



**The Immunisation
Advisory Centre**

Antigen Literature Review for the New
Zealand National Immunisation
Schedule, 2016:
Herpes zoster

Prepared as part of a Ministry of Health contract for services by
the Immunisation Advisory Centre
Department of General Practice and Primary Health Care,
The University of Auckland

This review is part of a series of antigen literature reviews commissioned by
the Ministry of Health to help inform the National Immunisation Programme.

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Executive summary

This review summarises selected literature published from January 2013 to November 2016 on the use of the live attenuated varicella-zoster virus vaccine for the prevention of herpes zoster in adults from 50 years of age.

Incidence and burden of disease

Herpes zoster (commonly known as shingles) is a condition that occurs when the ability to suppress latent varicella-zoster virus (VZV) is lost. The virus reactivates in the sensory nerve ganglia and infection travels along sensory nerves to the skin. The condition causes pain and a characteristic blistering rash, most commonly along one dermatome. The virus first enters the body as a varicella (chickenpox) infection and remains suppressed by the immune system often for years to decades.

It is well documented that the incidence of herpes zoster increases with age. Worldwide, the incidence of zoster across all age groups appears to be around 1-2 per 1000 person-years, increasing to 7-8 per 1000 person-years in those aged over 60 years and to over 10 per 1000 person-years in those aged 80 years or older. Zoster can lead to work absence (average duration 5.4 days) and a loss of productivity in around two-thirds of cases. The pain of zoster can be particularly debilitating for older people, at times resulting in a loss of independence.

Complications can lead to hospitalisation. In New Zealand (NZ) during 2015, 361 people were hospitalised with a primary diagnosis of zoster. The most common complications are pain related, such as long-lasting postherpetic neuralgia (PHN), and visual loss in patients with herpes zoster ophthalmicus, whereby viral reactivation occurs in the trigeminal cranial nerve. The rate of hospitalisation is around 2-25 per 100,000 person-years across all adult age groups. This rate increases significantly in adults aged 80 years or older.

Severe immunosuppression is a significant risk factor for zoster, notably in those with conditions or during treatments that affect cell-mediated immunity, including haematological malignancies such as lymphoma, symptomatic human immunodeficiency virus (HIV) infection, haematopoietic stem cell transplantation and treatment with high doses of corticosteroids or biological disease-modifying drugs. Antiviral treatment can reduce disease severity and reduce the incidence of PHN in these patients, including in those for whom the vaccine is contraindicated. There is some evidence that females have a greater risk of zoster and PHN than males. Immune-mediated inflammatory disease (IMIDs; autoimmune diseases) like rheumatoid arthritis, and depression and sleep disorders have also been associated with increased risk of zoster.

The risk of PHN is significantly increased in patients with prodromal pain, severe acute pain, severe rash and ophthalmic involvement. It also increases with increasing age. After adjusting for age, certain conditions are associated with increased risk of developing PHN after a zoster episode, including lymphoma, leukaemia, systemic lupus erythematosus (SLE) and chronic obstructive pulmonary disease (COPD), as well a recent trauma, personality disorders and diabetes.

Individuals who have had, or have, zoster have an increased risk of cerebrovascular disease and myocardial infarction, particularly in adults aged 40 years or younger at time of zoster incidence, and an increased risk of peripheral arterial disease. An increased risk of stroke has been observed in adults with autoimmune diseases immediately following zoster

episodes. Prompt antiviral treatment was found to reduce this risk in patients with rheumatoid arthritis.

Vaccines

The focus of this review is on the only licensed zoster vaccine currently available worldwide: Zostavax® contains live attenuated 'Oka' strain varicella-zoster virus. It was first licensed in 2006 in the United States (US) and the European Union (EU) for the prevention of zoster and PHN in adults from the age of 50 years.

Also presented is a summary of key phase III clinical trial data on an adjuvanted subunit vaccine (Shingrix™) that is in development and for which regulatory approval applications have been submitted in the US and EU. It has been specifically designed through new adjuvant technology to induced VZV-specific T cell immunity.

Safety

The safety data of live attenuated zoster vaccine are consistent between clinical trials and post-market settings. Outside of known contraindications, no serious adverse events have been associated with this vaccine. However, for those with undiagnosed cell-mediated immune deficiencies, there is a potential risk. No safety concerns were detected for use of the vaccine in the elderly or in certain patient groups, such as those receiving low-dose immunosuppression therapy and those who have had previous zoster episodes. The vaccine is well-tolerated when given concomitantly with inactivated influenza vaccine and pneumococcal polysaccharide vaccine.

There is some evidence of an increased risk of mild allergic reaction, and a slightly increased incidence of local inflammation, cellulitis and infection following zoster vaccination. The vaccine is contraindicated for individuals with known hypersensitivity to vaccine constituents, including gelatin and neomycin, or previous anaphylaxis following a VZV-containing vaccine. As with all vaccines, there is a small risk of anaphylaxis in those with previously undetected hypersensitivity to vaccine components.

A moderate increase in the incidence of zoster disease was suggested for patients receiving corticosteroids following zoster vaccination. It appears the zoster in these cases is due to reactivation of latent virus and not vaccine-associated. In view of low numbers, the historic recommendations to have a delay of four weeks between stopping treatment and vaccination for those on high-dose steroid treatment is still advised. Zoster vaccination in immunosuppressed patients has not been associated with disseminated VZV in patients receiving low doses of oral corticosteroids or non-biological DMARDs, but the vaccine continues to be contraindicated for severe immunosuppression. One case of fatal disseminated vaccine-type zoster was reported in an elderly man who had completed chemotherapy for chronic lymphocytic leukaemia six months prior to zoster vaccination.

The incidence of vaccine-strain zoster appears to be very low. Post-licensure, only one case was reported following administration of more than 16 million doses of vaccine, worldwide. It should be noted that the VZV strain in mild zoster cases is unlikely to be identified. Cases of zoster occurring after vaccination are highly likely to be as a result of reactivation of latent wild-type infection.

Immunogenicity

Cell-mediated immunity (CMI) to VZV is inversely correlated with the risk of developing zoster. Lower VZV-CMI responses are seen following zoster vaccination of those aged over 70 years than the 60-69 year age group. However, when zoster occurs in vaccinated individuals, a higher initial VZV-CMI response to the vaccine is associated with decreased

severity of zoster and lower risk of PHN. Although in older people vaccination does not sufficiently boost VZV immunity to prevent viral reactivation and zoster, it can be sufficient to reduce disease severity.

The effects of zoster vaccination on VZV-CMI were seen to persist for more than ten years and VZV-CMI is boosted by the second dose given to adults aged 70 years or over at least ten years after the first dose. The duration of protection and clinical benefit of a booster dose has not yet been determined.

Low-dose immunosuppression blunts the cellular immune response to zoster vaccine. However, studies suggest that this may not be a reason not to vaccinate those aged 60 years or older. As in the elderly, VZV immunity is boosted by zoster vaccination in these patients, and can provide protection against severe zoster and associated complications in at-risk groups, such as patients with SLE and inflammatory bowel disease (IBD).

Elderly adults with untreated depression are at increased risk of developing zoster and its complications, but respond less well to zoster vaccine than those who receive treatment for depression.

Simultaneous administration of zoster vaccine and pneumococcal polysaccharide vaccine (PPV-23) does not increase the risk of zoster in vaccine recipients. It is recommended, when needed, that both vaccines be given during the same medical visit to avoid missed opportunities to vaccinate.

Comparable VZV immunogenicity was observed when zoster vaccine was given intramuscularly or subcutaneously.

Effectiveness

Vaccine effectiveness of the live attenuated zoster vaccine has been shown in post-licensure studies to be around 50% in preventing zoster, and around 60% in preventing PHN and prodromal pain during the first 1-3 years following vaccination. However, this effectiveness in preventing zoster wanes markedly after 5 years following vaccination. Zoster vaccine helps to reduce the severity of zoster-related pain and the long-term pain complications associated with post herpetic neuralgia (PHN). The vaccine is most effective in preventing zoster the younger age groups (50-69 years). For the older age groups, it helps to prevent PHN and reduces burden on quality of life caused by zoster pain.

In high-risk groups, the effectiveness of zoster vaccine remains when chemotherapy is commenced at least 60 days after vaccination. The incidence of zoster in patients aged over 60 years with end-stage renal disease is halved by vaccination. The vaccine is shown to be most effective when administered within two years of dialysis initiation.

There have been few recent studies investigating the long-term benefit of zoster vaccination, because the vaccine was introduced relatively recently and coverage has been quite low in most countries. A booster dose, later in life may be necessary to continue to provide protection for vaccine recipients as they age and immunity wanes. However, the effectiveness or safety of this strategy is not yet understood. The duration of protection, against zoster incidence, severity and PHN, for both the primary and booster doses is also undefined. The effectiveness of booster doses have not been assessed clinically. Further data is expected over time as more countries introduce zoster immunisation programmes.

Policy implications

Countries that have introduced the vaccine on their schedule tend to do so for older adults, at either 65 or 70 years or age, in acknowledgement of the concerns of waning protection if the vaccine is given younger, and the greater health gains for the elderly. While, in general,

older individuals are at higher risk of zoster complications, certain groups or medical conditions are likely to be at higher risk of zoster disease than others and may benefit from zoster vaccination; these include mild to moderate immunosuppression, diabetes mellitus, untreated depression, very high or low body mass index, smokers or ex-smokers, sleep disorders or renal dialysis due to chronic kidney disease.

Live zoster vaccine is most effective in preventing zoster incidence in the younger age groups, however, the duration of protection may not extend to an age when recipients are likely to be at greatest risk of disease and a second dose may be required later in life.

As adults age, their risk of comorbidities increase, further increasing the risk of developing zoster complications. Therefore, despite limitations in the effectiveness and immune response to zoster vaccine in the elderly, universal vaccination is likely to provide the greatest benefit by reducing the debilitating symptoms of severe zoster, particularly in those with undiagnosed conditions causing insufficiency in VZV-CMI, such as depression.

International studies have shown that the burden of zoster is significant in the elderly. However, there is insufficient data to quantify this burden in New Zealand. Surveillance is also needed in the long term to assess any possible impact the introduction of varicella vaccination of children may have on the incidence of zoster in the future.

Adjuvanted subunit vaccine

According to data from the phase III zoster efficacy clinical trials, ZOE-50 and ZOE-70, the adjuvanted subunit zoster vaccine (HZ/su) significantly reduces the risk of zoster in older adults. Vaccine efficacy was shown to be 97% (95% CI 93-99) when administered as two doses given two months apart to adults aged 50 years or older. Efficacy in prevention of zoster incidence did not decline with age, as seen with the live attenuated zoster vaccine, and was 89% (84-94) in adults aged older than 70 years. The risk of PHN was also significantly reduced in adults aged 70 years or older with 89% (69-91) vaccine efficacy.

HZ/su showed significantly greater reactogenicity than placebo during clinical trials, predominantly following the second dose. Most reactions were mild-moderate in severity, although some vaccine recipients reported that symptoms affected daily activities (17% compared with 3% in the placebo group). However, there were no safety concerns and no serious adverse events were identified as being causally related to vaccine receipt.

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Acknowledgements

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Abbreviations

| | |
|---------------|---|
| ACIP | Advisory Committee on Immunization Practices |
| AE | Adverse event |
| AEFI | Adverse Events Following Immunisation |
| CDC | Center for Disease Control and Prevention |
| CI | Confidence interval |
| CMI | Cell-mediated immunity |
| COPD | Chronic obstructive pulmonary disease |
| DMARD | Disease-modifying anti-rheumatic drugs |
| ELISPOT | Enzyme-linked immune-spot |
| ESRD | End-stage renal disease |
| ESR | Institute for Environmental and Scientific Research |
| EU | European Union |
| α -gal | galactose-alpha-1,3-galactose |
| gE | Glycoprotein E |
| GMFR | Geometric mean fold rise |
| GMT | Geometric mean titre |
| gpELISA | glycoprotein enzyme-linked |
| GSK | GlaxoSmithKline Ltd |
| HR | Hazard ratio |
| HIV | Human immunodeficiency virus |
| HRQoL | Health-related quality of life |
| HSV | Herpes simplex virus |
| HZ | Herpes zoster |
| HZO | Herpes zoster ophthalmicus |

| | |
|---------------|---|
| HZ/su | Herpes zoster subunit vaccine. |
| IBD | Inflammatory bowel disease |
| IFN- γ | Interferon-gamma |
| IL-2 | Interleukin-2 |
| IM | Intramuscular |
| IMID | Immune-mediated inflammatory disease |
| IRR | Incidence risk ratio |
| KPSC | Kaiser Permanente Southern California |
| LTPS | Long Term Persistence Study |
| MSD | Merck Sharp & Dohme Ltd (Merck & Co in US and Canada) |
| NMDS | National Minimum Data Set |
| NZ | New Zealand |
| OR | Odds ratio |
| PAD | Peripheral arterial disease |
| PHN | Post herpetic neuralgia |
| PBMC | Peripheral blood mononuclear cell |
| PPV-23 | 23-valent pneumococcal polysaccharide |
| RCF | Responder cell frequency |
| RCT | Randomised control trial |
| RR | Relative risk |
| SAAE | Severe autoimmune adverse event |
| SAE | Serious adverse events |
| SAGE | Strategic Advisory Group of Experts on Immunization |
| SC | Subcutaneous |

| | |
|------------------|---|
| SLE | Systemic lupus erythematosus |
| SPS | Shingles Prevention Study |
| STPS | Short Term Persistence Study |
| TIA | Transient ischaemic attack |
| TNF- α | Tumour necrosis factor-alpha |
| TT | Tetanus toxoid |
| UK | United Kingdom |
| US | United States of America |
| VAERS | Vaccine Adverse Event Reporting System |
| VE | Vaccine effectiveness / efficacy |
| VSD | Vaccine Safety Datalink |
| VZV | Varicella-zoster virus |
| WHO | World Health Organization |
| ZEST | Zoster Efficacy and Safety Trial |
| ZOE-50 ZOE-70 | Zoster efficacy studies, from 50 years of age and from 70 years of age. |
| ZQOL | Zoster Quality Of Life study |

1 Background

Varicella-zoster virus (VZV) is a human alpha-herpesvirus most closely related to herpes simplex virus-1. It is a highly contagious pathogen that occurs worldwide and is exclusive to humans. The primary infection with VZV causes varicella disease (commonly known as chickenpox). It subsequently establishes life-long persistence in cranial and dorsal root sensory nerve ganglia: reactivation from latency produces the clinical condition referred to as herpes zoster (HZ, shingles).¹

Varicella-zoster virus used to derive varicella and zoster vaccines was first isolated in Japan and designated the Oka strain.²

VZV infection is followed by the production of VZV-specific antibody and VZV-specific T cell-mediated immunity. T cell immunity to VZV is more important than the antibody response, since VZV-specific T cell-mediated immunity maintains the suppression of latent VZV in sensory ganglia. The immune response is also boosted by subclinical reactivation of latent virus and potentially from environmental exposure to virus. As VZV-specific T cell-mediated immunity declines with age, or as a result of medications or chronic health issues that suppress immunity, suppression of latent virus is less well maintained.³

Herpes zoster is a manifestation of VZV reactivation. Zoster is frequently painful in all phases of the condition. About one third of the population experience zoster at least once in their life-time, with the incidence increasing after the age of 60 years as cell-mediated immunity declines. Recurrence is greater in females than males (about 7% after eight years compared with 4% of males). Up to half of the zoster cases over the age of 70 years develop postherpetic neuralgia (PHN) – PHN is defined as dermatomal distribution of pain that persists for more than three months after zoster rash clears.

This review evaluates the literature on vaccination against herpes zoster published from January 2013 to November 2016, since the previous review of this antigen in 2012.⁴ The focus of this review is on the VZV vaccines to protect against zoster. A separate review was conducted on varicella (chickenpox).

2 Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2016 New Zealand (NZ) antigen literature review and the specific specifications for zoster vaccines as listed below. The dates for eligible publications are between January 2013 and November 2016.

- General specifications
 - Safety
 - Effectiveness in disease control
 - Duration of protection
 - Implementation issues and impact of herpes zoster immunisation programmes
- Service specifications for herpes zoster vaccines
 - Different vaccine options for placement on the vaccine schedule, as described in the literature
 - Implications for burden of disease on health service
 - Consideration of international practice for timing of schedule and eligibility

This is neither a systematic review nor a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around the use of herpes zoster vaccines, but not varicella vaccines, for NZ.

The focus of this review will be on the currently licensed live attenuated zoster vaccine. However, clinical trial data for the adjuvanted subunit zoster vaccine will be reviewed briefly, since regulatory approval is being sought for this vaccine and it is expected to be licensed during 2017.

2.2 Literature search strategy

Medline search terms and strategy

MeSH term Herpes zoster vaccine; Limit to Humans, English, 2013 – current: 1022

NOT Cost and Cost analysis: 21

Cochrane Library search terms and strategy

MeSH term: Herpes zoster vaccine

Limit to Cochrane reviews, other reviews and trials, 2013-2016: 3 results (1 keep and view)

Scopus search terms and strategy

Herpes zoster vaccin* 2013-present: 879

Limit to: Medicine, articles, reviews, articles in press, conference papers: 470

Excluded: varicella-zoster vaccin* Limit to Human, English Medicine, articles, reviews, articles in press, conference papers: 182

Delete duplicates: 156

Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2013 and 2016. One abstract was accessed.

Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. All duplicates were removed from the final library.

Final Endnote library 238 articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

2.3 Participants/populations

The population of interest are adults over the age of 50 years and targeted with no contraindications.

High-risk persons that could particularly benefit from zoster vaccine identified from the literature include all adults aged over 50 years with:

- Low-dose immunosuppression e.g. rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease

- Renal dialysis
- Diabetes
- Aged over 70 years
- Major depressive disorder
- Chronic pain syndromes
- Pre- or post-chemotherapy
- Generally poor health (e.g. under or over weight, smoker or ex-smoker)
- Female

Individuals who are severely immunocompromised on highly immunosuppressive drugs, with haematological malignancies or HIV infection are also at high risk of developing zoster and PHN, but live zoster vaccine is contraindicated for these high-risk groups. Antiviral treatment is recommended to reduce the severity of zoster in people with these conditions.

2.4 Interventions

Zostavax®

Zostavax® is a live attenuated virus vaccine against VZV produced by Merck Sharp and Dohme (MSD) Ltd. Each 0.65mL dose of Zostavax® contains a minimum of 19,400 PFU (plaque forming units) of Oka/Merck varicella virus. Each dose also contains approximately 41.0mg of sucrose, 20.5mg of hydrolysed gelatin, 8.5mg of urea, 5.2mg of sodium chloride, 0.8mg of monosodium L-glutamate, 0.75mg of sodium phosphate dibasic, 0.13mg of potassium phosphate monobasic, 0.13mg of potassium chloride. The product also contains residual components of MRC-5 cells and trace quantities of neomycin and bovine calf serum from MRC-5 culture media. Zostavax® is the only currently available zoster vaccine worldwide.

Shingrix™

Shingrix™ (HZ/su) is an inactivated adjuvanted subunit zoster vaccine in late-stage development by GlaxoSmithKline (GSK) Ltd. It contains 50µg recombinant VZV glycoprotein E combined plus an AS01_B adjuvant system containing 50µg *Salmonella* lipid A (dMPL) and 50µg saponin (QS21). Licence approval applications were submitted in the US, Canada and Europe in October 2016 following two pivotal phase III trials (ZOE-50 and ZOE-70). Applications for approval in Japan are also anticipated in early 2017.⁵ It is not known if or when regulatory approval will be sought in New Zealand.

2.5 Study designs

The studies included in this review are meta-analysis, systematic reviews, reviews, randomised control trials, case-control studies, case reports and observational studies using database matching.

3 Epidemiology of zoster

3.1 New Zealand epidemiology

There is limited data on the burden of zoster globally. According to the New Zealand Ministry of Health in 2013, there were approximately 110 hospitalisations for herpes zoster in patients aged 70-79 years, compared with around 65 aged 50-59 years and fewer than 25 aged 40-49 years. Data from the National Minimum Data Set (NMDS) shows that there were 361 primary cases hospitalised in NZ during 2015, and more than double that when hospitalisations for any diagnosis were ICD-9 coded for zoster (053), as shown in Figure 1.

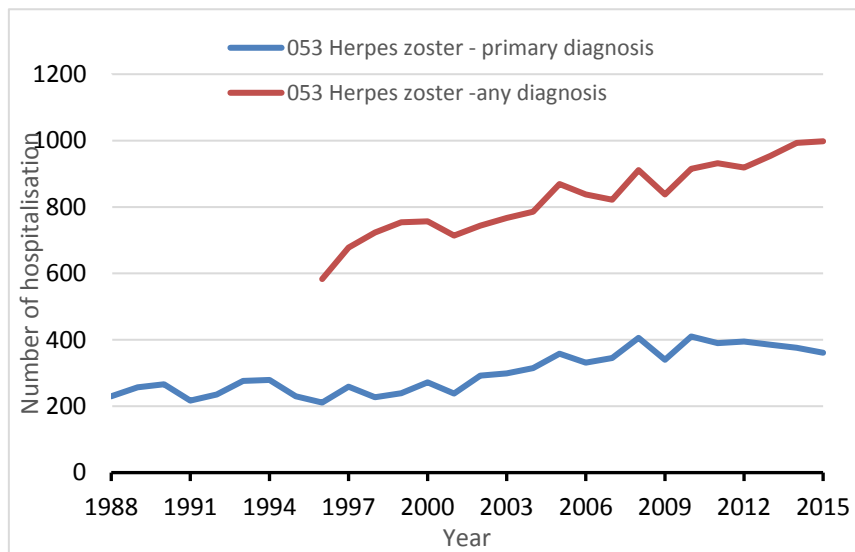


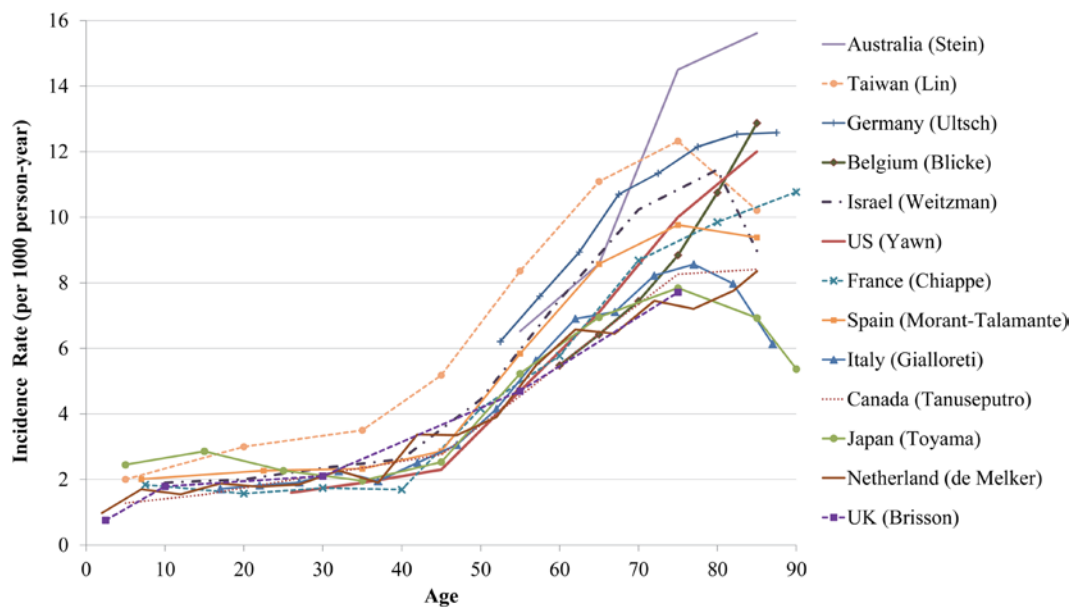
Figure 1: Annual Hospitalisations for Herpes Zoster in New Zealand, 1988-2015 (source: NMDS, Ministry of Health)

The incidence of zoster in general practice is poorly understood or recorded. A small retrospective study conducted over 5 years during 2009 to 2013 in a single general practice in the Wellington region (with a stable practice population of around 19,000 patients) found that the incidence of zoster was similar to that reported internationally, from 1-15/1000 per year increasing with age. A total of 287 cases were confirmed as having zoster and the overall rate of disease was 2.97/1000 patients per year. Of these, 203 (70.7%) were aged ≥ 51 years and of predominantly European ethnicity (92.6%), only six cases were Māori, two cases of Pacific ethnicity and seven cases were Asian. However, it should be noted that this spread also reflects the ethnicity of the patients enrolled in this practice (with 81% European, 6% Māori, 3% Pacific and 10% Asian) and does not represent NZ as a whole. Incidence increased with age: for those aged ≤ 50 years, incidence rate was 1.33 per 1000 per year, aged ≥ 51 years rate was 6.1 and for age >60 years the rate was 8.1. Females were more frequently affected than males. The rate in women aged >50 years was approximately 10% higher than that seen in the men of the same age; for women in the 61-70 year age group, the incidence rate was 7.23 vs 5.25 per 1000/year for men. The highest rates were seen in the >80 years age groups – female 12.96/1000/year, male 14.78/1000/year. The cumulative risk of zoster over a 30 year period from age 51 to 80 years was approximately 18%. No statistical analysis was reported.⁶

3.2 International epidemiology

A systematic review was conducted by Kawai et al to review the global burden of herpes zoster. Although there was a scarcity of data from other regions, similar age-specific incidence was found in North America, Europe and Asia-Pacific as shown in Figure 2. The incidence rate ranged between 3-5/1000 person-years and the risk of recurrence of zoster ranged from 1% to 5-6% in long-term follow-up studies. The review reported that several studies have shown an increase in zoster incidence over time, since before the introduction of varicella vaccination programmes.⁷

Figure 2: Age-specific incidence rate of herpes zoster in North America, Europe and Asia-Pacific (open access source Kawai et al. 2014)



A systematic review of zoster in European countries found the incidence in the under 50 year-old age groups was steady at around 1-2/1000 person years and this increased dramatically in the over 50 year-olds to 7-8/1000 person-years and in the over 80 year-olds to >10/1,000 person-years.⁸

Based on the number of antiviral drug prescriptions from inpatient care, outpatient primary and specialised care data, the incidence of zoster and PHN in Sweden was estimated to be 315/100,000 across all ages and 577/100,000 for those age ≥ 50 years during 2011; mortality was 0.12/100,000 (11 cases).⁹

3.3 Burden of zoster

A cross-sectional study in the UK was conducted to quantify the burden of acute zoster presentation on the quality of life in 229 patients with zoster aged ≥ 50 years and compared with age-matched controls. The Zoster Quality of Life (ZQOL) study found that pain was prominent, and 57.9% of patients with zoster reported pain (as measured by Zoster Brief Pain Inventory score) in the preceding 24 hours at levels considered to have a significant impact on Health-Related Quality of Life score (HRQoL). The impact on HRQoL score was greater as pain levels increased. No association was seen between acute pain severity and age. In this study, 20.1% of patients reported experiencing a recurrent episode of zoster; for the remaining 79.9%, this was their first episode of zoster. Of the 63/229 patients who were working, 39 reported that their work was affected by zoster and 32 of these required

to take time off work for an average of 5.4 days (range 0-28 days). Across all the zoster patients, the mean number of days for which they were unable to take part in their usual activities was 3.9 days (range 0-21). Clinician reports showed that zoster patients were taking an average of four medications to manage zoster (3.89, standard deviation 1.01), 88.2% were prescribed antivirals and many were prescribed analgesia (71.2% prescription and 41.9% non-prescription analgesia).¹⁰

3.3.1 Age-related burden

As highlighted above, age plays a significant role in the incidence of zoster. The negative impact of zoster is associated with functional decline in the elderly. As reviewed, multiple factors interplay in the impact zoster has on the elderly. Higher mortality rates and longer hospital stays have been observed following an episode of zoster in patients with underlying disease, such as diabetes, cardiovascular, renal or respiratory disease and nervous disorders. Older patients with malignancies (haematological or solid tumours) are at increased risk of zoster, often due to immunosuppressive therapies. The pain associated with zoster influences medications and drug interactions with already prescribed drugs (polypharmacy), resulting in mood and sleep disturbance increasing the risk of poor social and cognitive function as well as depression, a loss of physical function and increased fall risk, and a combination of all of these. Depression is also associated with poor treatment adherence and functional decline. These factors can lead to a loss of coping strategies, autonomy and independence.¹¹

3.4 Complications of zoster

3.4.1 Postherpetic neuralgia

The systematic review conducted by Kawai et al found that the risk of PHN varied from 5% to over 30% (depending on study design and age of study population). More than 30% of patients with PHN experienced persistent pain for longer than one year.⁷

A systematic review and meta-analysis conducted by Forbes et al in 2015 found that certain clinical features of acute zoster were associated with significant increases in the risk of PHN – prodromal pain (summary rate ratio of 2.29; 95% confidence interval [CI] 1.42-3.69), severe acute pain (rate ratio 2.23, 1.71-2.92), severe rash (2.63, 1.89-3.66; defined in some studies by extent of rash e.g. >75% of dermatome covered) and ophthalmic involvement (2.51, 1.29-4.86). Out of nearly 120,000 patients diagnosed with zoster, 5.8% developed PHN.¹²

This systemic review also considered risk factors. Single studies have found association between PHN and systemic lupus erythematosus, recent trauma and personality disorder symptoms. The risk of PHN was slightly reduced the longer the time from rash onset to presentation in primary care and diagnosis (rate ratio 0.93, 95% CI 0.86-0.99). The systematic review found that there was conflicting evidence that gender was a risk factor. Severe immunosuppression was significantly associated with increased risk of PHN (in three out of five studies), including leukaemia and lymphoma (13.7%, odds ratio [OR] 2.07 and 12.7%, OR 2.45, respectively), immune-mediated inflammatory disease (IMID; autoimmune conditions) such as rheumatoid arthritis (9.1% OR 1.2) and comorbidities such as asthma and diabetes (one out of four studies). For those with severe immunosuppression, PHN risk was less pronounced in patients given antivirals to treat zoster. No evidence was found for higher PHN risk in patients with depression or cancer.¹²

To further investigate the risk factors for PHN, Forbes et al. conducted a cohort study using primary data from the Clinical Practice Research Datalink in the UK. The study included

119,413 eligible zoster cases. It found that the risk of PHN increased with age, particularly from 50 to 79 years (adjusted OR for a 10 year increase was 1.70; 99% CI 1.63-1.78). The risk was found to be higher in women than men (6.3% vs 5.1%; OR 1.19, 1.10-1.27). Severe immunosuppression, due to disease or therapies, was a strong risk factor for PHN. Chronic obstructive pulmonary disease (COPD) increased the risk of PHN by 53% and recent depression increased the risk by 40%. When adjusted for immunosuppressive therapies, age and other comorbidities. COPD, diabetes, current smoker or being obese had a slightly stronger effect in patients age <70 years; asthma, chronic kidney disease, diabetes and being under or over weight had an effect in those <60 years. IMIDs, particularly SLE were associated with increased risk of PHN. Data is summarised in Table 1.¹³

Table 1: Examples of adjusted associations between PHN and health risk factors (adapted from Forbes et al 2016)

| Comorbidity | Number of zoster cases with PHN (%) | Age-adjusted Odds Ratio [99% CI] |
|---|-------------------------------------|----------------------------------|
| Severe immunosuppression | | |
| Leukaemia | 21 (13.7) | 2.32 (1.25-4.33) |
| Oral corticosteroids (high-dose) | 53 (14.5) | 2.55 (1.71-3.78) |
| Immune-mediated inflammatory disease | | |
| Rheumatoid arthritis | 225 (9.1) | 1.27 (1.06-1.54) |
| SLE | 29 (9.4) | 1.95 (1.16-3.27) |
| Other conditions | | |
| COPD | 669 (13.2) | 1.66 (1.48-1.86) |
| Chronic kidney disease | 635 (10.6) | 1.17 (1.04-1.32) |
| Depression | 380 (7.0) | 1.39 (1.20-1.62) |
| Diabetes | 789 (9.3) | 1.26 (1.13-1.40) |
| Health behaviour | | |
| Current smoker | 1646 (5.4) | 1.32 (1.15-1.39) |
| Ex-smoker | 2946 (7.1) | 1.21 (1.12-1.30) |
| Underweight (BMI<18.5) | 188 (8.7) | 1.38 (1.12-1.70) |
| Obese (BMI>30) | 1560 (6.4) | 1.05 (0.98-1.12) |

3.4.2 Other complications

3.4.2.1 Vascular disease

A retrospective cohort study in the UK found that risk factors for cerebrovascular disease (stroke and transient ischaemic attack [TIA]) and myocardial infarction (MI) in patients with acute zoster were significantly increased compared with matched controls (total zoster case cohort n=106,601 and controls n=213,202). Over a follow-up period of 1-23.7 years (median 6.3), adjusted hazard ratios for TIA and MI were significantly increased in all patients with zoster, but not for stroke (hazard ratio [HR] 1.15 [95% CI 1.09-1.21; p<0.05], 1.10 [1.05-1.16; p<0.05] and 1.02 [0.98-1.07], respectively). Where zoster occurred in cases aged 18-40 years, the risk of TIA, MI and stroke were all increased

(adjusted HR TIA= 2.42 [1.34-4.36], MI=1.49 [1.04-2.15] and stroke = 1.74 [1.13-2.66]; $p < 0.05$ for each). Hazard ratios were adjusted for sex, age, obesity and medical history (cholesterol, diabetes, heart disease). The authors suggested screening for vascular risk factors in patients presenting with zoster, especially younger patients.¹⁴

In a US-based retrospective cohort study, Medicare data (2006-2013) was used to identify patients with IMIDs (ankylosing spondylitis, IBD, psoriasis, psoriatic arthritis and rheumatoid arthritis). The final cohort consisted of 43,527 patients. The study found that the incidence risk ratio (IRR) of stroke within the first 90 days following zoster episode was 1.36 (95% CI 1.10-1.68) compared with stroke more than a year after a zoster episode. The risk was greater for patients with zoster complications involving the cranial nerves (IRR 2.08, 0.99-4.36; incidence rate 2.29 [1.43-3.69] per 100 patient-years within 0-90 days versus 1.37 [0.94-2.0] in 366-730 day window; $n=3,080$). When prompt antiviral therapy was given the incidence of stroke following zoster was decreased (IRR 0.83, 0.70-0.98).¹⁵

The risk of peripheral arterial disease (PAD) was investigated in 35,391 patients newly diagnosed with zoster during 2000-2010 on the Taiwan National Health Insurance Research Database and compared with 141,556 matched controls. Baseline comorbidities (obesity, hyperlipidaemia, hypertension, heart failure, diabetes, COPD and asthma) were significantly more prevalent in patients with zoster than controls ($p < 0.05$). However, after adjustment for age, sex and comorbidities, the risk of PAD in patients with zoster was 13% higher than controls (incidence density rate of PAD were 4.64 versus 3.81 per 1000 person years, respectively; adjusted HR 1.13 [95% CI 1.09-1.16]; $p < 0.001$).¹⁶

3.4.2.2 Herpes zoster ophthalmicus

Herpes zoster ophthalmicus (HZO) with or without eye involvement is a complication that occurs when VZV reactivation affects the ophthalmic branch of the trigeminal nerve. In several studies, reviewed by Kawai et al, the overall incidence of HZO corresponded to around 10% of zoster patients and was similar across age groups. A range of eye complications can occur, including keratitis, uveitis and conjunctivitis, the risk for which ranged from 30-78% in patients with HZO. In a US population-based study, 2.5% of patients with zoster had eye involvement.^{7, 17}

A retrospective medical record review of 90 patients with a clinical diagnosis of HZO found that patients with ocular hypertension and uveitis were at increased risk of recurrent and chronic zoster (OR 6.7; 95% CI 1.5-31.2; and 6.74; 1.46-31.16, respectively); when adjusting for gender and age, only ocular hypertension remained with a significant risk factor for recurrent and chronic disease. Patients were followed up for a mean of 3.9 ± 5.9 years (range 0-33) and 82% were not vaccinated during follow up.¹⁸

3.4.3 Hospitalisations and mortality

In the systematic review conducted by Kawai et al, 28 studies were identified that reported zoster-associated hospitalisation. The rates of hospitalisations related to zoster ranged from 2 to 25/100,000 person-years across all age groups. One US-based study reported medical record confirmed zoster-associated hospitalisations to range from 10/100,000 in adults age 60-69 years to 65/100,000 in those age > 85 years. In Australia, rate of hospitalisations for zoster (primary diagnosis) ranged from 13 to 96/100,000 in adults age 60-69 years and ≥ 80 years, respectively. The review found that mortality rates associated with zoster ranged from 0.017-0.465/100,00 person-years, the majority of deaths occurred in adults aged ≥ 60 years.⁷

A systematic review was conducted by Bricout et al to assess mortality associated with hospitalisation for zoster in Europe. It found that, although data were sparse, there was a

clear association between mortality and increasing age, particularly from the age of 70-74 years in those with underlying disease and with increased risk of functional decline and loss of independence, if hospitalised. Zoster case-fatality rate was estimated to be around 2/100,000 in those aged 45-65 years and 61/100,000 in those age ≥ 65 years, in the UK. The available data were too heterogeneous for comparisons between countries.¹⁹

3.5 Additional risk factors for zoster

3.5.1 Rheumatoid arthritis

A systematic review and meta-analysis, found that the pooled risk of zoster reactivation was significantly increased, to up to 61%, in patients with rheumatoid arthritis when receiving tumour necrosis factor-alpha (TNF) blockers. In the British Society for Rheumatology Biologics Register, 320 cases of zoster were reported. Of these, there were 257 cases/11,881 patients on TNF blockers and 45 cases/3673 on conventional DMARDs (disease-modifying anti-rheumatic drugs). In a US registry study, 266 zoster cases/24,384 patients who received TNF blockers and 90/11,828 on DMARDs were identified. The German rheumatology registry, RABBIT, reported 86 cases of zoster, 62/3266 treated with TNF blockers and 21/1774 treated with DMARDs. The absolute risk of developing zoster was 1.19 per 100 person-years in TNF-blocker group and 0.93 per 100 person-years in conventional DMARD group. Infliximab was more implicated than other TNF blockers.²⁰

3.5.2 Sleep disorders

A population-based cohort study was conducted in Taiwan to investigate the incidence and risk of zoster in 64,548 patients with diagnosed sleep disorders using the national Longitudinal Health Insurance Database 2000 claims data. Patients with sleep disorders had a higher incidence of zoster when compared with controls (5.84 vs 4.72 /1000 person-years), across all age, sex and comorbidity groups. No significant difference was observed between men and women. Zoster incidence was higher in patients with sleep disorders and comorbidities than those without comorbidities (cancer, diabetes or autoimmune disease). Cancer and autoimmune disease were independent risk factors for increased zoster incidence (adjusted HR: sleep disorder 1.125 (1.18-1.32); cancer 1.89 [95% CI 1.56-2.30]; cancer + sleep disorder 1.79 (1.52-2.12); autoimmune 1.71 (1.36-2.4); autoimmune + sleep disorder 1.97 (1.57-2.47); $p < 0.001$ for each).²¹

3.5.3 Type-2 diabetes mellitus

A retrospective matched cohort study, using the Integrated Healthcare Information Services database in the US from January 1997 to May 2006 (prior to the introduction of the zoster vaccine in the US) found that type-2 diabetes, but not type-1 diabetes, was associated with an increased risk of zoster ($p < 0.0001$, adjusted for age). The hazard ratio of zoster was 3.12 (95% CI 2.77-3.52) in adults aged ≥ 65 years and 1.51 (1.42-1.61) aged 40-64 years with type-2 diabetes, when adjusted for gender and comorbidities. The hazard ratio for type-1 diabetes across age groups ranged between 0.70-1.94. The study also found that multiple comorbidities further elevated risk (such as COPD or coronary heart disease plus type-2 diabetes); however, the risk was not additive and the total risk was less than the sum of the risk of each single comorbidity.²²

Other conditions that have been associated with increased risk for zoster in the literature, include traumatic brain injury (incidence of zoster nearly three times more than general population) and balanitis (1.54-fold increased risk) in men.^{23, 24}

3.6 Summary of epidemiology and burden of disease

It is well documented that the incidence of zoster increases with age. Worldwide, the incidence of zoster appears to be around 1-2/1000 person-years across all age groups, increasing to 7-8/1000 person-years in those over 60 years and >10/1000 in those aged over 80 years. Zoster can lead to work absences (average duration 5.4 days) and a loss of productivity in 2 out of 3 people affected. The pain of zoster can be particularly debilitating for older people, at times resulting in a loss of independence.

Complications can lead to hospitalisation. In New Zealand, 361 people were hospitalised in 2015 with a primary diagnosis of zoster (approximate rate 7.8/100,000 population). The most common complications are pain related, such as PHN, and HZO with eye involvement. A systematic review found the rate of hospitalisation was found to be around 2-25/100,000 person-years in all adult age groups. This rate increases significantly in adults aged ≥ 80 years. Since these data were based on ICD-10 coding, no further details of duration of hospital stays or follow-up were presented.

Severe immunosuppression is a significant risk factor in developing zoster, particularly in conditions or during treatments that affect cell-mediated immunity, such as haematological malignancies, HIV infection, haematopoietic stem cell transplantation and high doses of corticosteroids or biological DMARDs. Antiviral treatment can reduce disease severity and reduce the incidence of PHN in these patients, including those in whom the vaccine is contraindicated. There is some suggestion that females have a greater risk of zoster and PHN than males. Rheumatoid arthritis, sleep disorders and type-2 diabetes have also been associated with increased risk of zoster.

The risk of PHN was shown to be significantly increased in patients with prodromal pain, severe acute pain, severe rash and ophthalmic involvement. The risk also increased with increasing age. After adjusting for age, certain conditions were associated with increased risk of developing PHN after a zoster episode, including lymphoma, leukaemia, SLE and COPD.

Individuals who have had, or have zoster have an increased risk of cerebrovascular disease and myocardial infarction, particularly in adults who were aged ≤ 40 years at time of zoster incidence, and an increased the risk of peripheral arterial disease. One study found that the incidence of stroke following zoster could be reduced by prompt antiviral treatment in patients with rheumatoid arthritis.

4 Safety of live attenuated vaccine

4.1 Background

The live attenuated herpes zoster vaccine, Zostavax[®], was first approved in 2006 for the prevention of herpes zoster and PHN in the EU and the US, and in NZ in 2012. The dose of live attenuated VZV contained within this vaccine is much higher than that within the varicella vaccine, and is therefore contraindicated in those with severe immunosuppression.

In this section the most recent safety data for currently licensed live zoster vaccine is reviewed including literature published between January 2013 and November 2016. Only adverse events following immunisation (AEFI) that have been published subsequent to the pivotal clinical efficacy trials are reviewed.

4.2 Review

Post-licensure 'real-world' studies, as reviewed by Ansaldi et al, have found the safety of live zoster vaccine to be generally consistent with pivotal clinical trials and no new safety concerns were detected in both the general populations and certain patient groups with immune compromise. No increased risk for cerebrovascular, cardiovascular or neurological adverse events were found in a study using Vaccine Safety Datalink (VSD) project data in the US. A large cohort study consisting of around 29,000 vaccinated adults aged ≥ 60 years enrolled through Kaiser Permanente North California did not identify any long or short-term safety issues.²⁵

Post-marketing study findings were shown to support the findings of earlier clinical trials and confirmed that zoster vaccine is generally safe and well tolerated in adults aged ≥ 50 and ≥ 60 years. Another review highlighted one study that used VSD data from 193,083 vaccinated adults aged ≥ 50 years which showed that vaccine recipients had a significantly higher risk of an allergic reaction (urticaria or pruritus) up to 7 days post-vaccination. In this study, no cases of anaphylaxis were found to be associated with vaccination. Using a case-centre approach, the relative risk of allergy was 2.13 (95% CI 1.87-2.40) and with a self-controlled case series risk was 2.32 (1.85-2.91) following zoster vaccination. An increased risk of injection site cellulitis and infection was also observed with by case-centred approach, but not in the self-controlled case series (RR 2.13, 1.18-1.44) - this finding was consistent with the SPS clinical trial.^{26, 27}

4.3 Immunocompetent vaccine recipients

4.3.1 Prior episodes of zoster

To assess the safety of the zoster vaccine in elderly adults with a history of zoster, a follow-up study was conducted from the pivotal Shingles Prevention Study (SPS), in which zoster vaccination was offered to study participants who had previously received placebo. In the original SPS study, prior zoster episodes were a contraindication to participation. A total of 13,681 participants from the SPS placebo group, including 420 who had developed documented zoster episodes during the SPS study, were monitored for SAE 28 days after zoster vaccination. The mean time interval between prior zoster episode and zoster vaccine receipt was 3.61 years (range 3-85 months; < 5 years for 80% of participants). There was no significant difference in severe adverse events (SAEs) between those with prior zoster episodes or those without (0.95% vs 0.66%; mean age 74.2 years). None of the SAEs were considered vaccine related. No unsolicited reports of serious or unexpected injection site reactions were reported during telephone interviews on day 29 post-vaccination.²⁸

4.3.2 Subcutaneous versus intramuscular administration

An open label, randomised trial compared the safety of subcutaneous (SC) and intramuscular (IM) administration of zoster vaccine in 354 participants aged ≥ 50 years. Both routes of administration were well tolerate and the frequency of systemic adverse events (AE) were comparable between groups. Injection site reactions were less frequent with IM than SC injections (erythema= 15.9% vs 52.5%; pain = 25.6% vs 39.5%; swelling = 13.6% vs 37.3%, respectively).²⁹

4.3.3 Two-dose schedule

A multicentre randomised study funded by Sanofi Pasteur investigated the safety of two doses of zoster vaccine in adults aged ≥ 70 years. Participants were randomised to receive zoster vaccine in one of three schedules: a single dose, two doses at 0 and 1 month or two

doses at 0 and 3 months. Adverse event incidence did not significantly increase following either of the two-dose schedules when compared with a single dose. After the first dose, systemic AEs were reported in 28% of recipients and vaccine-related AEs were reported for 6.4% of participants, most commonly, headache (2.3% of participants); the frequency of reported severe intensity AEs was very low (0.9% for each of headache, pain, rash or pruritus). The incidence of systemic AE following a second dose was lower than after the first dose (20.7% for 1-month and 15.4% for 3-month regimes). Between screening, and 12 months after the last vaccine dose, 19 participants reported SAEs, none of which were considered by the investigator to be vaccine-related. VZV associated rashes were observed in 10 participants (zoster, zoster-like, varicella, varicella-like) – of those tested, none contained vaccine-type virus.³⁰

4.3.4 Concomitant use

Concomitant administration of zoster vaccine was generally safe and well tolerated when given with influenza vaccine and pneumococcal polysaccharide vaccine. No vaccine-related SAEs were reported.³¹

4.3.5 Diabetes

In a Japanese pilot study conducted, no systemic adverse reactions were reported via questionnaires up to 42 days following zoster vaccination of patients with diabetes mellitus or healthy volunteers aged 60-70 years. One patient in each group reported local pruritus.³²

4.3.6 Severe autoimmune adverse events

A matched case-control study of events reported to the US Vaccine Adverse Event Reporting System (VAERS) identified a total of 18,534 adverse events following zoster vaccination from May 2006 - November 2014, including 102 severe autoimmune adverse events (SAAE). The study showed a statistically significant increase in odds of alopecia and arthritis in individuals who received zoster vaccine compared with gender and age-matched controls who received tetanus-toxoid (TT) containing vaccine: odds ratio 2.2 (95% CI 1.2-4.3; $p < 0.015$) and 2.7 (1.7-4.3; $p < 0.001$), respectively. However, it should be noted that the number of cases reported were very low – for alopecia, 13 cases and 40 controls were vaccine exposed (HZ or TT-containing vaccine, respectively); and for arthritis, 42 cases received zoster vaccinated compared with 61 vaccine-exposed controls. The median time to onset of symptoms after vaccination was 4 days for both. No significantly increased risk of exacerbation or induction of other severe autoimmune diseases was found after zoster vaccination, including Guillain-Barré Syndrome, multiple sclerosis and optic neuritis, systemic lupus erythematosus, thrombocytopenia and vasculitis. Overall, the study concluded that, although there were reports of SAAE following zoster vaccination in the VAERS database, these rare events did not occur more frequently than after other vaccines.³³

4.3.7 Vaccine-strain zoster

A case study reported a case of vaccine-strain zoster in a 68 year-old immunocompetent adult occurring 9 months after zoster vaccination. The case was relatively mild with no complications. The investigators were unable to conclude whether the patient had had prior wild-type VZV infection, but assumed it to be very likely. This appears to be a very rare event: out of more than 16 million doses of zoster vaccine (as at the time of this case-study), this is the only case of vaccine (Oka strain) VZV reported. During two clinical trials (including SPS), out of 634 zoster vaccine recipients who had zoster and were tested for VZV-type, there was only one case in which vaccine-strain VZV was detected (0.16% [95% CI 0- 0.47%]).³⁴

4.3.8 Allergic reaction

A case of anaphylaxis occurred within minutes following receipt of zoster vaccine in a pharmacy in the US. The patient had a history of food allergies and IgE antibodies to galactose-alpha-1,3-galactose (α -gal), beef, lamb, pork and porcine gelatin. When a VAERS search was conducted, 5 of 14 potential anaphylaxis cases reported following zoster vaccination had known beef, pork, gelatin or α -gal allergy. Zoster vaccine was shown to have a high α -gal content.³⁵ In another study, zoster vaccine was safely administered to a patient with known α -gal allergy, however, the researchers advised continued safety assessment when administering zoster vaccine and other gelatin-containing vaccines to patients with allergy to red meat, gelatin or α -gal.³⁶ The incidence of red meat allergy is higher in South-eastern US than elsewhere and it has been causally associated to lone-star tick bites.³⁵ Zoster vaccine is contraindicated for anyone who has a history of gelatin hypersensitivity.³⁷

4.4 Immunocompromised individuals

A randomised control trial (RCT) assessed the safety of zoster vaccine in 206 patients aged ≥ 60 years receiving chronic/maintenance systemic corticosteroid therapy (equivalent of 5-20 mg prednisone daily) for up to 2 weeks prior to and 6 weeks after vaccination and compared with 100 placebo controls. A higher percentage of vaccine recipients reported injection site AEs than controls (21.5% vs 12.1%; risk difference 9.4%; 95% CI -0.1 to 17.6). The only SAE to be considered by the study investigator to be vaccine-related was a case of HZO in a vaccine-recipient (onset day 16); it was later determined to be caused by wild-type VZV not vaccine-strain VZV.³⁸

The risks associated with giving zoster vaccine to patients taking immunosuppressives, including oral corticosteroids, non-biological DMARDs and oral anti-rejection drugs, were assessed in a retrospective study using VSD data during 2006 to 2009. A total of 14,554 patients were identified as having been dispensed immunosuppressive medication from a year before and up to 5 days after vaccination (4826 current-use and 9728 with remote-use whereby medication was stopped >30 days prior to vaccination). The most commonly dispensed medication was low-dose steroids (82.7% of all patients) i.e. <20 mg/day prednisone for <14 days. Of the current-use patients, 550 (13.6%) were taking high-dose steroids (≥ 20 mg prednisone/day). During the 42 days post-zoster vaccination, no cases of disseminated VZV were identified. In the current-use group, there were 25 cases of zoster and 17 cases in the remote-use group within 42 days of vaccination – unadjusted incidence rate was 45 per 1000 person-years (95% CI 30.4-66.7) and 15/1000 person years (9.6-24.6), respectively; OR for current vs remote-use 2.97 (1.16-5.51). These data suggested a modest increase in the risk of zoster in the patients currently taking immunosuppressives compared with the remote-use cases. This increase in zoster was attributed to reactivation of latent VZV rather than dissemination of vaccine-type virus and may reflect the increased risk of zoster in patients taking steroids. It was subsequently noted that for patients on low-dose steroids, vaccination without delay in treatment is unlikely to increase the risk of disseminated disease. However, since the number of patients on high-dose steroids in this study was too low to determine the risk of disseminated disease, the investigators supported recommendations to withhold immunosuppressive drugs for 4 weeks prior to zoster vaccination in these patients.^{39, 40} It should be noted injected or infused immunosuppressive drugs were not captured by the VSD pharmacy dispensing data.

4.4.1 Inflammatory bowel disease

A US-based prospective study found no difference in AEs or any SAEs to zoster vaccination between two groups of patients with inflammatory bowel disease (IBD): one group were receiving low-dose immunosuppressive therapy and the other were non-immunosuppressed on either on 5-aminosalicylic acid or no IBD therapy.⁴¹

4.4.2 Chronic lymphocytic leukaemia

Cases of disseminated varicella have been reported in adults who have received varicella vaccine following severe immunocompromise, however, cases are rarely reported in adults who had received zoster vaccine. One case of fatal disseminated vaccine-strain VZV infection was reported of a 79 year old man with chronic lymphocytic leukaemia, who had not received immunosuppressive treatment for 6 months. Two weeks after receiving zoster vaccine, he developed flu-like symptoms and was treated with intravenous aciclovir and other antimicrobial medications. He presented with fever and widespread vesicular rash one month following vaccination and died from multi-organ failure due to disseminated vaccine-strain VZV infection 25 days later.⁴²

4.5 Summary of safety

The safety data of live attenuated zoster vaccine are consistent between clinical trials and post-market settings. Outside of known contraindications, no serious adverse events have been identified that are associated with this vaccine. However, for those with undiagnosed allergy or undiagnosed cell-mediated immunity deficiencies, there is a potential risk of SAEs. No safety concerns were detected for use of the vaccine in the immunocompetent elderly or in certain patient-groups, such as those receiving low-dose immunosuppression therapy and those who have had previous zoster episodes. The vaccine was well-tolerated when given concomitantly with influenza vaccine and pneumococcal polysaccharide vaccine.

There was some evidence of an increased risk of mild allergic reaction post-vaccination, and a slightly increased incidence of cellulitis and infection at the injection site. The vaccine is contraindicated for individuals with known hypersensitivity to vaccine constituents, including gelatin and neomycin.

A moderate increase in the incidence of zoster disease was suggested for patients receiving corticosteroids. It appears that zoster in these cases was due to reactivation of latent virus and not vaccine-associated. In view of low numbers, the historic recommendations to have a delay of 4 weeks between stopping treatment and vaccination for those on high-dose steroids is still advised. Zoster vaccination has not been associated with disseminated VZV in immunosuppressed patients receiving oral corticosteroids or non-biological DMARDs.

One case of fatal disseminated vaccine-type zoster was reported in an elderly man who was immunocompromised by chronic lymphocytic leukaemia.

The incidence of vaccine-strain zoster appears to be very low. Only one case has been reported following administration of more than 16 million doses of vaccine. It should be noted however that the VZV strain in mild zoster cases is unlikely to be identified. Cases of zoster occurring after vaccination are highly likely to be as a result of reactivation of latent wild-type infection.

5 Immunogenicity of live attenuated vaccine

5.1 Background

To maintain suppression of latent VZV, cell-mediated immunity is required. Zoster vaccine contains live attenuate virus at greater concentrations than found in the varicella vaccine and is designed to boost cell-mediated immunity (CMI), which declines with age, to help to prevent symptomatic reactivation of latent VZV resulting in zoster (shingles). In the oldest adults, the vaccine may not sufficiently boost the cell-mediated response against VZV to maintain suppression of latent virus, but could provide sufficient boost in VZV-specific immunity to enable the rapid mobilisation of the immune response to attenuate disease severity.⁴³

Protection provided by the zoster vaccine cannot be directly attributed to the presence of anti-VZV antibodies as VZV-specific CMI is necessary for the prevention of zoster.

Generally, to measure IgG antibody titres against VZV glycoprotein an enzyme-linked immunosorbent assay (gp-ELISA) is used. As markers for VZV-CMI response, the production of interferon-gamma (IFN- γ) and interleukin 2 (IL-2) cytokines by activated T cells are measured by enzyme-linked immune-spot (ELISPOT) assays.

The objective of this section is to review the most recent immunogenicity data for the currently licensed zoster vaccine. A summary of the results from studies and reviews on the immunogenicity of zoster vaccine in target age groups and groups for special consideration are presented.

5.2 Review

An immunogenicity substudy of the pivotal Shingles Prevention Study (SPS) clinical trial, found that a single dose of zoster vaccine given to adults aged ≥ 60 years was immunogenic. Significantly higher values in responder cell frequency (RCF), IFN- γ and VZV-gp antibody geometric mean titres (GMT) were detected in vaccine recipients than placebo controls at 6 weeks post-vaccination ($p \leq 0.001$). The immune response decreased during the first year, but remained over 3 years of follow-up. Lower VZV-specific CMI responses were seen at 6 weeks post-vaccination in vaccine recipients aged ≥ 70 years than those aged 60-69 years ($p < 0.001$), and the VZV-CMI response was inversely correlated with the risk of developing zoster. Where zoster occurred, a higher initial VZV-CMI response was associated with decreased severity of zoster and lower risk of PHN.²⁶

5.2.1 Subcutaneous and intramuscular administration

An open label, randomised trial compared the immunogenicity of IM and SC administration of zoster vaccine in 354 participants aged ≥ 50 years (mean age 62.6 years, range 50.0-90.5). SC administration is mainly conducted in the US, where much of the vaccine clinical development took place, whereas in Europe, IM administration is preferred. Immunogenicity between the two groups was comparable in terms of VZV immune response: IFN- γ ELISPOT geometric mean-fold rise of 3.3 (GMFR; 95% CI 2.8-3.9) and 3.4 (2.7-4.3) for IM versus SC, respectively; the gpELISA GMT ratio (IM/SC) was 1.05 (95% CI 0.93-1.18) and the antibody GMFR was 2.7 (2.4-3.0) vs 2.5 (2.2-2.8) at 4 weeks post-vaccination. The VZV antibody titres remained comparable when analysed by age groups (50-59 years, 60-69 years and ≥ 70 years).²⁹

5.2.2 Two doses

Vesikari et al compared the immunogenicity of zoster vaccine, when given in two-dose schedules or as a single-dose schedule, in 759 adults aged ≥ 70 years (mean age 76.1 years). Participants were randomised to receive a single dose of vaccine, two doses 1 month apart or two doses at 0 and 3 months. Antibody levels were found to be similar at 4 weeks after one or two doses – GMT ratio (GMT post dose two/post dose one) for the one and three-month schedules were 1.11 (95% CI 1.02-1.22) and 0.78 (0.73 and 0.85), respectively; and after 12 months, GMT ratios were 1.06 (0.96-1.17) and 1.08 (0.98-1.19), respectively. Similar antibody responses were observed in those age 70-79 years and ≥ 80 years. The study concluded that the two-dose vaccination schedule did not increase VZV antibody levels compared with a single-dose schedule, and antibody persistence was similar for all three schedules.³⁰

5.2.3 Booster dose

The immune response was assessed following a second (booster) dose of zoster vaccine given to participants aged ≥ 70 years, 10 years or longer after their first dose. VZV antibody titres and markers of VZV-CMI (IFN- γ and IL-2 as detected by ELISPOT assay) were compared in 200 participants receiving a booster dose of zoster vaccine with those given a first dose at 50-59 years, 60-69 years and ≥ 70 years (n=100, 100 and 200, respectively). Across all age and treatment groups, antibody responses were similar at baseline and after vaccination. In the older age groups, both baseline and post-vaccination VZV-CMI were lower than those seen in younger age groups. The GMFR from baseline in peak gp-ELISA titres generally correlated with high VZV-CMI at baseline and post-vaccination. The booster group had significantly higher IFN- γ and IL-2 levels at baseline and post-vaccination. Compared with age-matched controls receiving a first dose, at 52 weeks post-vaccination VZV-CMI was significantly higher in those who received a second dose: 65 versus 37 SFCs/ 10^6 peripheral blood mononuclear cells (cells secreting both IFN- γ and IL-2; $p < 0.0001$). These findings indicated that the effects of zoster vaccination on VZV-CMI persisted for more than 10 years and was boosted by the second dose. No clinical comparisons were made in this study.⁴⁴ The long term benefit of booster doses has not been determined as yet.

5.2.4 Concomitant administration with PPV-23

A review of two published studies found no direct evidence that simultaneous administration of zoster vaccine and pneumococcal polysaccharide vaccine (PPV-23) would increase the risk of zoster in vaccine recipients. In a placebo-controlled RCT, non-inferiority in VZV antibody GMT ratio was not met between giving zoster vaccine and PPV-23 concomitantly or 4-weeks apart in 235 adults aged ≥ 60 years. However, VZV antibody GMFR and pneumococcal antibody GMTs were deemed non-inferior. A large retrospective study did not find any statistical significant difference between the two groups (concomitant or separate vaccine administration). The hazard ratio comparing incidence rate of zoster was 1.10 (95% CI 0.81-1.74) for concomitant versus non-concomitant vaccination, and the between-groups cumulative risk was not significantly different ($p=0.76$). The reviewers concluded that to avoid missed opportunities to vaccinate that both vaccines could be given during the same office visit.⁴⁵

5.3 Immunogenicity in special groups

5.3.1 Diabetes mellitus

VZV-specific CMI and humoral immunity were boosted by zoster vaccine in 20 Japanese adults aged 60-70 years with and without diabetes mellitus. Immunogenicity was determined by VZV skin test, IFN- γ ELISPOT and immuno-adherence haemagglutination assay. There were no significant differences between the two groups for any assay.³²

5.3.2 Inflammatory bowel disease

A US-based prospective study found that 14 patients with IBD on low-dose immunosuppressive therapy (group A) had a statistically significant, but blunted, immune response to zoster vaccination compared with 25 non-immunosuppressed patients receiving either 5-aminosalicylic acid or no IBD therapy (group B). VZV-specific IgG increased significantly in both groups, but the response was lower in group A ($p=0.0002$). Secretion of TNF- α by PBMC did not increase in group A, and although IL-8 secretion increased in both groups, it was higher in group B.⁴¹

5.3.3 Corticosteroid therapy

A placebo-controlled RCT investigated the immunogenicity of zoster vaccine in participants aged ≥ 60 years receiving chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5-20mg prednisone) for at least 2 weeks prior to vaccination and more than 6 weeks post-vaccination. A total of 207 participants were vaccinated with zoster vaccine and 102 received placebo, with a mean age of 69.8 years (range 60-88) and 69.9 years (range 60-89), respectively. VZV antibody levels, as determined by gpELISA GMTs, were higher in the vaccinated group at 6 weeks post-vaccination and the estimated GMFR was 2.3 (95% CI 2.0-2.7) following zoster vaccination and 1.1 (1.0-1.2) following placebo. These findings were consistent with the vaccinated group in the SPS licensure study (estimated GMFR 1.7 [1.6-1.8]). No assessment of VZV-CMI was conducted. The study concluded that it provided support for the Advisory Committee on Immunization Practices recommendations that low/moderate doses of corticosteroids are not sufficiently immunosuppressive to impair vaccine immune response.³⁸

5.3.4 Systemic lupus erythematosus

In a prospective open-label study, 10 patients with mild SLE receiving mild-moderate immunosuppressive medications (mean age 60.5 years) and 10 health controls aged ≥ 50 years (mean age 55.3 years) were vaccinated with zoster vaccine. Although the VZV-CMI responses were found to be diminished in the patients with SLE, comparable proportions of participants had $\geq 50\%$ increase in IFN- γ ELISPOT titres following vaccination between groups: at 2 weeks post-vaccination in 63% SLE and 60% controls; at 6 weeks, 44% vs 56%, respectively; 44% in both groups at 12 weeks. Other investigations of the VZV-CMI and humoral immune responses were not found to be significantly or clinically different between the groups.⁴⁶

5.3.5 Major depressive disorder

A US-based two-year longitudinal cohort substudy of the SPS study investigated the immune response to zoster vaccine in community-dwelling adults with major depressive disorder aged ≥ 60 years. The participants were stratified by antidepressant medication use, and compared with age- and sex-matched controls with no history of depression or mental illness. The study found significantly lower VZV-CMI levels following zoster vaccination in patients with depression not undergoing antidepressant treatment ($n=12$) than those receiving antidepressants ($n=12$) or non-depressed controls ($n=30$). Significant increases in

VZV-responder cell frequency (RCF) of 69.7% (95% CI 31.4-119.2%) were measured in controls and 288.1% (90.9-689.0%) in those receiving antidepressants; untreated participants with depression showed a mean decrease in VZV-RCF of -32.9% (-65.5% to 29.7%). No significant differences were observed by IFN- γ ELISPOT or gpELISA. Among placebo recipients, the baseline VZV-CMI was marginally lower in depressed participants not receiving treatment compared with the other groups ($p < 0.07$). The study concluded that elderly adults with untreated depression responded poorly to zoster vaccine and were at higher risk of developing zoster and its complications than those being treated for depression, including those for whom treatment was not effective in controlling depression symptoms.⁴⁷

5.4 Summary of immunogenicity

Cell-mediated immune response (CMI) to VZV is inversely correlated with the risk of developing zoster. Lower VZV-CMI responses are seen following zoster vaccination of those aged ≥ 70 years than the 60-69 year age group. However, when zoster occurs in vaccinated individuals, a higher initial VZV-CMI response to the vaccine is associated with decreased severity of zoster and lower risk of PHN. Although in older people vaccination does not sufficiently boost VZV immunity to prevent viral reactivation and zoster, it can be sufficient to reduce disease severity.

The effects of zoster vaccination on VZV-CMI were seen to persist for more than ten years and VZV-CMI is boosted by the second dose given to adults aged ≥ 70 years at least ten years after the first dose. The duration of protection and clinical benefit of a booster dose has not yet been determined.

Low-dose immunosuppression blunts the cellular immune response to zoster vaccine. However, studies suggest that this may not be a reason not to vaccinate those age ≥ 60 years. As in the elderly, VZV immunity is boosted by zoster vaccination in these patients, and can provide protection against severe zoster and associated complications in at-risk groups, such as patients with SLE and IBD.

Elderly adults with untreated depression respond less well to zoster vaccine than those who receive treatment, but are at increased risk of developing zoster and its complications.

Simultaneous administration of zoster vaccine and pneumococcal polysaccharide vaccine (PPV-23) does not increase the risk of zoster in vaccine recipients. It is recommended, when needed, that both vaccines be given during the same medical visit to avoid missed opportunities to vaccinate.

Comparable VZV immunogenicity was observed when zoster vaccine was given intramuscularly or subcutaneously.

6 Efficacy and effectiveness of live attenuated vaccine

6.1 Background

The objective of this section is to review the most recent effectiveness data for currently licensed live attenuated zoster vaccine. The focus will be on the effectiveness in disease control and duration of protection.

A summary of the results of studies and reviews on the effectiveness and efficacy of zoster vaccine in preventing zoster-associated morbidity and mortality and reducing the burden of the disease is presented.

6.2 Review of efficacy

Pre-licensure, the pivotal SPS showed a two-fold reduction in zoster incidence in zoster vaccine recipients aged ≥ 60 years as compared with placebo recipients. The vaccine recipients who developed zoster after being vaccinated had less severe disease and of a shorter duration than those who received placebo. Vaccine efficacy was 61% in reducing the burden of zoster pain on quality of life and 67% in preventing PHN, and was not significantly different between the 60-69 year and ≥ 70 year age groups. However, the vaccine provided the best protection against the incidence of zoster disease in the 60-69 year age groups.⁴⁸

As summarised in Table 2, the protective efficacy of zoster vaccine was further investigated in follow-up studies to the SPS trial.^{26, 37} Since most of the findings for these studies were published prior to 2013, they are not reviewed in detail here.

6.2.1 Long-term efficacy

Findings for the Long Term Persistence Study (LTPS) were published in 2015 by Morrison et al. This study investigated the outcomes from year 7 to 11 post-vaccination in 6897 participants, vaccinated either as part of the SPS study or who were placebo controls in SPS and were offered zoster vaccine as part of the follow-on Short Term Persistence Study (STPS). The mean age at enrolment was 74.5 years (± 5.8 standard deviation). The estimated vaccine efficacy in the LTPS declined with time for all three outcomes (incidence of zoster, burden of illness and incidence of PHN) compared with the SPS trial. Statistically significant vaccine efficacy (greater than zero) persisted for 10 years post-vaccination for burden of illness and for 8 years for the incidence of zoster. Since the placebo controls in the original trial were later offered vaccine, comparisons were made with historical contemporary controls. As the population aged, no 'calendar effect' was observed in the incidence of PHN or worsening zoster severity. Vaccine efficacy for PHN incidence in the LTPS study appeared to be greater in the older age cohort. Sensitivity analyses, which were conducted to overcome the lack of placebo control, supported the primary findings and the continuation of temporal decline in vaccine efficacy that was observed in the STPS.⁴⁹

Table 2: Summary of vaccine efficacy as determined by Shingles Prevention Study (adapted from Medsafe Zostavax Datasheet and Keating 2016)

| Endpoint | SPS Efficacy (95% CI) | STPS Efficacy (95% CI) | LTPS Efficacy (95% CI) | ZEST† Efficacy (95% CI) |
|--|-----------------------------|------------------------------|------------------------------|-------------------------------|
| Incidence of HZ | 51% * (44-58%) | 39.6% (18.2-55.5) | 21.1 % (10.9-30.4) | 69.8 (54.1-80.6) |
| Incidence of PHN | 67% (48-79%) | 50.1% (14.1-71.0) | 37.3% (26.7-46.4) | - |
| HZ pain burden of illness [§] | 61% (51-69%) | 60.1% (-9.8 to 86.7) | 35.4 (8.8-55.8) | - |

* VE 64% in 60-69 years age group; 38% in ages ≥70 years

HZ – herpes zoster/shingles; PHN – post herpetic neuralgia; [§] composite score of incidence, severity, duration of pain over 6 month follow-up period.

SPS – Shingles Prevention Study

STPS – Short-Term Persistence Study, follow-up 3.3-7.8 years post-vaccination in SPS study

LTPS – Long-Term Persistence Study (compared with historical placebo controls), years 4.7-11.6 post-vaccination in SPS or STPS

ZEST – Zoster efficacy and safety trial in age 50-59 years†

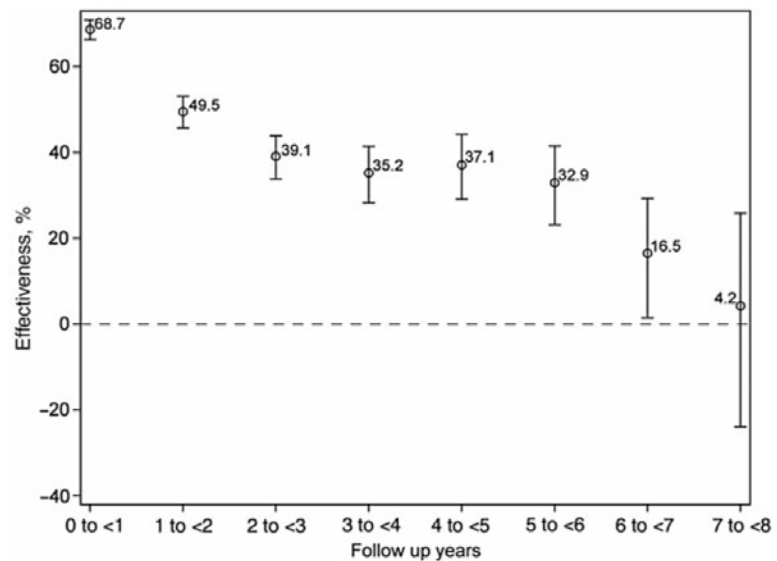
6.3 Effectiveness

A review of the 'real-world' effectiveness of zoster vaccine was conducted by Ansaldi in 2016. One study reviewed, analysed data from the Kaiser Permanente Southern California (KPSC) health plan during 2007 to 2009. Vaccine effectiveness (VE) of zoster vaccine was 55% (95% CI 52-58) in reducing zoster incidence, which was similar in all age groups (≥50 years) and in those with chronic diseases; VE for HZO was 63% (39-77) and prevention of zoster-related hospitalisations 65% (49-76).²⁵

A subsequent study analysed KPSC data of 176,078 individuals vaccinated from January 2007 to December 2014 aged ≥60 years who were compared with 528,234 unvaccinated matched-controls (excluding immunocompromised patients). The prevalence of chronic disease was lower in the vaccinated cohort. The zoster incidence rate ratio comparing vaccinated and unvaccinated individuals was 0.56 (95% CI 0.54-0.57). Vaccine effectiveness decreased by year of follow-up post-vaccination from 68.7% (66.3-70.9%) in year 1 to 16.5% (1.4-29.3%) in year 7, as shown in Figure 3. This decline was similar between the

60-69 years and ≥ 70 year age - groups. It should be noted that those who were vaccinated for over 6 years had received the vaccine soon after licensure and may have had compounding reasons to seek vaccination. The study did not investigate disease severity or PHN incidence.⁵⁰

Figure 3: Effectiveness and 95% CI of zoster vaccine by years after vaccination from 2007-2015 (reproduced with permission, Tseng 2016)



In another US-based cohort study using Medicare data from January 2007 to December 2009, a random 5% sample of eligible vaccinated and unvaccinated adults aged ≥ 65 years were used to assess the VE of zoster vaccine. Vaccine uptake was only 3.9% (0.6% in black people and 0.6% in those with low income). In the unvaccinated group, the overall zoster incidence rate was 10 (95% CI 9.8-10.2) per 1000 person-years versus 5.4 (4.6-6.4)/1000 person years in vaccine recipients (154 out of 28,291 person-years of follow-up). The adjusted VE against zoster was 48% (39-56) when adjusted for age, gender, ethnicity, immunosuppression, low income and comorbidity. The median time after vaccination for vaccine failure was 168 days. In immunosuppressed individuals, VE against zoster was 37% (6-58) based on 24 events in 1,981 person-years. Immunosuppressed individuals (for whom zoster vaccination is contraindicated) were identified as having, at any stage of the study, developed leukaemia, lymphoma or HIV, or had immunosuppressive medication prescribed within 6 months. The overall adjusted VE against PHN after 30 days was 62% (37-77) and after 90 days was 59% (21-79).⁵¹

6.3.1 Pain

A population-based matched case-control study was conducted that identified cases through active surveillance among adults aged ≥ 60 years with zoster onset and health care encounters during 2010-11 in Minnesota, US. The study found that zoster vaccination of adults aged ≥ 60 years was associated with a 54% (95% CI 33-87%) reduction in zoster, 58% (31-75%) reduction in prodromal symptoms and 70% (33-87%) reduction in medically attended prodromal pain. Zoster vaccination was 61% (22-80%) effective in preventing PHN at 30 days after rash onset. Among zoster cases, no differences in disease severity or duration of pain after rash onset were detected by vaccination status.⁵²

6.3.2 Chemotherapy recipients

A cohort study of data from KPSC investigated the effectiveness of zoster vaccination in adults aged ≥ 60 years who later underwent chemotherapy and concluded that zoster vaccine continues to protect against zoster if recipients receive chemotherapy more than 60 days after vaccination. The incidence rate of zoster in the vaccinated group was 12.9 (10.5-15.8; n=91) per 1000 person-years compared with a rate of 22.1 (20.3-23.9; n=583) per 1000 person-years in the unvaccinated group. The 30-month cumulative incidence was 3.3% in the vaccinated group and 5.3% in the unvaccinated ($p < 0.05$). Adjusted hazard ratio for zoster was 0.58 (0.46-0.73) with no significant variation by age, sex or race.⁵³

6.3.3 End-stage renal disease

A cohort study investigated the effectiveness of zoster vaccine in 582 patients aged ≥ 60 years with end-stage renal disease (ESRD). Vaccinated patients were matched 1:5 for age, sex and dialysis duration with unvaccinated controls using KPSC data during 2007-2013. Among the vaccinated patients, there were 16 zoster cases reported in 1373 person-years (incidence rate of 11.7 per 1000 person-years [95% CI 7.1-19.0]) and 126 unvaccinated cases in 5644 person-years (22.3 per 1000 person-years [18.7-26.6]). Adjusted hazard ratio following zoster vaccination was 0.49 (0.29-0.85). The study found that the reduced risk of zoster in vaccinated patients was most prominent if vaccine was given within 2 years of initiation of dialysis. It was noted that only 8.7% of patients received zoster vaccine compared with around 30% in the general population, and that most people with chronic kidney disease have sufficient immune function to safely receive live vaccines. This study supported the use of zoster vaccine in patients with ESRD if there are no other contraindications.⁵⁴

6.3.4 Durability of effectiveness

There are few studies around the duration of protection afforded by zoster vaccination. Clinical trials such as STPS and LTPS described above suggest protection is provided for up to 8-10 years if vaccinated at 60 years of age, and revaccination may be required. However, Tseng et al have shown that effectiveness is less than 20% after 6-7 years (Figure 3).⁵⁰ There are several factors that impact the duration of effectiveness of the vaccination, including age at vaccination, waning immunity with increasing age since vaccination and underlying health issues.⁵⁵

6.4 Summary of efficacy and effectiveness

Vaccine effectiveness of the live attenuated zoster vaccine has been shown in post-licensure studies to be around 50% in preventing zoster, and around 60% in preventing PHN and prodromal pain during the first 1-3 years following vaccination. However, this effectiveness in preventing zoster wanes markedly after 5 years following vaccination. Zoster vaccine helps to reduce the severity of zoster-related pain and the long-term pain complications associated with PHN. The vaccine is most effective in preventing zoster the younger age groups (50-69 years). For the older age groups, it helps to prevent PHN and reduces burden on quality of life caused by zoster pain.

In high-risk patients, zoster vaccine remains effective when chemotherapy is commenced more than 60 days after vaccination. The incidence of zoster in patients aged ≥ 60 years with ESRD is halved by vaccination, and shown to be most effective when administered within two years of dialysis initiation.

There have been few recent studies investigating the long-term benefit of zoster vaccination since coverage has been low in most countries. A booster dose given later in life may be required to sufficiently boost VZV-CMI as vaccine recipients age and vaccine immunity wanes. However, the effectiveness or safety of this strategy is not yet understood. The duration of protection, against zoster incidence, severity and PHN, for both the primary and booster doses is also undefined. Further data is expected over time as more countries introduce zoster immunisation programmes.

7 International policy and practice

The objective of this section is to provide a review of international vaccine schedules and recommendations for the prevention of zoster with live attenuated zoster vaccine (Zostavax[®]). This review is restricted to national immunisation schedules in Australia, Canada, Europe, the UK and the US as of November 2016.

7.1 Review

7.1.1 United States

The Advisory Committee on Immunization Practices recommends herpes zoster vaccine from the age of 60 years. People with chronic medical conditions may be vaccinated unless a contraindication or precaution exists. Zoster vaccine is contraindicated for individuals with a history of anaphylactic reactions to gelatin, neomycin or other vaccine components; for individuals with a history of primary or acquired immunodeficiency states, leukaemia, lymphoma, other malignancy of the bone marrow or lymphatic system, AIDS and clinical manifestation of HIV infection, and those on immunosuppressive therapy; and during pregnancy.⁵⁶

Following cost-effectiveness analyses and concerns around limited duration of immunity, the vaccine has not been recommended for use from the age of 50 years as described in its licensure.⁵⁷ However, consideration may be given to patients age 50-59 years who have pre-existing chronic pain, severe depression or other comorbidities, an intolerance or hypersensitivity to treatment medications, or extenuating employment-related factors.⁵⁸

7.1.2 Canada

As per the US, Canada recommends a single dose of the zoster vaccine from the age of 60 years without contraindications. Recommendations state that the vaccine may be used in adults aged 50-59 years with a history of zoster. Contraindications are as in the US for severely immunocompromised individuals. Individuals on low-dose immunosuppressive therapy may receive the vaccine, and those on anti-TNF biologicals may be considered on a case-by-case basis by an immunodeficiency specialist.⁵⁹

7.1.3 Australia

In Australia, zoster vaccine is recommended for the prevention of zoster and PHN from age 60 years, and routine vaccination is not recommended from age 50 years. For those aged ≥ 80 years, vaccination may be considered to help to provide protection against PHN. As of November 2016, zoster vaccine is funded as part of the National Immunisation Schedule for adults aged 70 years, with a catch-up available for those aged 71-79 years.⁶⁰

Zoster vaccination is contraindicated for those with severe immunocompromise due to primary or acquired medical conditions, or medical treatment (e.g. high-dose systemic immunosuppressive therapy). Persons with less severe immunocompromise (e.g. low-dose corticosteroids or DMARDs or asymptomatic HIV infection) may be considered for vaccination on a case-by-case basis with specialist guidance, since patients > 50 years are likely to have VZV immune memory which mitigates the risk of vaccine virus replication. The vaccine is contraindicated for anyone who has had anaphylaxis following receipt of any of the vaccine components or a VZV-containing vaccine.⁶⁰

7.1.4 United Kingdom

Zoster vaccine is funded on the UK national immunisation schedule at the age of 70 years. From 1 September 2016, catch-up is available for those age 71-73 years on this date, for those who were eligible for the vaccine but were missed in the previous three years of the programme up to their 80th birthday. This programme was initiated in 2013 to reduce impairment on the quality of life and independence seen in the elderly who develop severe zoster and PHN.⁶¹

Contraindications and precautions are the same as for the US for severely immunosuppressed individuals. Long term low-dose corticosteroids ($\leq 20\text{mg}$ prednisone daily for more than 14 days) with or without low-dose non-biological DMARDs (e.g. methotrexate $\leq 25\text{mg}/\text{week}$) are not considered sufficiently immunosuppressive and these patients can receive the vaccine.⁶¹

7.1.5 European Union

As of November 2015, the only other EU countries to recommended zoster vaccine are Austria, France and the Czech Republic. Zoster vaccine is funded in France between the ages of 65 and 74 years, a catch-up campaign for those aged 75-79 years was conducted in the first year of programme introduction in 2013.⁶²

Table 3: Summary of international immunisation recommendations for herpes zoster vaccines, as of 2016 (adapted from ECDC)

| Country | Age of zoster vaccination | Special recommendations |
|-----------------------|---|---|
| US | From age of 60 years | Recommended not funded |
| Canada | Recommended from age 60 years Funded in Ontario for those aged 65-70 years | Available from age 50 years with prior zoster history |
| Australia | Funded at age of 70 years | Not routinely recommended for ages 50-60 years Catch-up funded for those age 71-79 years |
| NZ | Available from age of 50 years | Not routinely recommended nor funded |
| Austria | From age of 50 years | Recommended not funded |
| Czech Republic | From age of 50 years | Recommended not funded |
| France | Funded for those aged 65 - 74 years | Catch-up for those aged 75-79 years in first year of programme introduction |
| UK | Funded at 70 years of age | Catch-up in for those aged 71, 72 and 73 years on 1 September 2016, and up to 80 th birthday if eligible and unvaccinated since 2013 |

7.2 Summary

As of November 2016, France, the UK, Australia and the Ontario province of Canada are the only regions that have funded zoster vaccine as part of their national immunisation programmes for those aged 65-74 or 70 years. Zoster vaccine is recommended, but not

publically funded, from the age of 60 years in the US, the rest of Canada and Australia, and from 50 years in Austria and Czech Republic.

8 Vaccines and options for scheduling

8.1 Background

Zoster is a debilitating disease, particularly in the elderly who are at high risk of long-term complications that affect quality of life and independence, and who are often less able than those in employment to afford the vaccine.

The objectives for this section are to present options for using zoster vaccines on the New Zealand National Immunisation Schedule. The focus will be on the prevention of zoster and reduction of complications, such as severe pain, PHN and HZO. Consideration will also be given to the disease incidence and surveillance in NZ.

8.2 Vaccine options

Currently, the only zoster vaccine available in NZ is the live attenuated vaccine, Zostavax[®], licensed for use in adults over the age of 50 years and available for purchase. Zoster vaccine is not funded for any special groups.

8.3 Schedule options

8.3.1 Target those age 50 years and over

The effectiveness of zoster vaccine is highest in the 50-59 year age group in preventing zoster rash. Zoster in this younger age group often results in a significant absenteeism from work and loss of productivity for employers. Around two thirds of people with zoster reported that it affected their work, the average absence from work was 5.4 days (range 0-28 days).¹⁰ However, if vaccinated at this age, the duration of protection from the vaccine may not extend to later in life when the complications and burden of disease increase. Although, the vaccine is licensed from the age of 50 years, it may not be cost-beneficial to vaccinate this age group since disease severity is often less with lower risk of PHN than in those aged ≥ 60 years. However, for those with underlying conditions that increase the risk of severe zoster and PHN, zoster vaccination could be beneficial.

8.3.2 Target those age 60 years and over

By targeting the over-60 year-olds, around 50% would be protected against zoster and severe disease for a period of around 5 years. The risk of PHN increases within this age group, and for some, other health issues will increase their risk of zoster complications. However, the duration of protection may not continue for the lifetime of the individual and a booster dose is likely to be required after the age of 70 years.

8.3.3 Target those aged over 70 years

The severity of zoster and the impact on quality of life increases with age, particularly since the incidence of PHN increases in the ≥ 70 year old age groups. Zoster vaccine is effective in reducing the severity and impact on quality of life of zoster illness in this age group, but does not reduce disease incidence. Significant protection is provided against PHN and loss of independence as a result of zoster-related illnesses in those aged 70 years or older.

8.3.4 Target high-risk groups

Not everyone ages the same manner and VZV-CMI status can vary within age groups. Some people aged 50-60 years have poorer health and more comorbidities that increase their risk of zoster than a healthy 70 year-old. Certain groups are at higher risk of zoster and the value of zoster vaccine may need to be considered on a case-by-case or condition-by-condition basis. Conditions that have been linked in the literature to an increased risk of zoster or more severe zoster, for whom vaccination is possible, include those with immune-mediated inflammatory disease and undergoing low-dose immunosuppression, such as SLE, rheumatoid arthritis and IBD; with diabetes; on renal dialysis; major depressive disorders; chronic pain syndromes and those with generally poor health status.

Not all individuals at high risk of zoster can receive the vaccine. There remain safety concerns for giving the vaccine to severely immunosuppressed individuals. The level of immunosuppression is an important factor for consideration when balancing risk from the vaccine with the risk of severe zoster and associated long-term complications in a group who are more likely to have severe zoster, particularly in the elderly. Those on mild-moderate immunosuppressive therapy may benefit from the vaccine, by reducing the severity of the disease, and when the risk from vaccination is less than if they were to develop zoster complications. Severe immunocompromise remains a contraindication to receiving the vaccine.

Studies have found that receipt of the vaccine after more than 60 days chemotherapy and within 2 years of initiating dialysis in patients with chronic kidney disease is effective in reducing the burden of zoster. Zoster vaccine has also been shown to be safe and immunogenic when given to patients with diabetes mellitus, and those receiving low-dose immunosuppression for the treatment of SLE and IBD.^{38, 41, 46, 54, 57}

For some, the VZV immune responses are blunted by their condition or medication, however, immunity also wanes naturally with age. For mildly immunocompromised individuals, the vaccine may be as effective against severe disease and PHN as it is for those aged ≥ 70 years.

Increased risk of PHN has also been observed for current and ex-smokers, those who were under- or overweight and with clinical depression.¹² Zoster vaccine may benefit those aged ≥ 60 years with generally poor health, although those in poorest health may have a weaker immune response to the vaccine, and the duration of immunity is expected to be shorter for older people.

8.3.5 Booster doses

The duration of protection provided by zoster vaccine is unclear. Current data show that vaccine effectiveness declines to around 33-39% within 2-5 years after vaccination.⁵⁰ Cell-mediated immunity, which is necessary to maintain suppression of latent VZV, wanes with age. The response to vaccination in older individuals is less than in younger age groups. If the vaccine is given at 60 years of age, it may not be protective by 65 or 70 years of age. A booster dose of zoster vaccine given later in life may not be sufficient to prevent reactivation of latent VZV. Although, it may be sufficient to reduce the severity of the disease in those most likely to be debilitated by zoster complications.

One study found that when a second dose of zoster vaccine was given at least 10 years after the initial dose, VZV-CMI was boosted in previously vaccinated adults aged ≥ 70 years compared with those who had not been vaccinated. However, it was not determined whether this boost in immunity was clinically sufficient to prevent zoster.⁴⁴ In the current context of lack of evidence around the duration of protection and effectiveness of zoster vaccine, there

are no recommendations around when and if to give booster doses. Most countries have opted to give the vaccine at 65 or 70 years rather than at a younger age.

8.3.6 Concomitant administration

A review of two studies evaluating concomitant administration of pneumococcal polysaccharide (PPV-23) and zoster vaccine in adults aged ≥ 60 years found that there was no direct evidence that giving both vaccines together reduced protection and increased the risk of zoster and recommended concurrent administration to avoid missed opportunities to vaccinate.⁴⁵

The US CDC advise that zoster vaccine can be administered with all other live and inactivated vaccines recommended for people ≥ 60 years, such as pneumococcal and influenza vaccines.⁵⁸

8.4 Surveillance

Varicella and zoster are not notifiable conditions in New Zealand and, since the vaccine is only available for purchase, there is no accurate measure of vaccine coverage.

More NZ data is required around the burden of zoster on the health system and individuals. Currently, the only dataset recording zoster incidence is hospitalisation data. However, few patients with zoster are hospitalised (around 0.1%). As determined in the UK based ZQOL study, the burden of zoster is on quality of life and independence of the elderly, in particular; zoster pain and PHN have a significant impact on the burden.¹⁰

Surveillance for zoster is needed to evaluate the impact of varicella vaccination on zoster incidence. A potential system for zoster surveillance must be a long-term effort as, according to modelling data, the impact the introduction of varicella vaccination on zoster may only be visible after more than 10-15 years.

8.5 Summary

Adults over the age of 50 years are at higher risk of developing zoster due to waning cell-mediated immunity. The zoster vaccine is available for this age group, unfortunately, for those who are at highest risk of developing severe zoster such as individuals with severely suppressed immunity through disease or medications, it is contraindicated as it is a live vaccine.

Many other individuals, for whom the vaccine is not contraindicated, have increased risk of zoster, such as those with mild immunocompromise as a result of medication or immune-mediated inflammatory diseases, inflammatory bowel disease, chronic kidney disease and diabetes mellitus.

Live zoster vaccine can help to prevent severe zoster, reduce the burden of zoster illness and the incidence of postherpetic neuralgia. The vaccine is most effective at preventing zoster incidence in younger age groups (50-69 years), however, the duration of protection may not extend to an age when recipients are likely to be at higher risk and a second dose may be required later in life. Currently there is no evidence to confirm whether a booster dose is clinically effective in older individuals.

As adults age, their risk of comorbidities increase, further increasing the likelihood of developing zoster complications. Therefore, despite limitations in the effectiveness and immune response to zoster vaccine in the elderly, universal vaccination is likely to provide

the greatest benefit to reduce the debilitating symptoms of severe zoster, particularly in those with undiagnosed conditions such as depression and insufficient VZV-CMI.

International studies have shown that the burden of zoster is significant in the elderly. However, there is insufficient data to quantify this burden in New Zealand. Surveillance is also needed in the long term to assess the possible impact of the introduction of universal varicella vaccination of children on the incidence of zoster in the future.

9 Adjuvanted recombinant herpes zoster vaccine

Shingrix™ (HZ/su) is a currently unlicensed zoster vaccine being developed by GSK. This inactivated vaccine is designed to boost VZV-specific T cell immunity and consists of VZV glycoprotein E (gE) subunit plus T cell stimulating adjuvant (AS01_B). As of late 2016, regulatory submissions for approval for the prevention of zoster in adults aged over 50 years have been submitted in the US, EU and Canada and include data from two pivotal randomised phase III efficacy clinical trials, namely ZOE-50 and ZOE-70.⁵ The vaccine is administered in two doses given intramuscularly two months apart.

Published data from these GSK-funded clinical trials are described in this section.

Table 4: Phase III study design for adjuvanted subunit zoster vaccine

| Study name | Endpoints | Study population | |
|---------------|---|------------------|-------------------|
| | | Number enrolled | Mean age in years |
| ZOE-50 | <p>Primary: Efficacy of HZ/su in reducing risk of zoster age ≥ 50 years</p> <p>Secondary: efficacy against zoster in ages 50-59, 60-69 and >70 years, PHN, safety and reactogenicity.</p> | 15,411 | 62.3 |
| ZOE-70 | <p>Primary: Efficacy of HZ/su in reducing risk of zoster and PHN age ≥ 70 years</p> <p>Secondary: Efficacy in reducing risk of PHN ≥ 50 years, safety and reactogenicity</p> <p>Included pooled data from ZOE-50.</p> | 14,816 | 75.6 |

9.1 Safety

The safety profile of the adjuvanted HZ/su vaccine was deemed as acceptable in clinical trials (for trial details refer to Table 4). During the phase III ZOE-50, vaccine recipients experience more solicited injection site and systemic events than placebo controls - in a reactogenicity subgroup that recorded local and systemic reactions on diary cards for 7 days post-vaccination, 84.4% reported solicited or unsolicited symptoms within 7 days of vaccination compared with 37.8% of placebo recipients. Most of these were mild-moderate, although, 17% vaccine compared with 3.2% placebo recipients reported symptoms that interfered with everyday activities. Pain was the most common injection site reaction and myalgia the most common systemic response. Grade 3 systemic reactions were more

frequent after the second dose than the first dose (8.5% vs 5.9%). After a mean follow-up of 3.5 years the overall numbers and types of SAE were similar between groups.⁶³

During the ZOE-70 study, injection site solicited reactions occurred in 74.1% of the HZ/su recipients and 9.9% of the placebo recipients in a reactogenicity cohort; most reactions were mild-moderate in intensity and the most common was pain, the most common systemic response reported was fatigue (32.9% versus 15.2% of placebo group). Grade 3 injection site reactions were reported in 8.5% vs 0.2% of vaccine and placebo recipients, respectively. The reactions were transient with a median duration of 1-3 days. Overall, the frequency and severity of solicited reactions did not increase significantly after dose two. One death (out of 426 HZ/su and 459 placebo recipients who died) was considered related to the trial intervention: a 90 year old with pre-existing thrombocytopenia was diagnosed with acute myeloid leukaemia 75 days after dose one of HZ/su.⁶⁴

9.2 Immunogenicity

A phase II RCT was conducted to evaluate the immunogenicity of adjuvanted zoster vaccine formulations (gE/ASO1_B) compared with gE/saline in adults aged ≥60 years of age. The frequency of activated VZV-gE-specific CD4+ T cells was >three-fold higher after two doses of gE/ASO1_B (given 2 months apart) than one dose of gE/ASO1_B or two doses of gE/saline. Serum anti-gE antibodies levels were comparable between groups. Two doses with gE/ASO1_B induced higher immune response than one dose; gE/saline impacted on humoral immunity but not cellular response.⁶⁵

In a follow-up study, gE-specific cellular and humoral immunity was shown to persist for 6 years following two doses of gE/ASO1_B. At 36 months post-vaccination, cell-mediated gE-CMI and anti-gE antibody responses had decreased by 20-25% but remained higher than pre-vaccination values. At 72 months, gE-specific CMI response was 3.8 times higher than the pre-vaccination level.⁶⁶

9.3 Efficacy

In the phase III ZOE-50 study, the overall incidence of zoster was determined to be 0.3/1000 person-years in the HZ/su group and 9.1 in the placebo group (six cases vs 201 after mean follow up of 3.2 years, respectively). The overall vaccine efficacy in preventing zoster was 97.2% (95% CI 93.7-99.0; p<0.001) among participants who were aged ≥50 years following two doses of HZ/su. Vaccine efficacy was similar among three age groups (50-59 /60-69 /≥70 years; range 96.6-97.9%). A key finding in this trial was that, unlike the live zoster vaccine, protection against zoster incidence did not appear to decline in the older age groups (as illustrated in Figure 4).⁶³

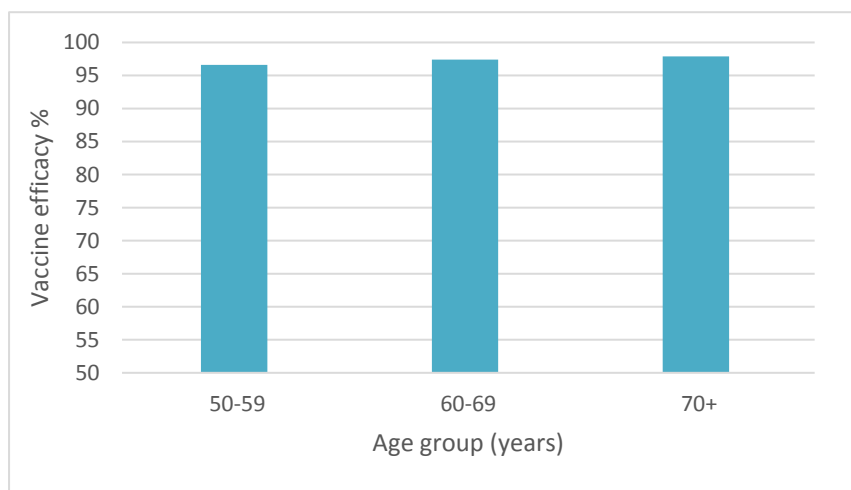


Figure 4: Adjuvanted zoster vaccine efficacy against zoster incidence from ZOE-50 trial (data from Lal et al 2015)

Findings from the phase III ZOE-70 study showed that two doses of HZ/su significantly reduced the risk of zoster among adults aged ≥ 70 years. Vaccine efficacy was calculated to be 89.8%

(84.2-93.7; $p < 0.001$ compared with placebo). Vaccine efficacy against zoster incidence did not differ between the 70-79 and ≥ 80 year age groups (91.3% vs 91.4% respectively). Pooled analysis of participants aged ≥ 50 year from ZOE-50 and ZOE-70 studies also showed HZ/su significantly reduced the risk of PHN compared with placebo (VE 91.2% [75.9-97.7]; $p < 0.001$). However, since PHN did not occur in any of the HZ/su group under the age of 70 years, a pooled analysis of participants aged ≥ 70 year was conducted which also showed a significant reduction in the risk of PHN (VE 88.8% [68.7-97.1]; $p < 0.001$) following HZ/su vaccination. Compared with placebo, the incidence of PHN in those HZ/su recipients who developed zoster did not differ significantly (9.6% and 12.5%, respectively, $p = 0.54$).⁶⁴

9.4 Future studies

Clinical studies are underway to evaluate the revaccination with HZ/su in prior live vaccine recipients and the vaccination of high-risk populations such as immunocompromised individuals.⁵ A further open-label study is being conducted to collect additional safety data in ZOE-50 and ZOE-70 participants who received placebo and were subsequently offered HZ/su.⁶⁴

9.5 Summary

Adjuvanted subunit zoster vaccine showed significantly greater reactogenicity than placebo during clinical trials, and following the second dose. Most reactions were mild-moderate in intensity, although more vaccine than placebo recipients reported that symptoms affected daily activities (17% vs 3%). However there were no safety concerns related to vaccination with HZ/su, and few serious adverse events were identified as being causally related to vaccine receipt. One death was associated with the trial intervention.

The adjuvanted subunit vaccine significantly reduces the risk of zoster in older adults. Vaccine efficacy was 97% (95% CI 93-99) when administered as two doses given 2 months apart to adults aged ≥ 50 years. Efficacy did not decline with age and was 89% (84-94) in adults aged older than 70 years. The risk of PHN was also significantly reduced in adults aged ≥ 70 years with VE of 89% (69-91).

The long term duration of protection of this vaccine is undetermined. The follow-up periods of these trial data were less than 4 years after the second dose. Further clinical trials are underway and follow-up continues.

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