HOW TO TREAT shingles

Shingles has a one-in-three lifetime risk and is frequently debilitating because of the severe and sometimes protracted pain it causes. This article provides a clinical update on shingles, postherpetic neuralgia, antiviral treatment and pain management, the shingles vaccine and the logistics for implementing coverage in the largely unprotected over-50s population. It was written by **Stewart Reid**, GP, Ropata Medical Centre, Lower Hutt.

Shingles emerges as immunity declines

Do you need to read this article?
Try this quiz

1. The lifetime risk of shingles is one in three. **True/False**
2. The ideal time to administer antiviral agents following the appearance of rash is within one week. **True/False**
3. The most common complication of shingles is postherpetic neuralgia. **True/False**
4. The percentage of shingles patients aged >80 years who develop pain persisting for at least 90 days after rash onset is 10 per cent. **True/False**
5. Hutchinson's sign involves a lesion on the nose. **True/False**
6. The annual incidence of shingles at 80 years of age is approximately 12 to 15/1000. **True/False**

Answers on page 7

In New Zealand, infection with varicella zoster virus (VZV) resulting in chickenpox is almost universal. It is anticipated that 3 per cent will be infected during infancy, followed by 8 to 9 per cent per annum during childhood, so that, by the age of 14 years, at least 90 per cent have been infected.

By 40 years of age, 97 per cent of individuals are expected to have been infected with VZV. This means almost everyone over the age of 40 is at risk of shingles, consistent with international data.[1,2]

While advancing age is the most important risk factor for shingles, some chronic diseases increase the risk as well.

A recent study indicated a raised risk of shingles for patients with various chronic conditions. Rheumatoid arthritis increases the relative risk of shingles by 1.46, inflammatory bowel disease by 1.36, COPD by 1.32, asthma by 1.21, chronic kidney disease by 1.14, depression by 1.15 and diabetes (type 1 but not type 2) by 1.27. Immune suppressing conditions result in a greater increase in risk.[3]

During primary infection with VZV, viraemia results in the characteristic widespread rash and the virus makes its way centrally along the cutaneous nerves to become seeded in the dorsal root and cranial ganglia, where it establishes lifelong latency. The viraemia may also result in direct seeding in the ganglia.

Once infected, humoral immunity becomes stable and gives long-term protection against chickenpox. Cell-mediated immunity is required to prevent shingles and, when this declines with age or immune suppression, the virus reactivates.

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Diagnosis obvious only when rash appears

The first sign of shingles is often pain, which, in the absence of rash, may lead to alternative diagnoses being considered.

It is the onset of the characteristic rash that usually makes the diagnosis obvious. Prior to the rash, and in the presence of the rash, there is often marked sensitivity of the skin, with light brushing or touch causing pain – so-called allodynia. Most patients present when the characteristic rash, which does not cross the mid-line, appears (Figure 1).

Diagnosis is usually straightforward but herpes simplex can be mistaken for shingles, and other rashes may also mimic it. For example, a patient presented recently with "insect bites" on her cheek and neck, which seemed to be infected. On review, following a few days of antibiotic treatment, the resolution of the rash was less than expected and the pain seemed rather prominent and out of proportion to the settling redness and crusting.

A swab for VZV polymerase chain reaction (PCR) confirmed the diagnosis was herpes zoster. Fortunately, being under 40 years of age, she made a rapid, uneventful recovery.

Herpes simplex is the most common mimic, but the shingles diagnosis can be confirmed, as above, by PCR, and the distinction made between the two.

In general, the pain from shingles becomes more severe and long-lasting with increasing age. Before the age of 50 years, shingles results in a rash lasting two to three weeks, usually with little pain, but, with older age, pain can be significantly disabling.

In one study, herpes zoster pain was rated as being worse than renal colic and labour pain, and the pain of postherpetic neuralgia (PHN), the most common complication of shingles, was rated as one of the most severe of the chronic pains.[5]

The site of shingles is the trunk (usually thoracic but, occasionally, lumbar) in 50 to 70 per cent of cases, cervical in 10 to 20 per cent of cases and ophthalmic also in 10 to 20 per cent of cases.[6]

Complications of shingles

The most important and most common complication is PHN, which is usually now defined as pain continuing beyond onset of the rash for 90 days or longer. Various definitions have been used, from pain at rash healing to pain lasting 180 days, but 90 days seems reasonable and is the definition used in the shingles prevention study.[7]

PHN occurs much more frequently with age and, beyond 80 years, 20 per cent of those with shingles has PHN, using the 90-day definition.[8]

Other risk factors for PHN include a severe shingles prodrome, a severe rash, sensory abnormalities and female sex. In the frail elderly in particular, the chronic persistent pain of PHN can be very debilitating.

Another important complication is ophthalmic involvement when the nasociliary branch of the trigeminal nerve is affected. Hutchinson's sign, with skin lesions on the tip, side or root of the nose, indicates likely eye involvement, and ophthalmic referral is advised if this is seen.

Other complications – neurologic, ophthalmic, cutaneous and disseminated disease – are listed in Panel 1.

PANEL 1
COMPLICATIONS OF SHINGLES

Neurologic
- acute neuropathic pain (>90 per cent of patients over 60 years)
- postherpetic neuralgia
- limb weakness
- sensory loss
- peripheral palsies
- meningitis
- myelitis
- encephalitis
- hearing loss

Ophthalmic
- visual impairment
- ptosis

Cutaneous
- scarring
- bacterial superinfection

Disseminated disease
- pneumonia
- hepatitis.

Continued from page 1

Reactivated VZV initially causes inflammation and necrosis in the dorsal or cranial ganglia, resulting in the prodromal pain. It then spreads along the segmental peripheral nerves to cause the characteristic, unilateral, dermatomal rash, possibly in an area where the chickenpox rash was most florid.

Subclinical reactivation may occur from time to time, but the virus is suppressed by the cell-mediated immune response, resulting in endogenous boosting.

Repeat exposure to chickenpox results in a boost to humoral immunity against VZV, but this may not result in the boosting of cell-mediated immunity and protection against shingles.

There are conflicting data on the role of this exogenous boosting. Some data indicate a higher number of exposures to chickenpox results in a reduced incidence of shingles. However, although one would expect, intuitively, women would be more likely to be exposed to chickenpox than men, women have a higher incidence of shingles than men.[4]

Postherpetic neuralgia (PHN), with pain of 90 days or more, is the most common complication of shingles, and it can be very debilitating, especially in the elderly.

The effects of shingles can be reduced through prevention using the vaccine now available in New Zealand, which provides approximately 60 per cent protection against the burden of disease caused by shingles.

Disseminated disease is rare and probably only occurs with significant immune compromise. Bacterial superinfection with group A streptococcus may require hospitalisation. Apart from PHN, ophthalmic involvement, cutaneous scarring and bacterial superinfection, the other complications are, in my experience, rare.

One additional complication is stroke, the incidence of which may be increased following shingles. A recent publication has reported the risk of stroke in the six months following shingles: for weeks one to four following shingles, the incidence rate is increased by a factor of 1.63 (95% CI 1.32–2-02); for weeks five to 12, it is increased by 1.42 (95% CI 1.21–1.68); and in weeks 13 to 26 the rate is increased to 1.23 (95% CI 1.07–1.42).[9] A three-fold increase in stroke following herpes zoster ophthalmicus was also reported.

Two papers from Taiwan have reported an increased stroke risk of 1.3-fold (95% CI 1.1–1.6)[10] in the year following herpes zoster and 4.5-fold (95% CI 2.5–8.3)[11] in the year following herpes zoster ophthalmicus.

Various studies have looked at interference with daily living, and it is no surprise, when pain scores are higher, there is more and quite severe interference with work, enjoyment of life, activities of daily living and psychological wellbeing. Severe herpes zoster in the elderly can result in the loss of independence.

Epidemiology of shingles

Hope-Simpson did the classic herpes zoster epidemiology study (see Figure 2).[12] These data derive from a study performed over 25 years in his practice of approximately 3800 patients, and he was among the first to suggest herpes zoster resulted from a reactivation of the chickenpox virus.

The study shows incidence rises with age to around 11/1000 per annum by age 80, and about one-third of shingles sufferers older than 80 years have persistent pain for greater than one month, the definition of PHN used in that paper.

These data are replicated in other studies with, in general, an incidence of around 12–15/1000 for those aged 80 years and older. In Australia, for those aged over 60 years, the rate of shingles is now 15/1000 per annum.[13]

The lifetime risk of shingles is approximately one in three and, if one lives to 85 years, the risk is one in two. As populations age, shingles will be seen more frequently.

There is a paucity of data on shingles incidence in New Zealand. Preliminary data for the recorded diagnosis of shingles over a five-year period at the Ropata Medical Centre practice of 19,000 patients in Lower Hutt indicate the incidence of shingles is what would be expected from international data.

Second attacks of shingles are rare, but, then, so are first attacks. An average GP with 1500 patients, 30 to 40 per cent of whom are older than age 50, would expect to see three to five cases of shingles per year on average. Second attacks of shingles are more common in women, the immune compromised and those who had severe pain at the first episode. Recent data indicate second attacks occur at close to the same rate as first attacks, with a 6 per cent recurrence rate over a period of eight years.[8]

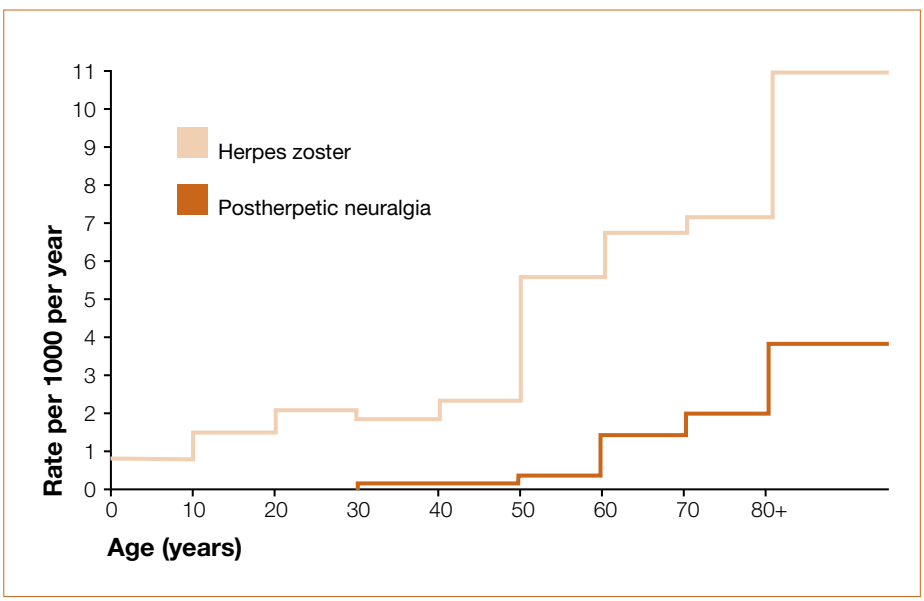

Figure 2. Incidence of herpes zoster and postherpetic neuralgia with age in a UK general practice. Hope-Simpson RE. *J R Coll Gen Pract* 1975;25:571–75. Reproduced with kind permission of the Royal College of General Practitioners

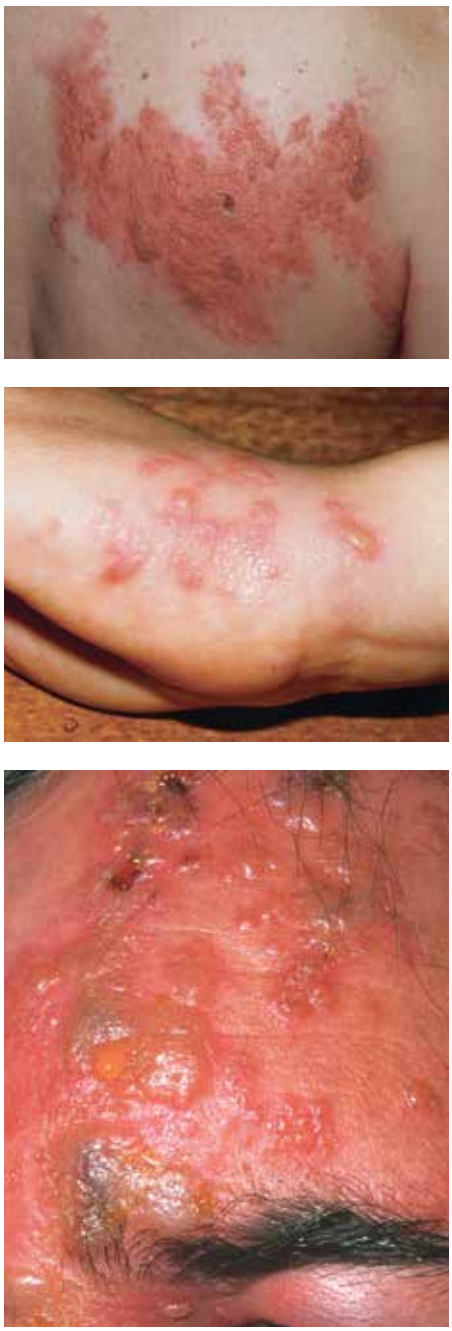

Figure 1. Unilateral shingles rash of the shoulder (top), wrist and forehead (bottom)

Use systemic antivirals as early as possible

Three relatively recent review papers covering the treatment of shingles are broadly in agreement.[2,14,15] In addition, a recent *Best Practice* article covers treatment of shingles.[16]

Topical antiviral therapy lacks efficacy and should not be used. Systemic antiviral medication is the most important treatment; ideally, it is instituted as early as possible in the course of the illness (Panel 2).

Systemic antiviral treatment is indicated for those aged over 50 years, those who are immune suppressed or on immune-suppressive medication and those who have severe prodromal pain and/or a severe rash.

It is recommended treatment with antivirals commences within 72 hours of rash onset – the earlier the better – but most experts recommend commencing treatment if new blisters are still appearing, and, in the elderly, it is difficult to deny any possibility of benefit.

In New Zealand, treatment is usually oral aciclovir 800mg five times daily for seven to 10 days.

Oral aciclovir is indicated for the treatment of shingles, the reduction in the severity and duration of the associated pain and rash and the reduction of the incidence and duration of PHN.[17]

An alternative is valaciclovir, which has similar indications. The dosage of valaciclovir is 1000mg three times daily for seven days.[18] The latter may be more effective because a three times daily dosage is easier than five times daily, but it is not funded for this indication.

However, valaciclovir is funded for recurrent ophthalmic shingles where vision is at risk and for immune-compromised individuals with shingles.[16] Famciclovir, also administered three times daily, is licensed but not funded in New Zealand.[16]

When ophthalmic shingles occurs, institute treatment with aciclovir or valaciclovir, if appropriate, and refer urgently for assessment by an ophthalmologist. Further treatment of this condition is outside the scope of this article.

Evidence of antiviral efficacy

Aciclovir 800mg five times daily, started within 48 hours of the appearance of the rash, has been shown to reduce new lesion formation, hasten full crusting and reduce pain.[19] Numerous studies have confirmed this finding for aciclovir, valaciclovir and famciclovir. As stated above, valaciclovir is subject to Special Authority requirements and famciclovir is not subsidised in New Zealand.[16]

In contrast to the aciclovir data sheet, a recent Cochrane review concluded antiviral therapy within 72 hours of onset of herpes zoster rash does not significantly reduce the incidence of PHN.[20] This makes sense because it is likely the initial inflammatory and necrotic damage to the sensory ganglia is what is responsible for PHN, and this has occurred before the onset of rash and before treatment is instituted.

Modifiers of the disease course

Systemic corticosteroids

Systemic corticosteroids have also been recommended for the treatment of herpes zoster, but only when antivirals are also used, and never on their own. There is conflicting evidence of efficacy, but some data indicate a reducing course over three weeks may reduce the duration and severity of pain; there is no effect on PHN.

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For example, in a study comparing aciclovir treatment with and without the use of steroids, the group receiving steroids had a faster resolution of lesions and shorter time to cessation of acute neuritis and return to uninterrupted sleep, though the differences did not reach statistical significance. The dose of prednisone was 60mg daily for one week followed by 30mg and 15mg daily each for one week.[21]

In another study, increasing the duration of aciclovir treatment to 21 days or adding

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CASE STUDY 1

Steroids trigger attack

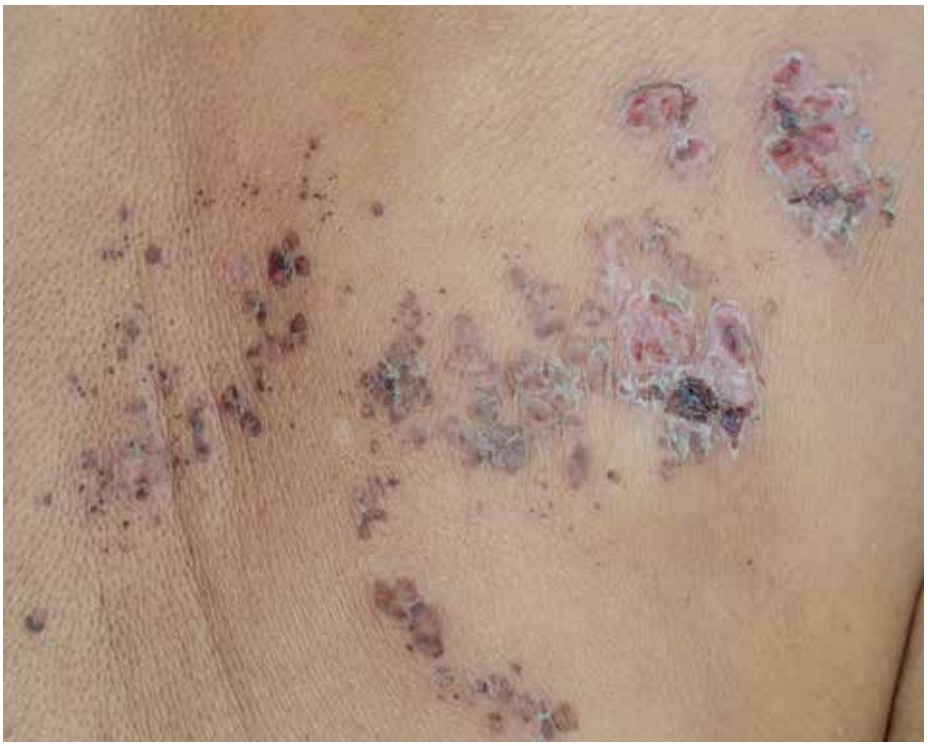
History and management

Barry is a 68-year-old who, eight years ago, presented with ophthalmic shingles when he was on steroids for temporal arteritis. Aciclovir was prescribed and he was referred to an ophthalmologist. He suffered no long-term sequelae from his eye involvement but he had severe pain requiring high doses of codeine and amitriptyline. He was off work for three months, which was a challenge as he was a self-employed tradesman.

Barry continued on codeine and amitriptyline. Sodium valproate was added, and later replaced with gabapentin. He remained on gabapentin until two years ago.

Outcome

Barry still requires amitriptyline and continues to suffer attacks of acute facial pain. I would consider his a very severe attack, and it is likely the steroid medications contributed to its severity.



Aciclovir started within 48 hours of rash appearance is shown to reduce new lesions, hasten full crusting and reduce pain

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40mg prednisone, tapering over three weeks, was observed to be superior to aciclovir alone for one week. However, any benefit was marginal and there was no reduction in the frequency of PHN.[22]

Neuropathic agents

There is some evidence tricyclic antidepressants and gabapentin reduce the neuropathic pain caused by herpes zoster, but the effect is not consistent between studies.[23,24]

In a study investigating gabapentin and nortriptyline in patients with neuropathic pain, including some with herpes zoster, it was noted both agents together were better than either separately. The authors suggested adding in the other if one did not offer adequate pain relief.[25]

In a randomised, double-blind study of 72 patients with herpes zoster, amitriptyline 25mg or placebo and antivirals were administered early. Amitriptyline and placebo were continued for 90 days. Pain prevalence at six months, the primary outcome, was reduced by more than one half in the amitriptyline group, making "a strong case for its preemptive prescription in those at increased risk for severe zoster".[26]

Pain management

Further treatment is that of pain management. Mild pain may be controlled by the use of mild analgesics, such as paracetamol and NSAIDs and, if that is achieved, all well and good. If not, the cascade of pain relief agents is well described.[19]

Most GPs will have dealt with individuals who have quite severe and disabling pain from herpes zoster. In such cases, mild narcotic analgesics, such as codeine and tramadol, or other strong narcotic analgesics, may be required, but their use brings the problems of sedation and constipation. If opiates are required, this limits the patient's ability to drive.

Management of postherpetic neuralgia

It is worth trying topical capsaicin when the rash has healed, and the pain is mild, but this is not likely to be sufficient for most patients with PHN.

Therapy, therefore, is likely to be systemic and directed at the neuropathic pain and will likely involve non-narcotic or narcotic analgesics and probably neuropathic pain agents, such as tricyclic antidepressants and gabapentin.

The combination of these medications may result in significant adverse effects, particularly sedation, and, because they are being used in individuals who may be on other medications because of long-term illness, there are interactions to consider. Referral to a pain clinic may be required.

In patients with PHN, control of long-lasting, severe pain is often problematic and rather unsatisfactory, which is why shingles prevention is an important consideration.

PANEL 2
TREATMENT RECOMMENDATIONS

Shingles

- Start aciclovir 800mg five times daily within 72 hours of rash appearance or if lesions are still appearing beyond 72 hours in those aged over 50, in those with impaired immunity and in those who have a severe prodrome or a severe rash.
- Prescribe appropriate analgesia on a regular rather than an as-required basis to keep pain suppressed, starting with non-narcotics but progressing to stronger analgesia as needed and tolerated.
- Consider starting a tricyclic antidepressant (nortriptyline in preference to amitriptyline) and/or gabapentin (as permitted by Special Authority) in those at increased risk of PHN (ie, aged over 80, severe prodrome, severe pain and/or severe rash). Have a lower threshold for women, who have a higher risk of PHN.
- Use steroids rarely, but consider in those who have severe rash and pain.
- If there is eye involvement or Hutchinson's sign, refer urgently to an ophthalmologist.

Postherpetic neuralgia

- Use appropriate analgesia with choice dependent on severity, comorbidities and current medication. If necessary (and it is likely to be so), add a tricyclic antidepressant if there is no contraindication, and, if not tolerated or insufficient, change to or add gabapentin. Consider referral to a pain clinic.

Shingles vaccine reduces burden of disease

The shingles vaccine Zostavax, available in New Zealand, is a live attenuated virus vaccine derived from the OKA strain of varicella zoster virus. It is presented as a lyophilised vaccine and, after reconstitution, is administered as a single subcutaneous dose. The vaccine contains a minimum of 19,400 plaque-forming units, which is 14 times the minimum titre of the varicella vaccine.[27]

The shingles vaccine has been studied in a large, double-blind, placebo-controlled efficacy trial with 38,546 participants aged 60 years and older. The participants were stratified by age: 60 to 69 and 70 and older. Individuals were randomised to receive shingles vaccine or placebo and were followed for up to four years.[7]

The primary hypothesis was that the vaccine would reduce the burden of disease, a measure of severity and duration of pain caused by shingles.

For example, if an individual had pain rated daily as eight on a one to 10 scale for 40 days then their burden of illness score would be 320. Secondary objectives were that the vaccine would reduce PHN and herpes zoster itself.

The vaccine demonstrated an overall efficacy of 61.1 per cent (95% CI 51.1–69.1) against the burden of illness caused by herpes zoster. Overall, efficacy against PHN was 66.5 per cent (95% CI 47.5–79.2) and against herpes zoster 51.3 per cent (95% CI 44.2–57.6). For those aged 70 and older, the efficacy against herpes zoster was lower (37.6 per cent) than for those aged 60 to 69 (63.9 per cent), but equivalent for burden of illness and PHN.

Apart from injection site reactions, which occurred in approximately 50 per cent of vaccine recipients, there were no clinically significant differences in serious adverse events or systemic adverse events between the vaccine and placebo groups.

A study in those aged 50 to 59 years demonstrated 70 per cent efficacy against herpes zoster and a similar excellent safety profile.[27]

These data have led to licensing of the vaccine in numerous Asia-Pacific and other countries. In New Zealand, the vaccine is recommended for healthy individuals from the age of 50 for the prevention of herpes zoster and PHN and the reduction in the burden of illness caused by herpes zoster. It can be administered irrespective of prior history of chickenpox, and can be given to those who have already suffered shingles.

The shingles vaccine is contraindicated in those who:

- have hypersensitivity to any vaccine component or anaphylaxis to neomycin
- have primary or acquired immunodeficiency
- are on immunosuppressive therapy, but not low-dose systemic steroids or topical steroids (see the adaptation below of the ACIP recommendations[4]).
- have active, untreated tuberculosis
- are pregnant.

Patients on immunosuppressive therapy, including high-dose corticosteroids (>20mg/day prednisone or equivalent for more than two weeks), should defer shingles vaccination for at least a month after discontinuation.

Short-term corticosteroid therapy, regimens of prednisone <20mg daily or equivalent, topical or inhaled steroids, steroids for intra-articular, bursal or tendon injections or long-term, alternate-day treatment with low-to-moderate doses of short-acting corticosteroids are not contraindications.

Persons receiving low-dose methotrexate (<0.4mg/kg per week), azathioprine (<3mg/kg per day) or 6-mercaptopurine (<1.5mg/kg per day) for the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease and other conditions can receive the vaccine.[4]

The duration of immunity provided is undetermined but data to date indicate it declines over a 10-year period and that an additional dose may be required at about this time. Data also indicate the response to the vaccine in those aged 70 or more is equivalent whether or not they received a dose of the vaccine 10 years previously.

Offering and prioritising the vaccine

Given that many individuals aged over 50 years are eligible to receive the shingles vaccine, how does one prioritise its delivery? (Cost will restrict its use, however.)

Eventually, once the "catch-up" phase is completed, the shingles vaccine is likely to be offered routinely at a specified age, or ages (50, 60 and 70 years?). The "catch-up" is, potentially, a significant logistical problem, but there are ways in which general practice can prioritise vaccine delivery.

The obvious initial step is to administer it to those who request it and those who have already had shingles and are keen to avoid a recurrence. After that, several options exist.

CASE STUDY 2

Late-presenting shingles

Presentation

Betty is a 77-year-old who presents late with lower thoracic shingles.

Treatment

She is not offered antiviral treatment because of her late presentation. She requires paracetamol and codeine to control the pain, and is prescribed amitriptyline 25mg nocte because her nocturnal pain interferes with her sleep. Betty continues with the analgesia for three months but, for the next five months, does not require it.

Outcome

After eight months, Betty still has allodynia (sharp pain with light touch) in the shingles dermatome; however, I would regard this as a relatively mild attack in someone of her age.

Age-prioritised delivery: select one or two ages (eg, 70 and 79) and inform them of the availability and cost of the vaccine, but omit those who have contraindications.

If capacity permits, select a further two ages, say 73 and 77, etc, until, gradually, all those aged over 70 are being offered vaccination. Then move on to those in their 60s, leading to all in their 60s and 70s being offered the vaccine.

Disease-prioritised delivery: offer the vaccine first to those at higher risk, as discussed above, but excluding those who are immune suppressed, in whom the vaccine is contraindicated. Finally, it would be offered to healthy individuals.

A combination of these two approaches could be taken, but there is no right answer. This is a logistic issue rather than a scientific one. ■

A draft letter to patients explaining the shingles vaccine is available online at www.tinyurl.com/vaccineletter

Conflict of interest
Stewart Reid has received honoraria, and travel and accommodation from MSD for speaking to colleagues about shingles and Zostavax.

KEY POINTS

- Herpes zoster/shingles is caused by reactivation of varicella zoster virus, which, after chickenpox, becomes dormant in the cranial and dorsal root ganglia.
- Almost everyone, by age 40, has had chickenpox and is susceptible to shingles.
- Shingles is more likely and more severe with advancing age.
- Postherpetic neuralgia, with pain of 90 days or more, is the most common complication, and it can be very debilitating.
- The lifetime risk of shingles is one in three, and one in two for those who live to age 85.
- Treatment of shingles and postherpetic neuralgia is problematic. Antiviral treatment given early in the course of illness, analgesia (non-narcotic and narcotic, as appropriate) and, if needed, medications directed at neuropathic pain are used.
- Shingles vaccine, now available in New Zealand, provides approximately 60 per cent protection against the burden of disease caused by shingles.

Quiz answers

1. True. **2.** False. **3.** True.
4. False. **5.** True. **6.** True

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