

# Zoster vaccines for Australian adults

This fact sheet provides information on herpes zoster disease and the available vaccines to assist immunisation providers in the delivery of zoster vaccinations.



Rarely, patients can develop disseminated varicella-zoster virus (VZV) infection with the vaccine (Oka) strain after receiving Zostavax vaccine. This has been associated with several deaths in Australia, including in patients on low-dose immunosuppressive medication. The risk increases with the degree of immunosuppression. The safety of administering zoster vaccine should be assessed on a case-by-case basis using the [Live shingles vaccine \(Zostavax\) screening for contraindications](#) tool. Where safety is uncertain, vaccination should be delayed and expert opinion should be sought from the patient's treating specialist and/or an immunisation expert.

## Disease

- Herpes zoster or 'shingles' is a localised, painful, vesicular skin rash resulting from reactivation of varicella-zoster virus (VZV, the same virus that causes chickenpox earlier in life).
- Although shingles is usually self-limiting, it 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 experience complications such as PHN.

## Vaccines

- From 2021 there are two zoster vaccines available in Australia for use in people aged ≥50 years to prevent herpes zoster:
  - **Zostavax** (Merck): a live-attenuated VZV vaccine. Zostavax requires a single dose
  - **Shingrix** (GlaxoSmithKline): an adjuvanted recombinant VZV glycoprotein E (gE) subunit (non-live) vaccine. Shingrix requires two doses, 2–6 months apart, to ensure adequate protection.

## Who should be vaccinated

- Unless contraindicated, all people aged ≥50 years, both immunocompromised and immunocompetent, are recommended to receive vaccination to prevent herpes zoster and its complications.
- The optimal age to receive vaccination depends on the patient's age and immune status; the duration of protection of the chosen vaccine; and the individual's desire to protect themselves from the disease.

- Currently the [Australian Immunisation Handbook](#) recommends vaccination for immunocompetent people from age 60 years. However, vaccination from age 50 years can be considered.
- People who are immunocompromised should consider vaccination from age 50 years as they are at a higher risk of disease.

### **Which vaccine should be used**

- In immunocompetent people aged  $\geq 50$  years Shingrix is preferred over Zostavax for prevention of herpes zoster and its complications.
- In people aged  $\geq 50$  years who are immunocompromised, Zostavax is generally contraindicated and so Shingrix should be used.
- Availability of Shingrix is expected to be limited, and it will need to be privately prescribed.
- Zostavax is a readily available and effective alternative for immunocompetent people aged  $\geq 50$  years if Shingrix is not available or affordable. Zostavax is NIP-funded for people aged 70 years (with catch-up available for those aged 71–79 years until October 2021). People should be encouraged to receive Zostavax if Shingrix is not accessible.
- Zostavax may be given to people with **mild immunocompromise** only where Shingrix is not available or affordable, after careful assessment of the degree of immunocompromise using the [Live shingles vaccine \(Zostavax\) screening for contraindications](#) tool, and after informed consent has been obtained.
- Very rarely, a non-localised VZV-like rash occurs around 2–4 weeks after receipt of Zostavax. People who have received Zostavax should be advised to seek immediate medical attention if they develop a VZV-like rash, and inform their medical practitioner that they have recently received Zostavax.

### **Contraindications to vaccination**

- Zostavax is generally contraindicated in people who are currently or recently immunocompromised due to disease or medication and so Shingrix should be administered in this population.
- Pregnant women should not receive Zostavax. There are currently no data on the use of Shingrix in pregnant women.
- People with anaphylaxis to a zoster vaccine or a vaccine component within Zostavax or Shingrix should not be vaccinated with that respective vaccine.

## **The disease**

Herpes zoster (also known just as ‘zoster’ or ‘shingles’) is caused by reactivation of varicella-zoster virus (VZV). Primary (or initial) infection with VZV causes varicella (chickenpox). Once the primary infection resolves, VZV remains dormant in nerves 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. Shingles occurs more frequently among older adults and in people who are immunocompromised.

## **Clinical features**

In the majority of patients, shingles presents as an acute, self-limiting, vesicular rash which is often painful, lasting 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, but capable of affecting any cutaneous area. 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.

## Complications

The most common complication of shingles is persistent chronic neuropathic pain known as post-herpetic neuralgia (PHN). PHN is usually defined as pain that persists beyond 90 days from the onset of rash.<sup>1,2</sup>

PHN can have a substantial impact on the quality of life in those affected and can be refractory to treatment. The majority of PHN cases occur in patients aged  $\geq 50$  years, and incidence increases with age,<sup>3-6</sup> from approximately 1 in 10 cases in 50–59 year olds to 1 in 4 cases in those aged  $>80$  years.<sup>4,5,7</sup>

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 patients<sup>1</sup>)
- cutaneous hypersensitivity or allodynia (in 5–10% of shingles patients<sup>8</sup>)
- neurological complications (commonly nerve palsies)

Disseminated disease, which can include generalised spread of skin lesions and, in some cases, organ involvement (e.g. meningitis, pneumonia), 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 herpes simplex virus 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).<sup>9</sup>

## Treatment

Antiviral medication can accelerate the healing of the zoster rash and reduce acute pain; however, it has not been conclusively shown to reduce the likelihood of PHN.<sup>2,9-11</sup> Antiviral therapy should be started within 72 hours of rash appearing for optimal benefit. The therapy may still be beneficial if it is started after this time, particularly if new lesions are still forming or if the patient is immunocompromised.<sup>1,9</sup>

Even with optimum early antiviral therapy for shingles, approximately 20% of people aged  $>50$  years who develop PHN will still have persistent neuropathy after 6 months. Zoster vaccines have not been studied as a ‘treatment’ for shingles or PHN, and should not be administered for that purpose.

## Disease transmission

Direct contact with skin vesicles can transmit VZV to cause chickenpox in susceptible people. However, the transmission rate is less from a person with shingles (about 15% of susceptible household contacts will be infected) than a person with chickenpox (61–100% of susceptible contacts will be infected).<sup>12-14</sup>

VZV is usually present in the skin lesions of shingles rash until the lesions dry and crust over. 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 and pregnant women.

## Epidemiology

Previous primary infection with VZV is a prerequisite for shingles to develop. 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 years. This means they had been previously infected with the virus.<sup>15</sup> Therefore, almost the entire adult population is at risk of shingles.<sup>16</sup>

Most cases of shingles (over 70%) occur in people aged >50 years. The lifetime risk of shingles is about 20–30% across the population, and about half of people who live to 85 years of age will develop shingles.<sup>3,9,17</sup> The rate of shingles rises with age, from 6.5 per 1,000 population in people aged 50–59 years to over 14 per 1,000 population in those aged >70 years.<sup>6,7,18</sup>

A decline in cell-mediated immunity with age appears to be the most important risk factor for shingles.<sup>19,20</sup> ‘Exogenous boosting’, from exposure to chickenpox cases in the community, and/or ‘endogenous boosting’, from either sub-clinical reactivation of VZV or an episode of shingles, may play a role in maintaining immunity.<sup>12</sup>

Incidence of herpes zoster is significantly higher among people with immunocompromise than in the general population. A large 2014 Australian cohort study reported that people who had a recent immunosuppressive condition had >50% higher risk of herpes zoster than the general population.<sup>21</sup> In people with severe immunocompromise, such as those with haematological malignancy, the risk can be up to four times higher.<sup>22</sup> People with immunocompromise are also significantly more likely to experience severe herpes zoster disease/complications, requiring hospitalisation, than the general population.<sup>23</sup>

Second or subsequent episodes of shingles are rare. The lifetime risk of recurrence in people who have had a previous shingles episode is about 1–5%. However, rates of recurrence are greater in people who are immunocompromised.<sup>24</sup>

## Which zoster vaccine to use?

### People who are immunocompetent

Shingrix is preferred over Zostavax for prevention of herpes zoster and associated complications in immunocompetent people.

Both Shingrix and Zostavax have good efficacy in preventing herpes zoster, but they have not been compared in head-to-head clinical trials. Studies of each vaccine against placebo, however, suggest that Shingrix may be substantially more efficacious, particularly in the elderly, and offer longer lasting protection against herpes zoster.<sup>25</sup> Recipients must complete the two-dose schedule of Shingrix to ensure an adequate level and duration of protection.

However, Zostavax remains an effective alternative where Shingrix is not available or affordable. A single dose of Zostavax is readily available on the NIP for those aged 70 years, and for those up to 79 years of age via a catch-up program until October 2021. People should be encouraged to receive Zostavax if Shingrix is not accessible.

The safety of administering Zostavax should be considered in all patients on a case-by-case basis. Immunisation providers are recommended to use the [Live shingles vaccine \(Zostavax\) screening for contraindications](#) tool to determine the suitability of Zostavax for their patients. Where safety is uncertain, vaccination should be delayed and expert opinion sought from the patient’s treating specialist and/or an immunisation expert.

### People who are immunocompromised

As with other live viral vaccines, Zostavax is generally contraindicated in people who are currently or recently immunocompromised due to disease or medication. Shingrix is the recommended vaccine in this population.

Zostavax may only be given to those with **mild** immunocompromise, if Shingrix is not available or affordable. This should be decided on a case-by-case basis after careful assessment of the degree of immunocompromise, using the [Live shingles vaccine \(Zostavax\) screening for contraindications](#) tool. If there is any uncertainty about the level of immunocompromise, Zostavax should not be administered.

Refer to the section Use of Zostavax in people with immunocompromise below, and the [Australian Immunisation Handbook](#), for more details.

## Who should be vaccinated

Unless contraindicated, all people aged  $\geq 50$  years, both immunocompromised and immunocompetent, are recommended to receive vaccination to prevent herpes zoster and its complications. However, the optimal age to receive vaccination will differ for individuals.

## When should people get vaccinated

Several factors should be considered when deciding on the optimal age to receive the vaccine:

- **age-related risk of herpes zoster and its complications.** Although both Zostavax and Shingrix are efficacious and registered for use from 50 years of age, the case for receiving zoster vaccination becomes stronger with increasing age because of the increasing risk of disease.
- **immune status.** People who are immunocompromised are at significantly higher risk of herpes zoster and severe complications than immunocompetent people of a similar age.
- **duration of protection offered by the vaccine chosen.** Duration of protection offered by Shingrix remains unknown, but appears to wane more slowly than that of Zostavax. Early vaccination may result in insufficient protection later in life when the risk is higher. There are currently no recommendations for booster doses for either vaccine; the role for these in the future is unclear.
- **individual's desire to protect themselves from disease.**

The recommendations for the use of Zostavax are outlined in the [Australian Immunisation Handbook](#).

## People who are immunocompetent

The potential benefits of receiving zoster vaccination are greater with increasing age due to increasing risk of disease. Vaccination at a younger age may potentially be associated with waning protection later in life when risk is higher. For this reason, the [Australian Immunisation Handbook](#) currently recommends Zostavax from 60 years of age in immunocompetent people. A single dose of Zostavax is funded on the NIP for all people at 70 years of age. This is based on the efficacy of Zostavax in this age group and their increased risk of shingles and PHN compared with those aged 50–69 years. A single catch-up dose is funded for adults aged 71–79 years until October 2021.

Vaccination from 50 years of age can be considered if a person wishes to reduce their risk of herpes zoster. However, providers and patients should consider the possibility of insufficient protection later in life, due to waning of vaccine protection, when the risk of herpes zoster is higher.

Immunocompetent people who elect to receive zoster vaccine at a younger age may benefit more from receiving Shingrix over Zostavax, if available, because Shingrix likely provides higher efficacy and longer duration of protection.

Additionally, people who elect to receive zoster vaccination at age  $\geq 80$  years may also benefit from receiving Shingrix over Zostavax because of likely higher efficacy in this age group. Zostavax efficacy is low in this age group, and its use is not routinely recommended.

## People who are immunocompromised

Providers should consider offering Shingrix to people who are immunocompromised from age 50 years because of their higher risk of disease.

As the duration of protection from Shingrix is less certain in this population, there is the risk of insufficient protection later in life. Currently there is no recommendation for booster doses. The requirement for booster doses in the future is unknown and recommendations may change. If there is uncertainty about the optimal timing of vaccination, this should be discussed with the patient's specialist.

Household contacts of unvaccinated individuals with immunocompromise may also consider receiving their zoster vaccination at a younger age to offer some indirect protection against VZV to the household member with immunocompromise.

## Use of Zostavax in people with immunocompromise

Zostavax **MUST NOT** be administered to people with severe immunocompromise. These include:

People with a primary or acquired immunodeficiency

- haematological neoplasms — leukaemia, lymphoma, myelodysplastic syndromes, including people under follow-up for chronic lymphoproliferative disorders, and people who are currently not receiving treatment or who have never received treatment
- post-transplant — solid organ transplant recipients who are on immunosuppressive therapy or have used immunosuppressive therapy within the past 6 months; people who have had a haematopoietic stem cell transplant within the past 24 months (or longer if they have immunosuppression or graft versus host disease)
- symptomatic HIV infection or AIDS
- other significantly immunocompromising conditions

People currently or recently (up to 1 year in some cases) receiving immunosuppressive therapy

- chemotherapy or radiotherapy
- corticosteroids ( $\geq 20$  mg per day of prednisolone equivalent dose)
- most biologic disease-modifying anti-rheumatic drugs (DMARDs)

Use of Zostavax in people who are immunocompromised can result in disseminated disease from the Oka vaccine strain and has been associated with several deaths in Australia.

However, people aged  $\geq 50$  years with mild immunocompromise **may** receive Zostavax on a case-by-case basis, after careful assessment, when Shingrix is not available or affordable.

Immunisation providers must undertake careful pre-screening and a risk-based assessment before administering Zostavax to any person who is immunocompromised. This should include use of the [Live shingles vaccine \(Zostavax\) screening for contraindications](#) tool. Assess each person individually and, if uncertain, DO NOT administer Zostavax and seek appropriate specialist advice. It is important to monitor for a disseminated (non-localised) VZV-like rash as a potential adverse event after Zostavax administration in these people. Refer to the *Australian Immunisation Handbook* for more details.

People who are anticipated to become immunocompromised/immunosuppressed (e.g. because of an existing illness or future immunosuppressive therapy/immunotherapy) may also be considered for Zostavax at least 1 month before they become immunocompromised. If this is not possible, do not give the vaccine, and seek specialist advice.



## Serological testing in people with mild to moderate immunocompromise

In people with mild immunocompromise assessed as safe to receive Zostavax, such as those on low-dose immunosuppressive therapy, and eligible HIV patients, check for previous VZV infection using serological testing before vaccination. In someone with a mild level of immunocompromise, pre-existing immunity provides additional reassurance about the safe use of the vaccine. If a person who is immunocompromised is seronegative, that is, there is no evidence of previous VZV natural infection, they may have very severe outcomes after receiving Zostavax and so should not be vaccinated.<sup>26</sup>

Serological testing prior to administration of Shingrix is not necessary in people who are immunocompetent or immunocompromised.

Serological testing after administration of either zoster vaccine is not necessary or recommended.

## Use of zoster vaccines in other groups

### Women who are pregnant

Live-attenuated VZV-containing vaccines are contraindicated in pregnancy. However, having a non-immune pregnant household contact is *not* a contraindication to Zostavax or varicella vaccination. Women should avoid pregnancy for 28 days after vaccination with a live-attenuated VZV-containing vaccine.

There are currently no data on the use of Shingrix in pregnancy (Category B2).<sup>27</sup>

### Breastfeeding women

Breastfeeding women can receive Zostavax if they are eligible for vaccination.

There are currently no data on the use of Shingrix in breastfeeding women.<sup>27</sup>

### 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.<sup>16</sup>

In people who are seronegative, Zostavax is likely to be well tolerated and immunogenic, although the incidence of injection site reactions may be slightly higher.<sup>28</sup> It is *not* necessary to provide laboratory evidence of a history of chickenpox in **immunocompetent** people aged >50 years before administering Zostavax. For people with **mild immunocompromise**, pre-vaccination serological testing may have a role. Refer to the section [Use of Zostavax in people with immunocompromise](#) above.

### People with a history of shingles

People who have experienced a prior episode of shingles are at risk of recurrence (refer to [Epidemiology](#)). The safety and immunogenicity profile of both Shingrix and Zostavax in people with a documented history of shingles is similar to that in those with no known history of shingles.<sup>29-31</sup> Therefore, it is recommended that people with a clinical history of shingles can receive zoster vaccine.

The optimal time for administration of zoster vaccine following an episode of shingles is uncertain. It is suggested that zoster vaccine should be given at least 12 months after an episode of shingles.<sup>32</sup>

## People previously vaccinated with Zostavax

People who have previously received Zostavax can receive Shingrix if they wish to increase their protection against herpes zoster. Although evidence in this population is limited, a single study identified no safety concerns when Shingrix was administered to those who had received Zostavax a minimum of 5 years earlier, and the vaccine appears to be immunogenic in this population. In the absence of evidence to support a minimum interval, 12 months between receipt of Zostavax and receipt of Shingrix is currently recommended.

A trial in this population is ongoing to investigate this issue.<sup>33</sup>

There are currently no recommendations for the use of Zostavax booster doses in those who have previously received Zostavax or Shingrix.

## Contraindications and precautions

### Contraindications

Zostavax is **contraindicated** in people with current or recent significant immunosuppression. These people are recommended to receive Shingrix.

Zoster vaccines should not be administered to people with a history of anaphylaxis to any component of that individual vaccine. Zostavax should additionally not be administered to people who have had anaphylaxis following a previous dose of varicella vaccine.

Zostavax is contraindicated in pregnant women. There are currently no data on the use of Shingrix in pregnant women (Category B2).

### Precautions

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

Zoster vaccines are not indicated for therapeutic use during an acute shingles episode or for the treatment of PHN.

Zoster vaccines are *not* indicated to provide primary protection against varicella infection. 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).

Zostavax is not recommended in people who have previously received varicella vaccine at this time.

Use of Zostavax in people with mild to moderate immunocompromise may only be considered after careful case-by-case assessment (refer to the section [Use of Zostavax in people with immunocompromise](#)).

There are currently no data on the use of Shingrix in breastfeeding women. However, Zostavax is safe to give if the woman is eligible for the vaccine.

## Co-administration with COVID-19 vaccines

Avoid co-administration of zoster vaccines concomitantly with COVID-19 vaccines.

## Managing people who are immunocompromised and inadvertently receive Zostavax

In Australia, three people have died from disseminated infection with the Oka VZV vaccine strain following receipt of Zostavax. Two of these patients had severe immunocompromise (due to



chronic lymphocytic leukaemia<sup>26</sup> or prednisone/checkpoint inhibitor use) and one had a mild immunocompromise due to long-term hydroxychloroquine and low-dose prednisolone use (5 mg per day<sup>34</sup>), but was not contraindicated to vaccination.

It is important for Zostavax recipients to monitor for a disseminated (non-localised) VZV-like rash as a potential adverse event after vaccination. If present, consideration should be given to possible disseminated VZV infection.

If a person with immunocompromise is inadvertently vaccinated with Zostavax, the immunisation provider should:

- promptly assess them
- discuss their appropriate management with an infectious diseases and/or immunisation expert
- notify the relevant state or territory health authority, and the Therapeutic Goods Administration (TGA).

Patient management may include (depending on the degree of a person's immunocompromise and risk of vaccine-associated adverse effects):

- pre-emptive or therapeutic use of antiviral medication as soon as possible after inadvertent administration of Zostavax
- clinical investigations, such as laboratory testing for VZV from any rash or other affected sites, to determine if infection is due to the Oka vaccine strain or due to wild-type virus
- cessation of immunosuppressant therapy, if appropriate, in consultation with the patient's treating specialist.

The TGA and the Australian Technical Advisory Group on Immunisation (ATAGI) continue to monitor global evidence on the safety of Zostavax.

## Vaccines

### Zostavax

Zostavax (Seqirus/Merck Sharp & Dohme) is a live-attenuated viral vaccine using the VZV vaccine strain (Oka-derived), similar to varicella vaccines but about 14x higher dose. This higher viral potency is needed to get a satisfactory boost in the immune response in older adults.<sup>35</sup> (See also [Vaccine efficacy](#).) Zostavax is registered for use in people aged ≥50 years in Australia.

### Administration

Zostavax is given as a single 0.65 mL dose by subcutaneous injection.

### Vaccine efficacy

In the Shingles Prevention Study (SPS), 38,546 immunocompetent adults aged ≥60 years received either Zostavax or a placebo.<sup>36</sup>

In this study, Zostavax was efficacious against incidence of shingles and PHN.<sup>36</sup> Overall, efficacy against shingles was 51.3% and against PHN was 66.5% over a median of 3.1 years of follow-up.<sup>36</sup>

In a separate study in adults aged 50–59 years, Zostavax vaccine efficacy (VE) against shingles was higher (69.8%).<sup>37</sup>

In the SPS, Zostavax was more efficacious in reducing the incidence of shingles in people aged 60–69 years than in those aged >70 years. However, efficacy in reducing the incidence of PHN and the burden of illness of shingles (a composite measure used in the clinical trial to describe the total pain, severity and duration of shingles) was similar across both age groups.<sup>36</sup> In people

aged >80 years, VE was lower and not statistically significant, but the number of participants in this age group was low in this study.<sup>12</sup>

## 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 was followed up for up to 11 years, suggested significant waning of Zostavax VE with time.<sup>38,39</sup>

In the STPS (4–7 years after vaccination), VE had reduced to 39.6% against shingles and 60.1% against PHN.<sup>38</sup> In the LTPS (7–11 years after vaccination), VE was 21.1% against shingles and 35.4% against PHN. However, these LTPS data were not as robust as they were compared with ‘modelled’ control estimates.<sup>39</sup> Currently, revaccination with Zostavax is not recommended.

In several large population-based post-licensure studies in the United States of America (USA), early estimates of the effectiveness of Zostavax against shingles and PHN in people aged ≥60 years were, in general, comparable with those from the SPS. A recent population-based cohort study in the USA showed that in people aged ≥60 years, Zostavax VE 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.<sup>40</sup>

## Vaccine safety

Based on clinical trials, Zostavax is safe and well tolerated among adults aged ≥50 years.<sup>36,41–43</sup> 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.<sup>36</sup> The incidence of serious adverse events after vaccination was very low and did not differ between vaccine and placebo recipients.

Zostavax recipients rarely developed varicella-like rashes around the injection site (0.1% of recipients in clinical trials). Generalised varicella-like rashes were similar between Zostavax 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, indicating coincidental natural shingles, with only very few participants found to have rashes due to the Oka/Merck VZV vaccine strain.<sup>44</sup>

The rate of systemic symptoms was somewhat higher in Zostavax recipients than in placebo recipients (6.3% versus 4.9%), with the most frequently reported systemic symptoms being headache and fatigue. Fever >38.3°C after Zostavax occurred in <0.1% of subjects overall, no different from placebo.<sup>36,37</sup>

The safety profile of Zostavax 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.<sup>42,43</sup>

Very rarely, a non-localised VZV-like rash occurs around 2–4 weeks after receipt of Zostavax. This type of rash may be due to the Oka vaccine strain. In vaccine recipients who are immunocompromised, this may indicate disseminated infection. Management of these patients should be as detailed in the section [Managing people who are immunocompromised and inadvertently receive Zoster vaccine](#).

## Concomitant administration

Zostavax can be given at the same visit as inactivated influenza vaccine (at separate sites and using separate syringes) with no effect on safety or efficacy of either vaccine.<sup>45</sup>

Zostavax can also be given at the same time as 23-valent pneumococcal polysaccharide vaccine (23vPPV)<sup>46</sup> or 13-valent pneumococcal conjugate vaccine, using separate syringes and injection

sites. Although in one clinical trial antibody responses for Zostavax were lower when it was co-administered with 23vPPV,<sup>47</sup> VZV antibody levels have not been shown to directly correlate with clinical protection.<sup>48</sup>

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

However, currently it is recommended to separate Zostavax from a COVID-19 vaccine by a minimum interval of 7 days. Please refer to the [ATAGI clinical guidance on COVID-19 vaccine in Australia](#) for the most up-to-date information regarding COVID-19 vaccines.

As with other live viral vaccines, if Zostavax is to be given around the same time as another live viral parenteral vaccine (e.g. measles-mumps-rubella, yellow fever), the vaccines should be given either at the same visit or at least 4 weeks apart.<sup>12,32</sup>

## Shingrix

Shingrix (GlaxoSmithKline) is an adjuvanted recombinant varicella zoster virus glycoprotein E (gE) subunit vaccine, available in Australia from June 2021.<sup>27</sup> It is registered for use in people aged ≥50 years. This vaccine does not contain live virus and can be administered to both people who are immunocompetent and immunocompromised in the eligible age groups.

Shingrix will be available in limited quantities through private prescription only in Australia.

For more information regarding Shingrix vaccine please refer to [Shingrix Product Information TGA](#).

### Administration

Shingrix requires two doses administered intramuscularly, with an interval of 2–6 months between doses.

### Vaccine efficacy

Shingrix is highly efficacious in preventing herpes zoster episodes. In two large clinical trials Shingrix provided 97% protection against herpes zoster among immunocompetent adults aged ≥50 years and 91% protection in immunocompetent adults aged ≥70 years.<sup>49,50</sup> Protection against PHN was also high (about 89–91%).

There has been no head-to-head comparison to date of Shingrix and Zostavax efficacy. Indirect evidence, in the form of a network meta-analysis, suggests Shingrix is probably more effective than Zostavax in protecting against herpes zoster, but the evidence for the relative efficacy against other complications of zoster remains uncertain.<sup>25</sup>

Evidence for VE against herpes zoster and associated complications in people who are immunocompromised is more limited than in those who are immunocompetent. Shingrix has been shown to provide good protection against herpes zoster, post-herpetic neuralgia and HZ-related hospitalisation in a highly immunocompromised post-haematopoietic stem cell transplant (HSCT) population.<sup>51</sup> Shingrix VE against herpes zoster in a population of haematological malignancy patients was also high, at 87%.<sup>52</sup>

Shingrix has shown a robust immune response (based on immunogenicity data) in a broader range of people with immunocompromise aged ≥18 years (including patients with HSCT, haematological malignancy, HIV, solid tumour receiving chemotherapy and post renal transplant).<sup>51-56</sup> This suggests the vaccine is likely to be effective in the immunocompromised population more generally.

## Duration of protection

Shingrix has shown high rates of protection against herpes zoster up to 4 years post vaccination in people who are immunocompetent, with minimal waning over that time (efficacy remained >80%).<sup>49,50</sup> Although there are no clinical follow-up data beyond 4 years post vaccination, immunogenicity data demonstrate a persistent immune response to at least 10 years post vaccination.<sup>57</sup> The waning of protection from Shingrix appears slower than that from Zostavax.

Evidence for the duration of protection against herpes zoster in people who are immunocompromised is more limited. A single randomised controlled trial in post-HSCT recipients indicated significant protection was maintained to 2 year post vaccination;<sup>51</sup> however, no data beyond this follow-up point are currently available.

## Vaccine safety

Shingrix causes moderately high rates of local and systemic reactions, and non-serious adverse events. Common reactions include injection site pain (up to 79%), redness (up to 39%) and swelling (up to 26%). Systemic symptoms include fatigue and myalgia (up to 46%), headache (up to 39%), shivering (up to 28%), fever (up to 22%) and gastrointestinal symptoms (up to 18%).<sup>49,50</sup> Shingrix appears to be associated with higher rates of non-serious reactogenicity than Zostavax;<sup>25</sup> however, the two vaccines have not been compared head-to-head.

In a small proportion of people (about 10%), reactions may be severe enough to disrupt normal functioning, but these generally resolve within an average of 1–3 days.

Shingrix has demonstrated safety in clinical trials, with rates of serious adverse events in the Shingrix arm no different from those in the placebo arm in clinical trials.<sup>49,50</sup>

Immunisation providers should counsel recipients regarding expected local and systemic reactions before vaccination and the importance of completing the two-dose schedule for an adequate level and duration of protection.

Preliminary US data suggest a very rare association between cases of Guillain Barre Syndrome (GBS), a demyelinating neurological condition, and Shingrix (an estimated 3–6 additional cases per million doses administered).<sup>58</sup> However, GBS may also be triggered by an episode of zoster itself<sup>59</sup> and the overall benefits of vaccination currently outweigh the risks<sup>60</sup> of GBS.

## Concomitant administration with other vaccines

Shingrix may be administered concomitantly, in different injection sites, with most other vaccines.

Trials of concomitant administration of Shingrix with other vaccines (quadrivalent influenza vaccine, Pneumovax and Boostrix) suggest no safety concerns or interference with vaccine immune response.<sup>61-63</sup>

Safety and efficacy of concomitant administration of Shingrix with the adjuvanted influenza vaccine (Fluad Quad) and COVID-19 vaccines has not yet been evaluated.

A minimum 7-day interval between Shingrix and COVID-19 vaccines is currently recommended. However co-administration is considered acceptable in some situations. Please refer to the [ATAGI clinical guidance on COVID-19 vaccine in Australia](#) for the most up-to-date information regarding co-administration of vaccines with COVID-19 vaccines.

It is acceptable to co-administer Shingrix and Fluad Quad on the same day if necessary. However, given the lack of co-administration data for these two adjuvanted vaccines, it is preferred to separate their administration by a few days, and ensure that any adverse events following immunisation with the first vaccine have resolved before administration of the other vaccine.

## Additional resources for primary medical care/vaccination providers

- [The Australian Immunisation Handbook](#)
- [Therapeutic Goods Administration Product Information: Shingrix](#)
- [Immunise Australia](#)
- [NCIRS Zoster vaccine FAQ fact sheet](#)
- For information regarding the Varicella-zoster (chickenpox) vaccine refer to [The Australian Immunisation Handbook](#) and NCIRS fact sheet [Varicella-zoster \(chickenpox\) vaccines for Australian children](#)

## References

1. Cunningham AL, Breuer J, Dwyer DE, et al. The prevention and management of herpes zoster. Medical Journal of Australia 2008;188:171-6.
2. Johnson RW, Rice AS. Clinical practice: Postherpetic neuralgia. New England Journal of Medicine 2014;371:1526-33.
3. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clinical Journal of Pain 2002;18:350-4.
4. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clinic Proceedings 2007;82:1341-9.
5. Gauthier A, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiology and Infection 2009;137:38-47.
6. MacIntyre R, Stein A, Harrison C, et al. Increasing trends of herpes zoster in Australia. PLoS One 2015;10:e0125025.
7. Stein AN, Britt H, Harrison C, et al. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. Vaccine 2009;27:520-9.
8. Arvin AM. Varicella-zoster virus. Clinical Microbiology Reviews 1996;9:361-81.
9. Cohen JL. Herpes zoster. New England Journal of Medicine 2013;369:255-63.
10. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clinical Infectious Diseases 2007;44 Suppl 1:S1-26.
11. Chen N, Li Q, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database of Systematic Reviews 2014;(2):CD006866. doi:10.1002/14651858.CD006866.pub3.
12. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. Recommendations and Reports 2008;57(RR-5):1-30.
13. Sengupta N, Breuer J. A global perspective of the epidemiology and burden of varicella-zoster virus. Current Pediatric Reviews 2009;5:207-28.
14. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA 2004;292:704-8.



15. Ward K, Dey A, Hull B, et al. Evaluation of Australia's varicella vaccination program for children and adolescents. *Vaccine* 2013;31:1413-9.
16. Gidding HF, MacIntyre CR, Burgess MA, Gilbert GL. The seroepidemiology and transmission dynamics of varicella in Australia. *Epidemiology and Infection* 2003;131:1085-9.
17. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiology and Infection* 2001;127:305-14.
18. Nelson MR, Britt HC, Harrison CM. Evidence of increasing frequency of herpes zoster management in Australian general practice since the introduction of a varicella vaccine. *Medical Journal of Australia* 2010;193:110-3.
19. Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. *Neurology* 1980;30:582-7.
20. Weinberg A, Lazar AA, Zerbe GO, et al. Influence of age and nature of primary infection on varicella-zoster virus-specific cell-mediated immune responses. *Journal of Infectious Diseases* 2010;201:1024-30.
21. Liu B, Heywood AE, Reekie J, et al. Risk factors for herpes zoster in a large cohort of unvaccinated older adults: a prospective cohort study. *Epidemiology and Infection* 2015;143:2871-81.
22. Qian J, Heywood AE, Karki S, et al. Risk of Herpes Zoster Prior to and Following Cancer Diagnosis and Treatment: A Population-Based Prospective Cohort Study. *Journal of Infectious Diseases* 2019;220:3-11.
23. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster: population based case-control study. *BMJ* 2014;348:g2911.
24. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. *Mayo Clinic Proceedings* 2011;86:88-93.
25. Tricco AC, Zarin W, Cardoso R, et al. Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older: systematic review and network meta-analysis. *BMJ* 2018;363:k4029.
26. Alexander KE, Tong PL, Macartney K, et al. Live zoster vaccination in an immunocompromised patient leading to death secondary to disseminated varicella zoster virus infection. *Vaccine* 2018;36:3890-3.
27. Australian Government Department of Health, Therapeutic Good Administration (TGA). Shingrix Product Information. Canberra: TGA; 2021. (Accessed 18 June 2021). <https://www.tga.gov.au/sites/default/files/auspar-recombinant-varicella-zoster-virus-glycoprotein-e-antigen-181212-pi.pdf>
28. Macaladad N, Marcano T, Guzman M, et al. Safety and immunogenicity of a zoster vaccine in varicella-zoster virus seronegative and low-seropositive healthy adults. *Vaccine* 2007;25:2139-44.
29. Mills R, Tyring SK, Levin MJ, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine* 2010;28:4204-9.
30. Morrison VA, Oxman MN, Levin MJ, et al. Safety of zoster vaccine in elderly adults following documented herpes zoster. *Journal of Infectious Diseases* 2013;208:559-63.
31. Godeaux O, Kovac M, Shu D, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults  $\geq 50$  years of age with a prior history of herpes



zoster: A phase III, non-randomized, open-label clinical trial. Human vaccines & immunotherapeutics 2017;13:1051-8.

32. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian immunisation handbook. 10th ed (2017 update) ed. Canberra: Australian Government Department of Health; 2017.
33. National Library of Medicine (US). A study to evaluate the safety and immunogenicity of GlaxoSmithKline's herpes zoster subunit vaccine (HZ/su) when given on a two-dose schedule to adults at least 50 years of age (YOA) who had prior episode of shingles. National Library of Medicine (US); 2019. (Accessed 18 June 2021).  
<https://clinicaltrials.gov/ct2/show/NCT04091451>
34. Therapeutic Good Administration (TGA). Zostavax vaccine: Safety advisory - not to be used in people with compromised immune function. Australian Government Department of Health; 2021. (Accessed 18 June 2021). <https://www.tga.gov.au/alert/zostavax-vaccine-0>
35. Oxman MN. Vaccination to prevent herpes zoster and postherpetic neuralgia. Human Vaccines 2007;3:64-8.
36. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. New England Journal of Medicine 2005;352:2271-84.
37. Schmader KE, Levin MJ, Gnann JW, Jr., et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50–59 years. Clinical Infectious Diseases 2012;54:922-8.
38. Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the efficacy of zoster vaccine in the Shingles Prevention Study and the Short-Term Persistence Substudy. Clinical Infectious Diseases 2012;55:1320-8.
39. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. Clinical Infectious Diseases 2015;60:900-9.
40. Tseng HF, Harpaz R, Luo Y, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. Journal of Infectious Diseases 2016;213:1872-5.
41. Tyring SK, Diaz-Mitoma F, Padgett LG, et al. Safety and tolerability of a high-potency zoster vaccine in adults ≥50 years of age. Vaccine 2007;25:1877-83.
42. Baxter R, Tran TN, Hansen J, et al. Safety of Zostavax™—a cohort study in a managed care organization. Vaccine 2012;30:6636-41.
43. Tseng HF, Liu A, Sy L, et al. Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. Journal of Internal Medicine 2012;271:510-20.
44. Merck, Sharpe and Dohme (Australia) Pty Limited,. Product information: ZOSTAVAX® Zoster virus vaccine live (Oka/Merck), refrigerator stable. 2016. (Accessed October 2016).  
<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=Zostavax>
45. Kerzner B, Murray AV, Cheng E, et al. Safety and immunogenicity profile of the concomitant administration of ZOSTAVAX and inactivated influenza vaccine in adults aged 50 and older. Journal of the American Geriatric Society 2007;55:1499-507.
46. Tseng HF, Smith N, Sy LS, Jacobsen SJ. Evaluation of the incidence of herpes zoster after concomitant administration of zoster vaccine and polysaccharide pneumococcal vaccine. Vaccine 2011;29:3628-32.
47. MacIntyre CR, Egerton T, McCaughey M, et al. Concomitant administration of zoster and pneumococcal vaccines in adults ≥60 years old. Human Vaccines 2010;6:894-902.

48. Oxman MN, Gershon AA, Poland GA. Zoster vaccine recommendations: the importance of using a clinically valid correlate of protection. *Vaccine* 2011;29:3625-7.
49. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *New England Journal of Medicine* 2016;375:1019-32.
50. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *New England Journal of Medicine* 2015;372:2087-96.
51. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA* 2019;322:123-33.
52. Dagnew AF, Ilhan O, Lee WS, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infectious Diseases* 2019;19:988-1000.
53. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, et al. Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial. *Clinical Infectious Diseases* 2020;70:181-90.
54. Vink P, Delgado Mingorance I, Maximiano Alonso C, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: A randomized trial. *Cancer* 2019;125:1301-12.
55. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. *Blood* 2014;124:2921-9.
56. Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. *Journal of Infectious Diseases* 2015;211:1279-87.
57. Hastie A, Catteau G, Enemu A, et al. Immunogenicity of the adjuvanted recombinant zoster vaccine: persistence and anamnestic response to additional doses administered 10 years after primary vaccination. *Journal of Infectious Diseases* 2020.
58. US Food and Drug Administration. Risk of Guillain-Barré syndrome (GBS) following recombinant zoster vaccine (RZV). FDA; 2021. (Accessed 18 June 2021).  
<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/24-25/02-Zoster-Vaccines-Forshee.pdf>.
59. Kang JH, Sheu JJ, Lin HC. Increased risk of Guillain-Barré Syndrome following recent herpes zoster: a population-based study across Taiwan. *Clinical Infectious Diseases* 2010;51:525-30.
60. Centers for Disease Control and Prevention (CDC). Projected risks and health benefits of vaccination against herpes zoster and related complications: interim results. Washington, DC: CDC; (Accessed 18 June 2021).  
<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/24-25/03-Zoster-Vaccines-Prosser.pdf>
61. Schwarz TF, Aggarwal N, Moeckesch B, et al. Immunogenicity and Safety of an Adjuvanted Herpes Zoster Subunit Vaccine Coadministered With Seasonal Influenza Vaccine in Adults Aged 50 Years or Older. *Journal of Infectious Diseases* 2017;216:1352-61.

62. Maréchal C, Lal H, Poder A, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine co-administered with the 23-valent pneumococcal polysaccharide vaccine in adults  $\geq 50$  years of age: A randomized trial. *Vaccine* 2018;36:4278-86.
63. Strezova A, Lal H, Enweonye I, et al. The adjuvanted recombinant zoster vaccine co-administered with a tetanus, diphtheria and pertussis vaccine in adults aged  $\geq 50$  years: A randomized trial. *Vaccine* 2019;37:5877-85.