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This article discusses herpes zoster, the condition and its complications as well as the benefits, risks and challenges associated with the herpes zoster vaccine.

Introduction

Herpes zoster (HZ) affects 120,000 Australians every year¹. The burden of HZ in Australia is substantial, and is increasing with time. This increase in cases of HZ started prior to universal varicella-zoster virus vaccination in 2005 and has remained since, being most noticeable in the older population. This is reflected in GP consultations with an estimated incidence of 5.6 per 1,000 persons¹. The impact of HZ is higher in immunocompromised patients.

Almost all adults are at risk of developing HZ (also known as shingles). This is because over 95% of the Australian population aged over 30 years has been infected with varicella-zoster virus, colloquially known as chickenpox². Overall, 20- 30% of people will develop shingles in their lifetime, mostly after the age of 50 years³.

Risk Factors

The increased incidence of HZ is most notable after 50-60 years of age and continues to rise with age. This is likely to be related to decline in a cell-mediated immunity in the elderly. Other risk factors for HZ include: female gender, being immunocompromised and

Take Home Messages

- ✔ Up to 30% of people will develop shingles in their lifetime with the elderly and the immunocompromised being the most vulnerable.
- ✔ Up to one in five people who have shingles will develop post-herpetic neuralgia regardless of treatment with antiviral medication.
- ✔ Zostavax[®] is a live, attenuated vaccine that prevents herpes zoster in just over half of people aged over 60 years.
- ✔ Zostavax[®] is contraindicated in patients who are significantly immunocompromised either by their clinical condition or their therapy.
- ✔ Eligible patients should receive Zostavax[®] at the earliest opportunity before commencing immunosuppressive therapy.

having a family history of biological relatives affected by HZ⁴.

Reactivation of the varicella-zoster virus leads to a localised inflammatory response, with nerve cell damage and subsequent ganglionitis. The degree of inflammation is associated with disease severity and consequently, so is the risk of complications.

Clinical Manifestations

HZ arises from the reactivation of the varicella-zoster virus after latent infection and results in the virus being transferred along nerves to the skin. The exact triggers for reactivation are unknown. A prodromal period of dermatomal pain often precedes the acute eruption by several days, occasionally longer. The character of the acute pain (neuritis) in the affected dermatome has been variously described as burning, deep aching, tingling, itching or stabbing.

Patients not uncommonly experience neuropathic pain, such as paraesthesia (burning and tingling); dysaesthesia (altered or painful sensitivity to touch); allodynia (pain associated with non-painful stimuli); or hyperaesthesia (exaggerated or prolonged response to pain), depending on the degree of associated neuronitis/ganglionitis. However, although such symptoms usually commence during the acute phase, they may also be associated with ongoing pain (30-90 days post-onset) or chronic pain (over 90 days post-onset). Pain persisting for more than 3 months is known as "post-herpetic neuralgia" (PHN).

The acute rash of HZ is often pruritic as well as tender, and spreads throughout the affected dermatome. It evolves through a papular stage to a vesicular stage (lasting three to five days) and then crusts over five to seven days. Acute HZ takes two to four weeks to heal. Rarely (< 5% of cases) the rash does not follow the prodromal pain in a condition known as zoster sine herpete.

Previously a United Kingdom study highlighted the significant impact of acute HZ on patients' quality of life. Seven to 14 days after the initial visit to the doctor, 77% of patients were experiencing significant pain and 57% had problems with their usual activities; 36% had issues with either mobility or anxiety and 17% had problems with self-care. The patients' doctors were more likely to underestimate rather than overestimate the patients' pain⁵.

Complications

a) Post-herpetic neuralgia

Depending on the patient's age (and the definition of PHN), between 8% and 21% of patients who experience acute HZ will get PHN⁶. Most accept that PHN can be defined as pain that persists for at least three months after the onset of acute HZ. Approximately 20% of patients age over 50 with HZ will still report pain at six months despite adequate antiviral therapy^{6,7}.

A recent meta-analysis showed the risk of developing PHN was

significantly increased if the clinical features of the original acute HZ infection included prodromal pain (summary rate ratio 2.29, 95% confidence interval: 1.42-3.69), severe acute pain (summary rate ratio 2.23, 1.71-2.92), severe rash (summary rate ratio 2.63, 1.89-3.66), or ophthalmic involvement (summary rate ratio 2.51, 1.29-4.86). Older age, severe immunosuppression and diabetes were also significantly associated with PHN. However, neither depression nor cancer appeared to increase the risk of developing PHN⁸. Oral aciclovir given within seventy-two hours of the onset of HZ rash did not reduce the incidence of PHN significantly. There is currently insufficient evidence from randomised controlled trials to determine whether other antiviral treatments prevent PHN⁹.

b) Ophthalmic zoster

Ophthalmic involvement occurs in 10% to 20% of HZ cases¹⁰. This involvement may range from a cutaneous reaction limited to the eyelids, to corneal ulceration or retinal disease resulting in permanent loss of vision. Keratitis, uveitis and corneal erosion are common; however, fortunately, retinal necrosis and optic neuritis are not.

c) Skin complications

Skin complications of HZ include bacterial superinfection (commonly *Staphylococcus aureus*), scarring and post-inflammatory pigmentation changes.

d) Other less common neurological manifestations

In addition to vision and hearing problems that can occur with acute HZ, other neurological complications include myelitis, cranial and peripheral nerve palsies, polyradiculitis, stroke and encephalitis. The latter two complications are the result of small and large vessel vasculopathy¹¹.

Overall, the incidence of ischaemic stroke is significantly higher in the first weeks to months after acute HZ. During the first month after the acute infection, the pooled relative risk for ischaemic stroke is 1.55 (95% CI, 1.46 ± 1.65). At three months the relative risk is 1.17 (95% CI, 1.12 ± 1.23). This increased risk of stroke reverts to normal by 12 months post-acute HZ. There is a lower risk of stroke in patients who were treated with antivirals for their acute HZ¹².

Treatment

Herpes zoster antiviral therapy

Three antiviral drugs (aciclovir, valaciclovir and famciclovir) have established efficacy in the treatment of acute HZ, by accelerating the resolution of lesions, reducing viral shedding and decreasing the severity of acute pain. These drugs also reduce the overall duration of acute HZ pain. Oral aciclovir does not reduce the incidence of PHN significantly and there is insufficient evidence to determine the effect of other antiviral treatments on PHN⁹.

Corticosteroids

Controlled trials of prednisone (in doses of 40mg daily for seven days, tapering by 5mg daily over the subsequent two weeks), has shown benefit, particularly for acute HZ pain and quality of life. In contrast, there is no evidence that corticosteroids reduce the incidence of PHN nor the total duration of pain¹³. Corticosteroids should not be used for acute HZ without concomitant administration of antiviral drugs, as they are immunosuppressive.

Treatment of post-herpetic neuralgia

There is reasonable evidence that pharmacotherapy such as topical lidocaine patches¹⁴, gabapentin¹⁵, pregabalin¹⁶, tricyclic antidepressants¹⁷ or opiates¹⁸ can reduce the pain burden from PHN. Opioids should not be considered for first line therapy, given the uncertainty regarding long-term efficacy and concern about safety¹⁹.

However PHN remains difficult to treat. Fewer than half the patients with PHN in clinical trials of available therapies have had a 50% or greater reduction in pain. In addition, adverse effects are common, particularly in older patients⁶.

Prevention

Zostavax[®] is currently the only vaccination available in Australia to prevent HZ. This live-attenuated HZ vaccine is effective in preventing HZ and PHN. It is licensed in Australia for adults 50 years and over.

It is recommended for immunocompetent adults, aged 60 years and older and is funded under the National Immunisation Program for those aged between 70 and 79 years.

The Shingles Prevention Study was a double blind randomised controlled trial conducted with over 38,000 people over the age of 60 years²⁰. Subjects received a concentrated (14-fold) form of the live attenuated varicella (Oka strain) vaccine (Zostavax[®]) and were subsequently followed for a median of 3.1 years. Zostavax[®] was shown to be both safe and efficacious, preventing HZ in 51% of subjects, preventing PHN in 66% of subjects and reducing the burden of illness (a measure of severity and duration of pain) by 61 per cent.

While the efficacy in preventing shingles was found to be reduced in people over the age of 70 years and waned further with increasing age, the beneficial effect of the vaccine on the severity of illness and the incidence of PHN was similar among older subjects.

The subsequent follow-up studies suggested efficacy may wane, probably over five to eight years²¹. This has led to suggestions that a booster may be necessary at 10 years, although there are no current international recommendations for a booster.

Contraindications to Vaccination

Zostavax[®] is a live, attenuated vaccine and so it is contraindicated in patients who are significantly immunocompromised. Conditions where HZ vaccination is contraindicated include²²:

Primary or acquired immunodeficiency

- ✔ Haematological neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
- ✔ Cellular immune deficiencies. (Humoral deficiencies affecting IgG or IgA antibodies are not a contraindication, unless associated with T cell deficiencies)
- ✔ Any patient with metastatic cancer.
- ✔ Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months) and after this, only if they are determined not to have ongoing immunosuppression, or graft versus host disease.
- ✔ Immunocompromise due to primary or acquired (HIV/AIDS) immunodeficiency. Research suggests that in adults with HIV, a CD4 count above 350/μL may be a safe level for administration of the zoster vaccine²², however it is recommended that clinicians confer with the patient's treating specialist prior to vaccination.

Other contraindications

Zostavax[®] vaccine should not be given to a person who:

- ✔ is pregnant
- ✔ has had a confirmed anaphylactic reaction to a previous dose of varicella virus-containing vaccine or to any component of the vaccine (including neomycin or gelatin)
- ✔ is being treated with either oral or intravenous antivirals (such as aciclovir) until 48 hours after cessation of treatment
- ✔ Other significant immunocompromising conditions (See Table 1).

Patients anticipating immunosuppressive therapy

The risk and severity of HZ is considerably higher in immunosuppressed individuals. Therefore it is recommended individuals consider the HZ vaccine before commencing immunosuppressive therapy. See Table 1 for the timeline of giving the HZ vaccine, either prior to, or following, immunosuppressive therapy.

Immunisation for immunocompromised patients.

The increased incidence and severity of HZ is proportional to the

extent of any immunosuppression. For example, patients receiving allogeneic and autologous haemopoietic stem cell transplants have an incidence of HZ of 15% to 30% in their first year post-treatment and are also at increased risk of systemic, visceral dissemination²³.

Unfortunately, the risks associated with using a live-attenuated vaccine also increase with the severity of immunosuppression. Thus, it is currently contraindicated in a number of conditions resulting in severe immunocompromise, as stated above.

The safety and efficacy of the live attenuated HZ vaccine in milder immunocompromised conditions, such as autoimmune diseases treated with biologics (including tumour necrosis factor inhibitors) is still being determined.

Sulfasalazine is the exception to this statement, as it is safe at any dose if there is no other immunosuppressive medication being taken or no immunosuppressive condition present (See Table 1).

Recombinant subunit vaccines may be more suitable than live attenuated vaccines for severely immunocompromised individuals, because they avoid the risk of disease caused by replication of the vaccine virus²⁴. Therefore, the novel Herpes zoster adjuvanted subunit (HZ/su) vaccine may be safer in these patients, when it becomes

available, and should it prove efficacious in immunocompromised individuals. More research is still needed regarding HZ vaccination in immunocompromised patients. There is currently a large efficacy study of a HZ/su vaccine in autologous stem cell transplant patients²⁵.

Strategies to improve vaccine uptake

While the uptake of the HZ vaccine has been strong in the 70-79-year-old age group since its launch on the Australian National Immunisation Program in November 2016, a significant proportion of the target group remain unvaccinated.

Table 2 summarises the factors that appear to increase or reduce the likelihood of a patient having the HZ vaccine.

The strongest predictor of a patient getting the HZ vaccine is a recommendation from their GP. Researchers in the Australian Zoster Study⁴² interviewed 1332 patients aged 60-85 years of age, randomly selected from 50 suburban Adelaide general practices. After adjusting for all other predictors, patients who were recommended the zoster vaccine by their GP were found to be 10.6 times more likely to get vaccinated (95% CI, 6.3-18.0) with 89% agreeing to have the HZ vaccine. See Figure 1.

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HELP PROTECT YOUR ELIGIBLE 70-79 YEAR OLD PATIENTS FROM SHINGLES AND PHN^{1,2}

AVAILABLE FOR 70 YEAR OLDS, WITH A 5-YEAR CATCH UP PROGRAM FOR 71-79 YEAR OLDS¹

PHN = Postherpetic Neuralgia. Hypothetical patient profile. May not be representative of every patient's experience of shingles.

Before prescribing, please review the PBS and Product Information available in the Primary Advertisement in this publication.

References: 1. Department of Health, Immunise Australia Program. National Immunisation Program Schedule. <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/national-immunisation-program-schedule>. Accessed 31 August 2017. 2. ZOSTAVAX[®] approved Product Information, Amended August 2017. Product Information is available from Seqirus (Australia) Pty Ltd ABN: 66 120 398 067 63 Poplar Road, Parkville VIC 3052 www.seqirus.com.au; distributor for Merck, Sharp and Dohme (Australia) Pty Ltd. Seqirus Medical Information: 1800 642 865. ©ZOSTAVAX is a registered trademark of Merck & Co. Inc Whitehouse Station, NJ, USA. Seqirus[™] is a trademark of Seqirus UK Limited or its affiliates. Date of preparation October 2017. SEQ/ZOST/0917/0259. 02071SEQ/HE/HP.

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Table 1: The use of the Herpes zoster vaccine in immunocompromised conditions*

The authors are grateful to Prof. Kristine Macartney and Dr Benjamin Smith for permission to republish this Table.

Immunosuppressive Condition or Agent	Examples*	Safe Dose**	Comments
Anti-TNF	Etanercept Infliximab Adalimumab	NONE	Vaccinate one month before treatment initiation OR 12 months after treatment cessation
IL-1 inhibition	Anakinra	NONE	
Costimulation blockade	Abatacept	NONE	
B-cell depletion/inhibition	Rituximab	NONE	
Immunomodulators # (antimetabolites)	Azathioprine 6-Mercaptopurine Methotrexate	≤3.0mg/kg/day ≤1.5mg/kg/day ≤0.4mg/kg/week	If on higher dose, vaccinate one month before treatment initiation OR three months after treatment cessation
Corticosteroids	Prednisone	<20 mg/day	If ≥20 mg/day for less than 14 days, vaccinate one month before treatment initiation OR any time after treatment cessation. If ≥20 mg/day for more than or equal to 14 days, vaccinate one month before treatment initiation OR one month after treatment cessation.
T-cell activation/inhibition	Tacrolimus Cyclosporine	NONE	Vaccinate one month before treatment initiation OR three months after treatment cessation
Others	Cyclophosphamide Mycophenolate	NONE	
Sulfasalazine		Any dose	Provided patient is not taking other immunosuppressives or has no immunosuppressive condition**
HIV infection	CD4 T cells < 350/μL or CD4 T cells <15% of total lymphocytes***	NONE	Serologic confirmation of previous varicella-zoster viral infection must be obtained prior to vaccination.
Chemotherapy/radiotherapy		NONE	At least six months after the end of treatment AND after patients are demonstrated to be in remission.
Chronic lymphocytic leukaemia	Alkylating agents e.g. chlorambucil, cyclophosphamide; monoclonal antibodies e.g. rituximab, ofatumumab, obinutuzumab	NONE	Haematological malignancy is an absolute contraindication to live vaccination, regardless of therapy (even if no therapy is given).


*This Table has been adapted from the NCIRS Zoster FAQ sheet – see http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-FAQ.pdf

** Expert opinion of the NCIRS, unpublished NCIRS advice

*** The safety of administering the Herpes zoster vaccine should always be considered on a case-by-case basis. If there is uncertainty about the degree of immunocompromise and when vaccine administration may be safe, vaccination should be withheld and expert advice sought from the treating physician and/or an immunisation specialist.

All other immunomodulators are an absolute contraindication to being vaccinated with Zostavax®.

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Table 2: Factors influencing the uptake of the Herpes zoster vaccine

Increased Herpes Zoster Vaccine Uptake		
Demographic	Age	Older ²⁶⁻³¹
	Gender	Female ²⁷⁻³⁰
	Level of education	Higher ²⁶⁻³¹
Health knowledge and behaviour	Other vaccines	Regularly gets influenza or pneumococcal vaccines ^{27,28,30,32}
	Awareness about shingles and the zoster vaccine	Higher awareness ^{28-30, 32-35}
Beliefs about shingles	Belief HZ can be a severe condition	Agree ^{28,33}
Health care provider	Has a usual GP	Yes ³²
	GP recommendation to get the HZ vaccine	Strong recommendation ^{28-33,36}
Other	Family or friends	Have previously been affected with shingles or PHN ^{28,32,34}
	Availability of the HZ vaccine	Available ²⁹
Reduced Herpes Zoster Vaccine Uptake		
Beliefs about shingles or immunity	Risk of getting shingles	Low perceived risk ^{28-31,33}
	Vaccine not needed; rarely get sick	Agree ^{29,30,33}
	Immunity to shingles	Believe that they already have good immunity ^{28-30,33}
Beliefs about the HZ vaccine	Natural immunity is better; vaccines weaken the immune system	Agree ^{28,33}
	Concerned about the effectiveness of the HZ vaccine	Agree ^{30,31,33,35}
	Concerned about adverse effects from the HZ vaccine	Agree ^{28,30,32,33}
	Concerned about a possible allergic reaction to the vaccine	Agree ²⁸
Health care provider	Believe that the HZ vaccine can cause shingles	Agree ³³
	GP did not discuss the need for the HZ vaccine	Yes ^{30,32,33}
	Difficulty getting to see their GP	Yes ^{26,27}
Mixed Or Unclear Impact		
Co-morbidities	Chronic disease ³³	Diabetes (increased uptake) ³³
Smoking status	Smokers have lower levels of uptake of other adult vaccines ^{37,38}	
Opportunity	Less GP visits associated with lower vaccine uptake with other adult vaccines ^{39,40}	
Health status	Poorer health status associated with higher vaccine uptake with other adult vaccines ^{37,41}	



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PHN = Postherpetic Neuralgia

Hypothetical patient profile. May not be representative of every patient's experience of shingles.

PBS Information:

This product is listed on the National Immunisation Program (NIP). Refer to NIP schedule.

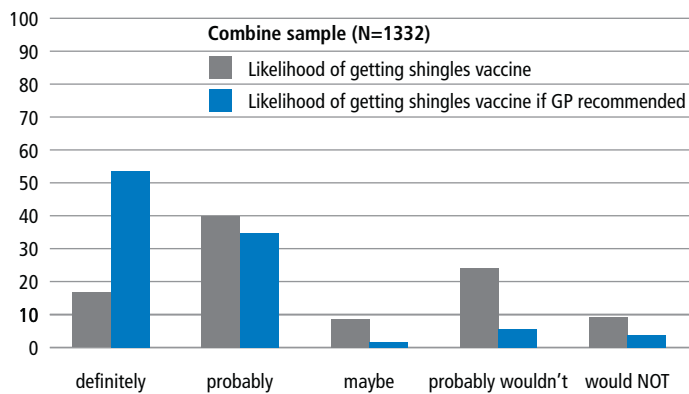
Before prescribing, please review the Product Information available at www.seqirus.com.au/PI

MINIMUM PRODUCT INFORMATION: ZOSTAVAX® Zoster Virus Vaccine Live (Oka/Merck), Refrigerator stable **Indications:** Prevention of herpes zoster (shingles) in individuals 50 years of age and older. Prevention of postherpetic neuralgia (PHN) and reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older. **Contraindications:** History of hypersensitivity to any component of the vaccine, including gelatin. History of anaphylactic/anaphylactoid reaction to neomycin. Primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukaemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS; cellular immune deficiencies. Immunosuppressive therapy including high-dose corticosteroids, but not topical/inhaled corticosteroids. ZOSTAVAX is a live, attenuated varicella-zoster vaccine and administration to individuals who are immunosuppressed or immunodeficient may result in disseminated varicella-zoster virus disease, including fatal outcomes. Active untreated tuberculosis. Pregnancy (see PRECAUTIONS). Precautions: Adequate treatment provisions, including adrenalin injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur. Consider deferral of vaccination in the presence of fever >38.5°C. Safety and efficacy not established in adults known to be infected with HIV. **Use in Pregnancy (Category B2)** Do not administer to pregnant females; pregnancy should be avoided for 3 months after vaccination. **Use in Lactation** It is not known whether varicella-zoster virus is secreted in human milk. **Use in the elderly** The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). ZOSTAVAX was demonstrated to be generally safe and effective in this population. **Interactions with other medicines:** ZOSTAVAX can be administered concurrently with inactivated influenza vaccine. ZOSTAVAX and PNEUMOVAX 23 should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX. Consider administration of the two vaccines separated by at least 4 weeks. **Adverse Effects:** headache, erythema, pain/tenderness, swelling, pruritus, fatigue, haematoma, warmth, induration, pain in extremity. **Post-marketing experience:** varicella, zoster, nausea, arthralgia, myalgia, injection-site rash, injection-site urticaria, pyrexia, transient injection-site lymphadenopathy, hypersensitivity including anaphylactic reactions, rash, necrotizing retinitis. **Dosage and Administration:** A single dose (0.65mL) administered subcutaneously. Administer vaccine immediately after reconstitution to minimise loss of potency. ZOSTAVAX is not a treatment for zoster or PHN. Based on Approved Product Information dated 17 August 2017.

References: 1. Department of Health, Immunise Australia Program. National Immunisation Program Schedule. <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/national-immunisation-program-schedule>. Accessed 31 August 2017. 2. ZOSTAVAX® approved Product Information, Amended August 2017. Product Information is available from Seqirus (Australia) Pty Ltd ABN: 66 120 398 067 63 Poplar Road, Parkville VIC 3052 www.seqirus.com.au; distributor for Merck, Sharp and Dohme (Australia) Pty Ltd. Seqirus Medical Information: 1800 642 865. ©ZOSTAVAX is a registered trademark of Merck & Co. Inc Whitehouse Station, NJ, USA. Seqirus™ is a trademark of Seqirus UK Limited or its affiliates. Date of preparation October 2017. SEQ/ZOST/0917/0259. 02071SEQ/HE/FP.

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Figure 1: The impact on patient intentions of a GP recommendation to get the Herpes zoster vaccine.



Litt JCB, et al. *Int J Infect Diseases* 2014; 21:436-7

While a GP recommendation to get the HZ vaccine tends to counter many patient worries about the vaccine, it is still important to address the specific patient concerns (see Table 3).

Many patients have misperceptions about the role of natural immunity and the ways to boost it, despite a lack of any evidence of effective strategies other than being vaccinated. Some people believe that vaccines weaken the body's defences. Allergic reactions are rare and patients may be reassured that if the HZ vaccine is given appropriately, then it is extremely unlikely to cause either varicella or HZ.

A sizeable proportion of the population (nearly 40%) believe that they don't need the HZ vaccine, as they rarely get sick (Table 3). This is despite the fact that nearly everybody will have a few copies of the HZ virus in a latent state in their dorsal root ganglia, and so therefore are at risk of getting acute HZ⁴³.

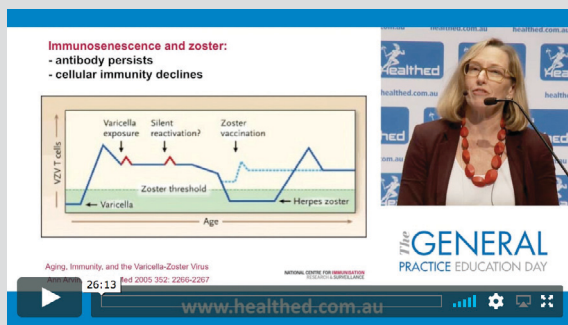
Table 3 Impact of GP recommendation for Zostavax® on patient intentions to get the HZ vaccine

*Adapted from Litt, Cunningham and MacIntyre. 'The Australian Zoster Study' presented at WONCA Meeting Cancun, May 2010⁴⁴.

N=1332; The red figures highlight the fact that even in the presence of a GP recommendation to get Zostavax, only a small percentage will do so if they hold particular beliefs

Belief	Positive response category		Patient intentions to get the HZ vaccine if GP recommends Zostavax®		Patient intentions to get the HZ vaccine if GP did NOT recommend Zostavax®	
	Positive attitude	% Positive attitude	% Positive attitude	% Negative attitude	% Positive attitude	% Negative attitude
I trust the advice on vaccination that I receive from health professionals	Agree	93.6	86.2	30.3	60.0	18.1
The shingles vaccine injection would reduce my risk of becoming seriously ill from the complications of shingles	Agree	83.9	87.9	57.5	63.4	27.6
I prefer to get natural immunity from getting the disease (e.g. shingles) rather than from a vaccine	Disagree	68.3	92.0	64.0	69.4	32.6
Vaccines weaken the body's defence	Disagree	72.5	90.1	64.5	66.3	35.4
Too many immunisations will weaken my immune system	Disagree	67.3	91.0	67.7	69.2	35.6
The shingles vaccine injection would prevent me from getting shingles	Agree	77.2	87.6	68.1	63.8	37.6
I do not need a shingles vaccine injection as I rarely get sick	Disagree	60.4	92.7	68.4	76.2	29.9
I am concerned about having an allergic reaction from the shingles vaccine	Disagree	58.0	92.2	70.8	67.2	44.8
I could get shingles from the shingles vaccine	Disagree	56.5	89.9	73.8	64.9	48.0
I would be concerned that a shingles vaccine injection may be painful or cause side-effects	Disagree	53.3	91.8	72.3	66.5	46.6
It is likely that I would feel unwell for a few days after having a shingles vaccine	Disagree	22.7	89.9	80.7	62.8	55.9

Video Resource



Zoster Vaccine
by A/Prof Kristine Macartney

For more interviews visit www.healthed.com.au/video

It is important to ensure that patients who receive the HZ vaccine are reported (and captured on) to the Australian Immunisation Register (AIR). Detailed information on how to use the AIR is available at <http://www.humanservices.gov.au/health-professionals/services/medicare/australian-immunisation-register-health-professionals>.

Future zoster vaccines

A new recombinant subunit vaccine (HZ/su) consisting of varicella-zoster virus glycoprotein E (gE) and the AS01B adjuvant system has been developed. AS01B is a liposome-based adjuvant system that contains two agents designed to increase the vaccine's immunogenicity: a monophosphoryl lipid A (MPL), a toll-like receptor 4 agonist, and, the saponin QS-21 (a purified extract from the Chilean Quillaja saponaria tree)⁴⁵.

Two randomised, blinded, placebo-controlled phase III trials of this vaccine were conducted concurrently in 18 countries (throughout Asia, Australia, Europe, Latin America, and North America) to determine the efficacy and safety of two doses of HZ/su in reducing the risk of HZ and PHN in adults aged 50 years or older (ZOE-50) and in those aged 70 years or older (ZOE-70)⁴⁶⁻⁴⁸.

The vaccine efficacy against acute HZ was 88.8% in the ZOE-50 group (95% CI 68.7-97.1%) and 91.3% (95% CI 86.0-94.9%) in the ZOE-70 group.

When the results from the two groups were combined, vaccine efficacy, four years after vaccination was 87.9% (95% CI 73.3 – 95.4%).

Injection-site reactions after the two doses of vaccine were very common and occurred in 81.5% of ZOE-50 participants and in 74.1% of ZOE-70 participants.

The varicella-zoster virus subunit protein gE is highly immunogenic, eliciting both neutralising antibody and CD4 T cells responses.

This substantial gE-specific immune response to HZ/su occurred in both older and immunocompromised populations. As stated previously, recombinant subunit vaccines are more suitable than live attenuated vaccines for severely immunocompromised individuals because they avoid the risk of disease caused by replication of the vaccine virus^{24,49}.

Phase I/II clinical trials have been conducted in several immunocompromised groups, including renal transplant patients; solid organ malignancy and haematopoietic malignancy. Phase III trials should be published soon.

Common Questions

What is the duration of immunity after Zostavax® and is re-vaccination necessary?

Shingles prevention follow-up studies found that protection wanes by five to eight years following the initial vaccination²¹, so in the longer term, a booster may be necessary but it is not currently recommended.

Is there an increased risk of cancer associated with acute HZ?

A recent systematic review⁵⁰ showed that acute HZ may be a marker for occult cancer, as the relative risk of any cancer being found in people with acute HZ is 40% higher than in the general population (RR 1.42 95% CI: 1.18, 1.71) and in the year after experiencing acute HZ, a person was over 80% more likely than their non-zoster counterpart to have had a cancer diagnosed (RR 1.83 95% CI: 1.17, 2.87).

The highest estimates were generally reported for haematological cancers. The absolute risk of any cancer at one year after presentation with HZ was 0.7- 1.8%.

What this means for clinicians is unclear. There is a lack of evidence on the benefits and harms of an extensive work-up for cancer in acute HZ patients. In addition none of the studies investigated whether the increased risk of occult cancer depended on the presence of classic risk factors for HZ e.g. the use of immunosuppressive drugs.

Can patients who have recently had acute HZ receive Zostavax®?

Recurrence of HZ in immunocompetent subjects is uncommon, occurring in about 5% of the population^{51,52}. It is unclear how long after experiencing acute HZ people are protected courtesy of their natural immunity being boosted. The HZ vaccine should be delayed for at least 12 months after acute HZ, with some recommending up to a three year delay⁵³. Zostavax® is not recommended for the treatment of acute HZ or PHN.

Should patients be checked to see if they have varicella antibodies prior to zoster vaccination?

Serological testing prior to zoster vaccination is recommended if vaccination is being considered for persons with asymptomatic HIV infection and for individuals anticipating significant immunocompromise. Persons in these categories who have negative VZV IgG should generally not be given Zostavax[®].

Can Zostavax[®] be administered at the same time as other vaccines?

Zostavax[®] can be administered at the same time as inactivated vaccines such as the influenza vaccine and 23-valent pneumococcal polysaccharide vaccine (PPV), using a separate syringe and injection site. Zostavax[®] can also be administered at the same time as other live vaccines. When the measles, mumps and rubella vaccine and Zostavax[®] are not administered at the same time, a minimum interval of four weeks should be observed between vaccines. A four-week interval should also be left between the administration of the yellow fever vaccine and Zostavax[®]. Zostavax[®] should not be administered to patients currently receiving oral or intravenous antiviral agents (such as aciclovir) or who are within 48 hours of cessation of such treatment, as the therapy may reduce the response to the vaccine.

Can the vaccine virus be transmitted to others?

There is a theoretical risk of acquiring infection from a person who has been vaccinated with a live vaccine. This risk may be greater for immunocompromised individuals. For Zostavax[®], no cases of transmission of vaccine virus were reported in clinical trials.

Transmission of vaccine virus has been rarely reported with other varicella virus-containing vaccines, however, not all vaccine recipients develop a varicella-like rash. In the Shingles Prevention Study, 0.11% of varicella zoster vaccine recipients versus 0.04% of placebo recipients developed a varicella-like rash at the injection site²⁰.

Any person who develops a vesicular rash after receiving Zostavax[®] should ensure the rash area is kept covered and physical contact is avoided with any susceptible person (i.e. someone who has never had chickenpox) until the rash has dried out and crusted. If the person who received the vaccine is themselves immunosuppressed, they should avoid contact with susceptible people until the rash is dry and crusted, due to the higher risk of virus shedding. Prophylactic aciclovir may be considered for vulnerable patients exposed to a varicella-like rash after recent HZ vaccination.

If a varicella (widespread) or HZ (dermatomal) rash develops after vaccination with Zostavax[®], a fluid sample from a vesical should be sent for analysis, to determine whether the rash is vaccine-associated or a wild varicella-zoster type.

Conclusion

HZ is a common and frequently disabling condition. The availability of the current live attenuated HZ vaccine and the HZ adjuvanted subunit (HZ/su) vaccine in the near future may reduce the burden of disease attributable to both HZ and PHN.

There has been a strong demand for the HZ vaccine within the National Immunisation Program target group (people aged 70-79 years). Patient attitudes and beliefs about natural immunity, vaccine effectiveness and an individual's likely risk of HZ need to be discussed with the GP. This will complement the potent impact of the medical recommendation to be vaccinated against HZ.

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Further Reading

NCIRS Zoster Vaccine FAQ Sheet http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-FAQ.pdf

Declaration

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