been obtained from timely medical therapy.

Duration of protection

Two extension studies of the SPS (the Short-Term and Long-term Persistence Substudies, STPS and LTPS), in which a subset of original participants were followed up for up to 11 years, suggested waning of vaccine efficacy with time.^{38,39} In the STPS (4–7 years after vaccination) there was a 39.6% reduction in the incidence of shingles, a 60.1% reduction in PHN and 50.1% reduction in BOI in those who received Zostavax[®] (compared to those who received placebo).³⁸ In the LTPS (7–11 years after vaccination) the reductions were 21.1% for shingles, 35.4% for PHN and 37.3% for BOI. However, this long-term follow-up data was not as robust as it was compared to ‘modelled’ control estimates because the placebo cohort of the original SPS were offered Zostavax[®] before the LTPS commenced.³⁹ It is unknown at this stage whether a repeat dose will be necessary for lifelong prevention of VZV reactivation. Currently, revaccination with Zostavax[®] is not recommended.

In several large population-based post-licensure studies in the USA, early estimates of the effectiveness of Zostavax[®] against shingles and PHN in people aged 60 years and over were, in general, comparable to those from the SPS. A recent population-based cohort study in the USA showed that, in persons over 60 years of age, Zostavax vaccine effectiveness decreased from 68.7% (95% CI: 66.3%–70.9%) in the first year to 4.2% (95% CI: –24.0% to 25.9%) in the eighth year.⁴⁰

Vaccine safety

Based on clinical trials, Zostavax[®] is safe and well tolerated among adults aged 50 years and over.^{30,37,41,42} In the SPS safety substudy, one or more injection site reactions (such as swelling, pain or redness) occurred in 48.3% of vaccine recipients, compared with 16.6% of placebo recipients. However, the reactions were generally mild and lasted less than 4 days; none were considered serious.³⁷ The incidence of serious adverse events after vaccination was very low and did not differ between vaccine and placebo recipients.

Vaccine recipients were significantly more likely than placebo recipients to have varicella-like rashes around the injection site, but rates were low overall – 20 cases (0.1%) in vaccine recipients compared with 7 cases (0.04%) in placebo recipients. Generalised varicella-like

rashes were rare and occurred at similar rates in vaccine and placebo recipients (0.1% in both groups). In clinical trials where rashes were analysed by PCR for VZV, the majority of rashes were due to wild-type virus, with only very few subjects found to have rashes due to the Oka/Merck VZV vaccine strain.⁴³

The rate of systemic symptoms was somewhat higher in vaccine recipients than in placebo recipients (Zostavax[®] 6.3% vs placebo 4.9%), with the most frequently reported systemic symptoms being headache and fatigue. Fever >38.3°C occurred in fewer than 0.1% of subjects overall, with no difference between vaccine and placebo groups.^{29,37}

The safety profile of the vaccine from post-marketing surveillance is consistent with that in clinical trials. In a study that used data from the Vaccine Safety Datalink network in the USA, the most common side effects were injection site reactions (83%). The remainder were localised or diffuse rashes.^{41,42}

Adverse events occurring after vaccination should be reported to the Therapeutic Goods Administration (TGA), via specific state and territory reporting mechanisms.^{28,44} If a varicella- or zoster-like rash occurs after or despite receipt of the zoster vaccine, the vaccine recipient should avoid contact with people who are immunocompromised and if they have household contacts who are susceptible they should cover their rash until the lesions have crusted.

Contraindications/precautions

Zoster vaccination is contraindicated when there has been anaphylaxis following a previous dose of any VZV-containing vaccine (either zoster or varicella vaccine), or anaphylaxis following any vaccine component (including gelatin or neomycin).

As with other live viral vaccines, people who are immunocompromised should *not* receive the zoster vaccine. Immunocompetent people who anticipate alteration of their immunity (e.g. because of an existing illness or future immunosuppressive therapy) can be given zoster vaccine under certain conditions, on a case-by-case basis after seeking appropriate specialist advice. People with asymptomatic HIV infection with CD4+ counts >200 per µL can also receive the vaccine. Refer to the *The Australian Immunisation Handbook* and the NCIRS [Zoster vaccine FAQ fact sheet](#) for further information on vaccination of these special risk groups, including patients who are receiving disease-modifying anti-rheumatic drugs (DMARDs).²⁸ Vaccination is also recommended for age-eligible household contacts of a person who is immunocompromised. VZV-containing

vaccines are contraindicated in pregnancy; however, having a non-immune pregnant household contact is *not* a contraindication to zoster or varicella vaccination.

As people eligible to receive zoster vaccine will, because of their age, generally already have antibodies to VZV from primary infection, the zoster vaccine can be given at any time before or after administration of immunoglobulin or any antibody-containing blood product.^{13,28}

Concomitant administration

Zostavax[®] can be given at the same visit as inactivated influenza vaccine (at separate sites and using separate syringes). A clinical trial demonstrated that simultaneous administration of these two vaccines did not alter the safety or efficacy profile of either vaccine.⁴⁵

Zostavax[®] can be given at the same time as 23-valent pneumococcal polysaccharide vaccine (23vPPV) or 13-valent pneumococcal conjugate vaccine, using separate syringes and injection sites. A large observational study from the USA did not find evidence of any impact on the protective efficacy of Zostavax[®] against shingles when it was co-administered with 23vPPV.⁴⁶ Although in one clinical trial antibody responses for Zostavax[®] were lower when it was co-administered with 23vPPV,⁴⁷ VZV antibody levels have not been shown to directly correlate with clinical protection.⁴⁸

Zostavax[®] can be administered at the same visit as, or at any time following, receipt of other inactivated vaccines (e.g. tetanus-containing vaccines), if required.

As with other live viral vaccines, if Zostavax[®] is to be given around the same time as another live viral parenteral vaccine (e.g. MMR, yellow fever), the vaccines should be given either at the same visit or at least 4 weeks apart.^{13,28}

Other considerations

Universal vaccination of children at 18 months of age to prevent primary varicella is recommended in Australia. Varicella vaccine is given under the NIP at 18 months of age as a combination vaccine that also includes vaccines against measles, mumps and rubella (MMRV). Refer to *The Australian Immunisation Handbook* for more details.²⁸ (See also NCIRS fact sheet [Varicella-zoster \(chickenpox\) vaccines for Australian children](#).)

A new recombinant subunit vaccine for zoster (HZ/su, GSK Biologicals) is under development with clinical trials demonstrating high levels of efficacy against shingles in adults 50 years and older following 2 doses.⁴⁹

Additional resources for primary medical care/vaccination providers

- *The Australian Immunisation Handbook*, 10th edition – the most up-to-date clinical recommendations are contained in the online version of the *Handbook* www.immunise.health.gov.au/internet/immunise/public/shing.nsf/Content/Handbook10-home
- Immunise Australia website www.immunise.health.gov.au
- NCIRS Zoster vaccine FAQ fact sheet www.ncirs.edu.au/assets/provider_resources/factsheets/zoster-vaccine-FAQ.pdf

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