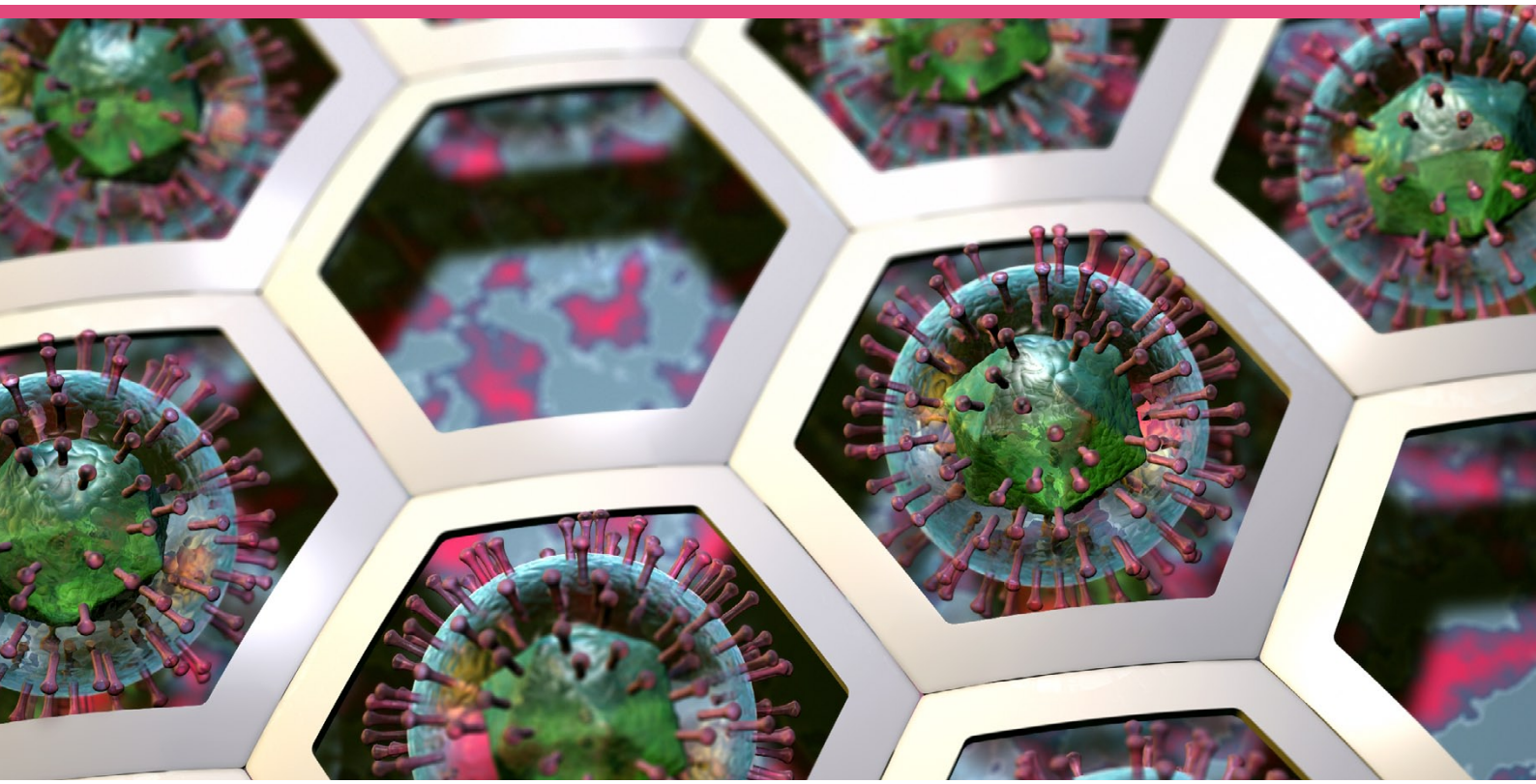


Zostavax vaccine: now fully subsidised

Zostavax is a herpes zoster (shingles) vaccine that will become fully subsidised from 1 April, 2018 for people aged 65 years. For a period of two years, people aged 66 to 80 years can also receive a fully funded catch-up vaccination.

Herpes zoster is a reactivation of varicella zoster virus

Herpes zoster (shingles) typically presents as a painful unilateral vesicular rash in the dermatomal distribution of the affected nerve.[1] It is caused by a reactivation of the varicella zoster virus (chicken pox), which remains latent in neural ganglia for many years after primary infection, until cell-mediated immunity to varicella zoster virus wanes with age or is otherwise compromised.[1]

Older people are most likely to develop herpes zoster

Approximately one-third of people will develop shingles in their lifetime; 50% of people will develop shingles if they reach age 85 years.[2] National incidence data is not available for New Zealand, but several regional studies have been conducted. An analysis of consultations over an 11 year period in 39 general practices in the lower North Island reported an overall incidence rate of 48.6 cases of herpes zoster per 10,000 patient-years*.[3] The age-adjusted incidence rate for Māori was 38.9 per 10,000 patient-years and 29.1 per 10,000 patient-years for Pacific peoples;[3] this may indicate a lower incidence rate in these ethnic groups, but it may also reflect a lower rate of presentation to general practice. The highest incidence rate was in the 80–84 years age group, which is an older age group than many studies have previously reported.[2, 3] Females were more likely than males to present to general practice with herpes zoster (32% higher incidence rate).[3]

Immunocompromised people, including those undergoing immunosuppressive treatment, are at higher risk of developing herpes zoster.[1] Other risk factors for herpes zoster include rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, sleep disorders and type 1 and 2 diabetes.[1,2] N.B. Herpes zoster vaccination is contraindicated in people who are significantly immunocompromised (see below).

* A patient-year is a standardised way of reporting incidence when the observation period differs between study groups. For example, if a data set included 100 patients over a period of 10 years, this would be 1000 patient-years. If another data set included 70 patients over 8 years, this would be 560 patient years. The incidence rate of the outcome in the second data set could be adjusted to a rate per 10,000 patient-years, if the data-sets were combined.

Summary: How to vaccinate with Zostavax

Indications:

- Prevention of herpes zoster (shingles), post-herpetic neuralgia and reduction of acute and chronic zoster-associated pain in older adults
- Subsidised from 1 April, 2018 for adults aged 65 years, with a two year catch-up period for those aged 66 to 80 years (until 31 March, 2020)
- Vaccination is appropriate regardless of varicella zoster (chickenpox) or herpes zoster history; consider delaying vaccination by at least one year if recent episode of herpes zoster

Contraindications:

- Children, pregnancy
- Severe allergy or anaphylaxis to any component of the vaccine
- Significant immunosupression: people undergoing immunosuppressive treatment, people with primary and acquired immunodeficiency such as leukaemia, lymphoma, other conditions affecting the bone marrow or lymphatic system, AIDS and cellular immune deficiencies
- Active untreated tuberculosis

Administration:

- Store Zostavax between 2°C and 8°C
- Reconstitute Zostavax with the diluent provided and use within 30 minutes, preferably immediately
- Administer reconstituted Zostavax as a single 0.65 mL dose subcutaneously into the region over the deltoid
- Do not inject intramuscularly or intravenously

Concurrent vaccinations and treatments:

- Zostavax can be administered concurrently with other vaccines, including seasonal influenza, tetanus/diphtheria and Pneumovax23†
- Due to the potential for reduced efficacy, if vaccinating with another live vaccine, administer at the same visit or at least four weeks apart; this is, however, an unlikely scenario as other live vaccines in New Zealand are Measles, Mumps and Rubella [MMR], rotavirus and varicella
- Antiviral medicine for herpes labialis (cold sores) should be ceased from at least 24 hours prior to Zostavax administration until 14 days post-vaccination

† The Zostavax datasheet states that concurrent vaccination with Pneumovax23 reduces Zostavax efficacy, but due to a lack of evidence for this the Ministry of Health recommends that the vaccines may be given at the same visit[1]

Common responses to vaccination:

- Injection site reactions, such as pain, erythema, swelling, pruritus, or rash
- Headache

Current zoster virus infection or exposure:

- Do not use Zostavax for treating a current herpes zoster (or varicella) infection
- Immunoglobulin is available for groups at high risk of severe infection who have no antibodies to varicella zoster virus, for prevention of infection after significant exposure to herpes zoster (or varicella)

Valaciclovir is the recommended treatment for herpes zoster

Antiviral medicines given within 72 hours of rash onset may reduce the severity and duration of the pain and rash, but are unlikely to prevent post-herpetic neuralgia (see below).[4] The recommended first-line antiviral treatment is valaciclovir 1 g, three times daily, for seven days.[5]

Post-herpetic neuralgia is a common complication of herpes zoster

While herpes zoster is self-limiting, the most common complication occurring in up to 30% of affected people is post-herpetic neuralgia.[1] Like herpes zoster, the risk and severity of post-herpetic neuralgia increases with age. It is usually experienced as a burning or shooting pain, itch, numbness, tingling, or hypersensitivity to touch or temperature. Post-herpetic neuralgia can persist for months to years.[1, 2]

In approximately 10% of patients with shingles, the ophthalmic branch of the trigeminal nerve is affected, and if the eye becomes involved, permanent visual loss can occur.[1]

For further information, see "The diagnosis and management of herpes zoster and its complications". Available from: **www.bpac.org.nz/bpj/2014/march/herpes.aspx**

Zostavax fully subsidised for people aged 65 years

The herpes zoster vaccine Zostavax will be fully subsidised for people aged 65 years*, from 1 April, 2018.[6]

A catch-up immunisation programme will be available for two years from 1 April, 2018 to 31 March, 2020, during which time people aged 66 to 80 years will be eligible to receive one fully subsidised dose of Zostavax.[6]

Funded Zostavax vaccinations will initially only be available at general practices.[6]

* The vaccine is subsidised for people turning 65 years, i.e. from the date of their birthday. People who are already aged 65 years as of 1 April, 2018 are also eligible for a subsidised Zostavax vaccination as part of the catch-up programme.

Vaccination may be considered for people aged under 65 years

Zostavax is currently approved for adults aged 50 years and older.[5] Although not subsidised, some patients aged under 65 years may consider vaccination, particularly if they are at increased risk of shingles, e.g. with co-morbidities such as diabetes, chronic kidney disease or autoimmune disease.[1] However, the effectiveness of Zostavax decreases over time and early vaccination may mean that protection is lost in older age, when there is a higher risk of developing shingles and its complications.[7]

There is no clinical reason not to vaccinate people aged under 50 years, except that the original studies on Zostavax did not include younger age groups and herpes zoster is less common in younger people. If considering vaccination in high risk people aged under 50 years, the non-approved status of the vaccine for this age group should be discussed and informed consent gained.

Consider delaying vaccination if herpes zoster has recently occurred

An episode of herpes zoster boosts immunity and therefore reduces the likelihood of it reoccurring in the short-term. Therefore, patients who have recently had herpes zoster may wish to wait at least one year before vaccination, in order to increase the overall number of years they are protected.[1,8]

Booster doses of Zostavax are not currently recommended

Booster doses of Zostavax are not currently recommended as no studies reporting efficacy for the prevention of herpes zoster have been performed.[1] However, adults who are eligible to receive a funded dose of Zostavax, may still receive this if they have previously purchased Zostavax.[8] It is recommended to allow at least one year between doses.[8]

Varicella vaccines do not prevent herpes zoster

Zostavax is a live attenuated vaccine containing the Oka strain of varicella zoster virus.[1] Varilrix and other varicella vaccines are also live attenuated Oka strain vaccines, but do not protect against herpes zoster due to their lower strength.[1]

A history of varicella is not a pre-requisite for herpes zoster vaccination

It is not necessary to confirm if the patient has had varicella, prior to considering a herpes zoster vaccination. Almost every adult will have been exposed to varicella infection at some point in their life, even if they have no history of clinical infection.

Serology to check varicella immunity is not required except for in adults with asymptomatic HIV infection who have a CD4+ lymphocyte count ≥ 200 cells/mm^3, and in adults who will be significantly immunocompromised in the near future, e.g. about to commence immunosuppressive treatment.[1] The reason for checking serology in these patients groups is to confirm whether varicella or herpes zoster vaccination is most appropriate.

Zostavax: efficacy, duration and safety

Zostavax halves the risk of herpes zoster

Zostavax approximately halves the incidence of herpes zoster (51% relative reduction in risk) and reduces the incidence of post-herpetic neuralgia by two-thirds (67% relative reduction in risk) in adults aged 60 years and over.[9] As shown in Table 1, Zostavax efficacy differs by age group; efficacy declines with increasing age and it is not significantly effective for the prevention of herpes zoster in people aged 80 years and older.[9–13]

Zostavax efficacy decreases over time

Long-term follow-up studies have demonstrated that the efficacy of Zostavax for the prevention of herpes zoster and post-herpetic neuralgia decreases over time.[11,12] In analyses by year since vaccination, Zostavax significantly reduces the risk of herpes zoster for up to eight years.[1,12]

Evidence for Zostavax was generated in large randomised controlled trials

In the Shingles Prevention Study, more than 38,500 adults aged 60 years and over were randomised to receive either Zostavax or placebo and followed up for 3.12 years.[9] A second randomised controlled trial investigated the efficacy of Zostavax in more than 22,000 adults aged 50 to 59 years over 1.3 years follow-up.[10] Long-term follow-up studies of the original Shingles Prevention Study cohort were conducted at 3.3 to 7.8 years post-vaccination or post-placebo (14,000 participants) and at 4.7 to 11.6 years post-vaccination (7000 participants).[11,12]

Table 1. Zostavax efficacy by age group and time since vaccination.[9–13]

	Vaccine efficacy* (95% confidence intervals)		
	Herpes zoster	**Post-herpetic neuralgia†**	**Burden of illness‡**
Age group			
50 to 59 years	70% (54 to 81)	No data	73% (53 to 85)
60 to 69 years	64% (56 to 71)	66% (20 to 87)	66% (52 to 76)
70 to 79 years	41% (28 to 52)	No data	No data
≥ 70 years	38% (28 to 52)	67% (43 to 81)	55% (40 to 67)
≥ 80 years§	18% (–29 to 48)	No data	No data
Time since vaccination			
0.0 to 3.1 years	51% (44 to 58)	67% (48 to 79)	61% (51 to 69)
3.3 to 7.8 years	40% (18 to 56)	60% (–10 to 87)	50% (14 to 71)
4.7 to 11.6 years	21% (11 to 30)	35% (9 to 56)	37% (27 to 46)

* Vaccine efficacy is the percentage reduction of disease in a vaccinated group of people compared to an unvaccinated group
† Vaccine efficacy for the prevention of post-herpetic neuralgia across all study participants, not specifically among those who developed herpes zoster
‡ Burden of illness is a composite measure of herpes zoster incidence, and severity and duration of acute herpes zoster pain
§ Estimates of vaccine efficacy vary in this age group, for further details see: "Evidence for Zostavax was generated in large randomised controlled trials".

A more recently published study reports different rates for vaccine efficacy than the Shingles Prevention Study.[19] Of particular note is a higher, and significant, rate of efficacy for preventing herpes zoster in people aged over 80 years of 42%. However, this study was an observational cohort study which means that the results are more likely to be affected by confounding than a randomised controlled study. What it does show is that vaccine efficacy data can be variable and should not be the only factor used to determine whether or not a vaccine is useful for a particular patient group.

Adverse effects of Zostavax are typically limited to local injection site reactions

In clinical trials, 48% to 64% of participants experienced a local injection site reaction following Zostavax administration compared with approximately 15% of those who received a placebo vaccination.[9, 10] The most frequent injection site reactions following Zostavax administration were erythema (36%), pain or tenderness (35%), swelling (26%) and pruritus (7%), and the most commonly reported systemic adverse event was headache, occurring in 9% of the vaccine group and in 8% of controls.[9, 10] The overall risk of serious adverse events was similar between Zostavax and placebo groups.[9, 10]

In post-licensure studies, Zostavax has been found to be safe and well-tolerated, with no increased risk of cerebrovascular events, cardiovascular events, meningitis, encephalitis, encephalopathy, Ramsay Hunt syndrome or Bell's palsy.[1, 14]

Zostavax is contraindicated in people who are significantly immunocompromised

Zostavax is a live attenuated vaccine and can cause disseminated infection in immunosuppressed people. It is contraindicated in people with current or recent severe immunocompromise due to:[1]

- Immunosuppressive therapy
- Primary and acquired immunodeficiency states, such as leukaemia, lymphoma, other conditions affecting the bone marrow or lymphatic system, immunosuppression due to AIDS, and cellular immune deficiencies. For patients with HIV infection, check with their treating physician.

Zostavax is **not** contraindicated in people who use only topical/inhaled corticosteroids, low-dose systemic corticosteroids, corticosteroids as a replacement therapy (e.g., adrenal insufficiency) or low-dose weekly methotrexate or azathioprine.[15]

For detailed information on the use of Zostavax in patients taking immunosuppressive treatment, see: **www.health.govt.nz/publication/immunisation-handbook-2017**

Further discussion on Zostavax in people taking immunosuppressive treatment

As Zostavax is a live vaccine, it is generally contraindicated in people taking immunosuppressive treatment. However, there are some exceptions to this for patients considered to be only mildly immunosuppressed.

The Ministry of Health Immunisation Handbook has further details on this, which can be found in Sections 4.3.3 and 22.6.2: **www.health.govt.nz/publication/immunisation-handbook-2017**

The Handbook states that:

> "As a general guide, low-level immunosuppression includes treatment with prednisone <2 mg/kg with a maximum of 20 mg/day; methotrexate ≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day. High-level immunosuppression regimens include treatment regimens with higher than the above doses, and those on biological agents such as tumour necrosis factor antagonists or rituximab. Combination therapies increase the level of immunosuppression."

Therefore, Zostavax is considered safe to administer in patients taking < 20 mg/day prednisone. However, some rheumatologists would recommend a lower threshold for safe administration of Zostavax vaccination, e.g. < 10 mg/day prednisone. A pragmatic solution is to routinely offer Zostavax vaccine to patients taking < 10 mg/day prednisone, and for patients taking 10 – 20 mg/day prednisone, consider their specific clinical scenario before deciding to vaccinate, e.g. duration of prednisone treatment, co-morbidities.

Patients taking a methotrexate dose of ≤ 0.4 mg/kg/week can safely receive Zostavax. Therefore, this would encompass most adults taking a standard once-weekly dose of <15–20 mg methotrexate.

Patients taking combination treatment, e.g. methotrexate with leflunomide, should not receive Zostavax vaccine as taking two treatments at once increases the level of immunosuppression.

Patients taking other DMARDS* and biologic medicines, such as the "mab" medicines, tacrolimus and cyclosporin, will not be able to receive a Zostavax vaccine until at least three to 12 months after treatment has stopped – in some cases immunisation with a live vaccine is absolutely contraindicated (discuss with the patient's rheumatologist or other treating clinician).

Sulfasalazine, hydroxychloroquine and sodium aurothiomalate (gold injection) are not considered to be significantly immunosuppressive, so patients taking these treatments at any dose may still receive Zostavax vaccine, unless they are taking it in combination with another immunosuppressive medicine.

Patients should not receive Zostavax vaccine within four weeks of the start of planned chemotherapy or radiotherapy and for at least three to six months after treatment has finished. Patients who have undergone stem cell or bone marrow transplant should not receive Zostavax until at least two years after treatment.

Zostavax may be a new vaccine for many patients

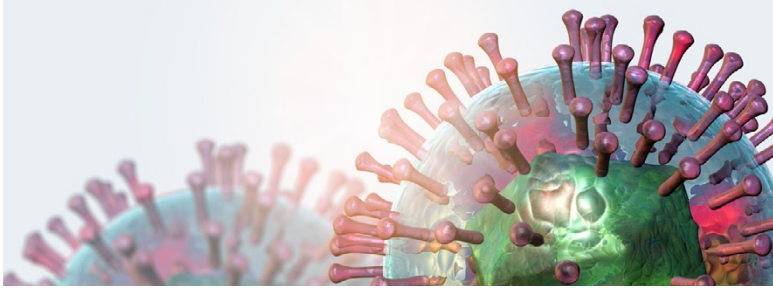
Zostavax has been available to purchase from general practices and some pharmacies in New Zealand since 2014. However, for many patients, it will be new vaccine for a condition that they may not be familiar with. Prior to administering the vaccine, patients are likely to require time to discuss herpes zoster, including its incidence, symptoms and potential complications, and Zostavax, including its efficacy and safety. Patients can then make an informed decision as to whether they would like to proceed with vaccination.

While it is considered clinically safe to administer seasonal influenza vaccination at the same time as Zostavax, for some patients there may be insufficient time to address questions about both vaccinations, and therefore vaccinations may have to be done on two separate occasions.

For further reading, see: Immunisation Advisory Centre. Zostavax. Available from: **www.immune.org.nz/vaccines/available-vaccines/zostavax**

Another shingles vaccine on the horizon

Shingrix is a newly developed shingles vaccine recently registered for use in the USA. It is a subunit vaccine, meaning that it does not contain live virus particles.[16, 17] Trials have demonstrated a high efficacy of Shingrix for the prevention of herpes zoster (90%) and post-herpetic neuralgia (89%).[17, 18] As Shingrix is unlikely to be available in New Zealand for some time, shingles vaccination should not be postponed, and vaccination with Zostavax is not expected to be a contraindication for future Shingrix administration.[6, 16]



* Disease Modifying Anti-Rheumatic Drugs

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This article is available online at:
www.bpac.org.nz/2018/zostavax.aspx

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