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ATAGI Targeted Review 2022: Vaccination for prevention of herpes zoster in Australia

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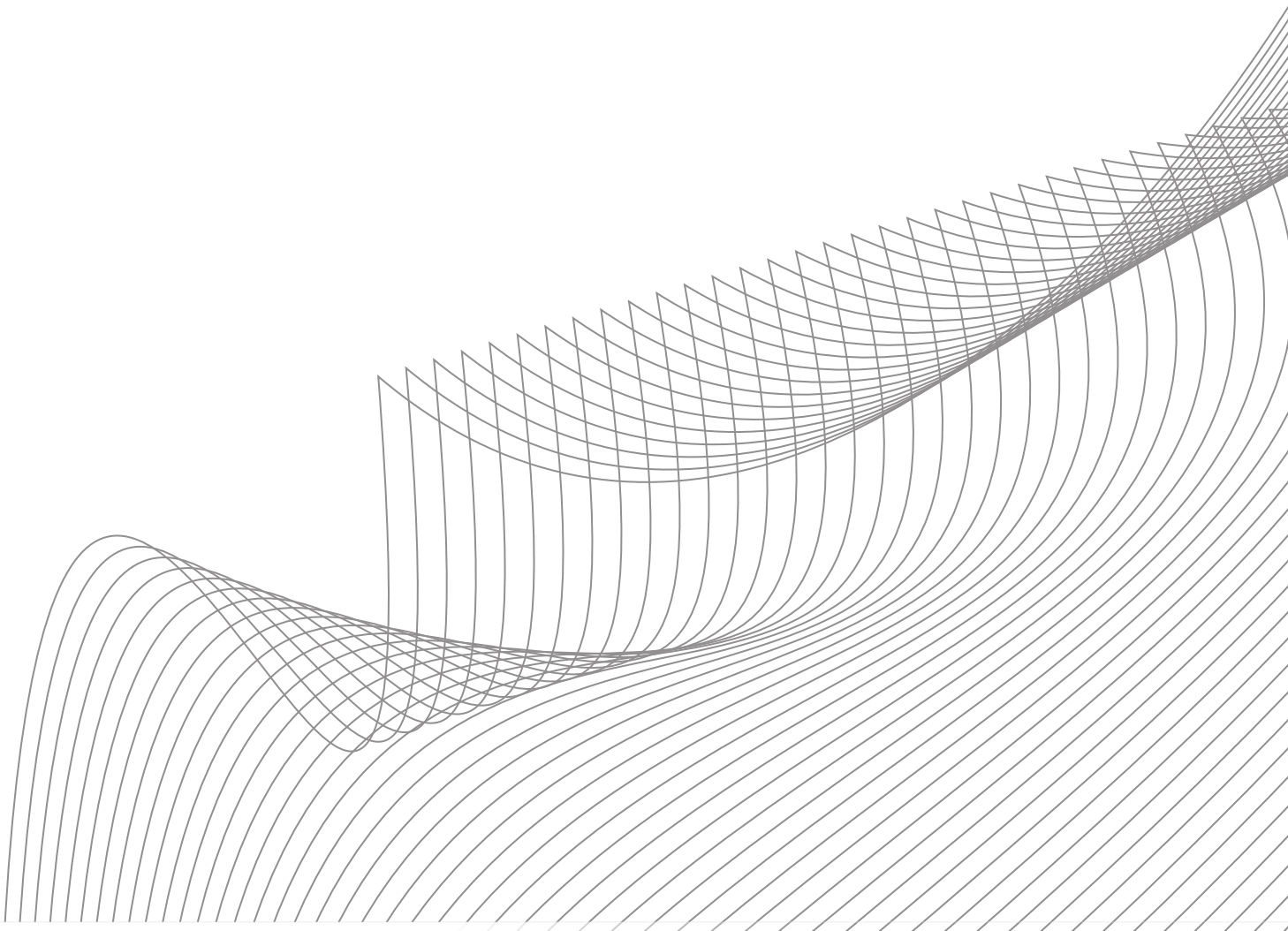

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Review article

ATAGI Targeted Review 2022: Vaccination for prevention of herpes zoster in Australia

Yuanfei Anny Huang, Jean Li-Kim-Moy, Sanjay Jayasinghe, Clayton Chiu, Kristine Macartney, Bette Liu, Penelope Burns, Michelle Giles, Nigel Crawford on behalf of ATAGI

Abstract

In November 2016, herpes zoster (HZ) vaccination for older adults, using the live-attenuated zoster vaccine (Zostavax; ZVL) was added to the Australian National Immunisation Program (NIP) with the aim of reducing morbidity from HZ and its complications, particularly for people at increased risk. Prior to the program, there were on average 5.6 cases of HZ per 1,000 persons annually in Australia, with highest risk of disease in older and in immunocompromised people. The burden of complications of HZ, such as post-herpetic neuralgia (PHN), was also highest in older and immunocompromised groups.

No formal comprehensive program evaluation has been undertaken since program commencement. This review examined published literature and available vaccine administration data to summarise the evidence and considerations underpinning current use of HZ vaccines and potential future program directions in Australia.

There have been modest reductions in the incidence of HZ and its complications since program introduction. However, five years into the program, challenges remain, including suboptimal vaccine coverage and significant safety concerns arising from inadvertent use of ZVL in immunocompromised people, who are contraindicated to receive this vaccine. This reduces opportunities to offset the burden of HZ-related disease.

The recombinant subunit zoster vaccine (Shingrix; RZV), first registered in Australia in 2018, became available on the Australian market in June 2021. This vaccine has higher efficacy than ZVL and, as a non-live vaccine, can be used in both immunocompetent and immunocompromised people. RZV has potential to address the unmet needs of at-risk population groups. However, it has not yet demonstrated cost-effectiveness for inclusion as a funded vaccine under the NIP.

The Australian HZ vaccination program has had limited effectiveness in meeting its aim in highest risk groups. Future options and challenges anticipated in using vaccination to reduce the burden of HZ and its complications are discussed in this review.

Introduction

Herpes zoster (HZ), otherwise known as shingles, is caused by reactivation of varicella zoster virus (VZV) that persists in a latent form in nerve root ganglia after a preceding infection with VZV.[1,2] Primary VZV infection manifests as varicella (chicken pox). HZ is characterised by a blistering rash in a dermatomal distribution, and is often associated with painful neuritis, particularly in older or immunocompromised people. HZ is usually self-limiting. However, disseminated zoster can also occur, particularly in immunocompromised people, with widespread dermatomal involvement and occasionally systemic complications.

Rarely, disseminated zoster can be fatal. Postherpetic neuralgia (PHN) is the most common complication of HZ and persists after resolution of the acute illness. It can be debilitating and can lead to reduced quality of life.

Vaccination of young children using chickenpox vaccine began under the National Immunisation Program (NIP) in Australia in 2005,[3] and is an effective strategy for preventing primary varicella and latent infection leading to HZ years later. At the other end of the age spectrum, HZ vaccines target older individuals, the majority of whom have been previously infected with VZV and are therefore at risk of HZ. The management of HZ occurs predominantly in primary care, with more severe complicated cases, often in the immunocompromised and elderly, requiring hospitalisation. Clinical guidance on both varicella and zoster vaccination is provided in the Australian Immunisation Handbook, and for the latter, via the Australian Technical Advisory Group on Immunisation (ATAGI) Statement on the clinical use of zoster vaccine in adults in Australia.[1,4]

This Targeted Review focuses on current HZ vaccination under the NIP, which commenced in 2016, and on potential future directions.

Epidemiological characteristics of herpes zoster

Notifications of HZ and PHN are not reliably and consistently captured in routine national surveillance systems, and have not been reported on in detail since 2016.[5] Prior to NIP-funded zoster vaccination, the estimated average annual incidence of HZ increased from 4.7 cases per 1,000 persons (95% confidence interval (95% CI): 4.3–5.0) in 2000–2006 to 5.6 cases per 1,000 persons (95% CI: 5.2–6.1) per year from 2006–2013.[6] HZ-related hospitalisation rates also increased from 9.7 per 100,000 population in 1999 (95% CI: 9.2–10.1) to 11.4 per 100,000 population (95% CI: 11.0–11.9) in 2013.[5] The Australian Institute of Health and Welfare estimated that there were 140,000 cases of HZ in Australia in 2015,[7] and a total of 268 HZ-related deaths over the years 2007–2016. In 2015, HZ and its complications accounted for 7% of the overall burden of all vaccine preventable diseases, with 1,152 disability-adjusted life years lost.[7]

The risk of developing HZ and complications increases with age and in those who are immunocompromised. From 2006 to 2013, the average annual HZ incidence was 15.3 per 1,000 persons in 70–79 year olds and 19.9 per 1,000 persons in those ≥ 80 years of age.[6] An international study reported a twofold higher incidence of HZ among immunocompromised people (9.15 compared to 4.65 per 1,000 person-years in immunocompetent people).[8]

Approximately 5–30% of people diagnosed with HZ develop PHN, noting that studies have used differing definitions of PHN.[9] In Australia, the overall population incidence of PHN was estimated to be 0.79 per 1,000 persons per year during 2006–2013.[6] This risk increased with age; PHN incidence in people ≥ 60 years of age was 3.1 per 1,000 persons per year during this period.

The risk of recurrence of HZ in the general unvaccinated adult population is 6.2% within eight years of the initial episode,[10] based on a study in the United States of America (USA). Recurrence risk is also higher in the immunocompromised, for example 2.4-fold higher compared to immunocompetent individuals over 7.3 years in one study.[10]

Herpes zoster vaccines

Two vaccines are currently registered in Australia for use in adults for the prevention of HZ and PHN (Appendix A, Table A.1).[1,4,11,12] ZVL (Zostavax; CSL/Merck) is a single-dose live attenuated vaccine registered for use in Australia, in people aged ≥ 50 years, since 2007. As a live vaccine, it is contraindicated in immunocompromised individuals and in pregnancy. RZV (Shingrix; GSK) is a two-dose recombinant protein subunit vaccine registered in Australia in people aged ≥ 50 years since 2018, and is

able to be used in both immunocompetent and immunocompromised people. TGA registration was extended, in 2021, to include a wider age range of immunocompromised people aged ≥ 18 years.[12]

ZVL

ZVL is moderately protective against HZ and PHN. The Shingles Prevention Study (SPS) and Zoster Vaccine Efficacy and Safety Trial (ZEST) assessed the efficacy of ZVL in adults aged ≥ 60 and 50–59 years, respectively, against HZ and PHN.[13,14] Among participants ≥ 60 years of age, vaccine efficacy against HZ was 51.3% (95% CI: 44.2–57.6%) over a median of 3.1 years. Efficacy decreased with increasing age, and was not statistically significant in individuals aged ≥ 80 years, impacting on the cost effectiveness of recommending programmatic vaccination for this age group (Table 1). Vaccine efficacy against PHN was 66.5% (95% CI: 47.5–79.2%) in the ≥ 60 year age group overall.

ZVL effectiveness wanes over time. In the SPS, long-term follow-up of individuals aged ≥ 60 years showed that by 8 years, vaccine efficacy against HZ had declined to 31.1% (95% CI: 11.2–47.6%).[16] International observational studies also reported declines in vaccine effectiveness against HZ, with one study showing an effectiveness of 68.7% (95% CI: 66.3–70.9%) in the first year decreasing to 16.5% (95% CI: 1.4–29.3%) before year 8, and another study reporting effectiveness of 50.0% (95% CI: 44.7–54.8%) at 1 year and effectiveness at 4 years of 30.5% (95%CI: 13.9–44.3%).[17,18] Similarly, among the ≥ 50 years age group, the effectiveness against PHN waned from 82.8% (95% CI: 77.6–86.7%) within one year post-vaccination to 48.7% (95% CI: 30.2–62.3%) by 8 years.[19]

Overall, ZVL has been found to be well tolerated in those indicated for vaccination. In immunocompetent participants in the SPS, adverse events rates were modestly higher in the intervention compared to placebo group for any vaccine-related systemic adverse event (risk difference 1.4%; 95% CI: 0.3–2.5%) and for varicella-like rash at injection site (risk difference 0.07%; 95% CI: 0.02–0.13%).[13]

Globally, post-marketing surveillance data from 2006 to 2016 included 18 reports of disseminated HZ in ZVL recipients.[20] Six of these involved administration of ZVL to immunocompromised individuals who were contraindicated to receive the vaccine, with two resulting in death. In Australia, three vaccine-related deaths have occurred after vaccination (see '*Vaccine program safety*' section below).[21]

RZV

The efficacy of RZV was assessed in two clinical trials, in immunocompetent participants aged 50 years and above, over 3.2 to 3.7 years.[22,23] Efficacy against both HZ and PHN following the second dose of RZV was high, with minimal waning against HZ with increasing age (Table 2). The efficacy of a single dose of RZV against HZ in individuals aged ≥ 70 years was

Table 1: Zostavax (ZVL) vaccine efficacy against herpes zoster (HZ) and post-herpetic neuralgia (PHN) in different age groups[a]

ZVL	Protection against HZ		Protection against PHN	
Age group (years)	% efficacy	95% CI[b]	% efficacy	95% CI[b]
50–59	69.8	54.1–80.6	N/A[c]	—
60–69	64.0	56.0–71.0	65.7	20.4–86.7
70–79	41.0	28.0–52.0	66.8	43.3–81.3
≥ 80	18.0	-29.0–48.0	N/A[c]	—

a Source: references 13–15.

b 95% confidence interval.

c N/A: not assessed.

Table 2: Shingrix (RZV) vaccine efficacy against herpes zoster (HZ) and post-herpetic neuralgia (PHN) in different age groups[a]

RZV	Protection against HZ		Protection against PHN	
Age group (years)	% efficacy	95% CI[b]	% efficacy	95% CI[b]
50–59	96.6	89.7–99.3	100.0	40.9–100.0
60–69	97.4	90.1–99.7	100.0	-442.8–100.0
70–79	91.3	86.0–94.9	93.0	72.5–99.2
≥ 80	91.4	80.2–96.9	71.2	-51.5–97.1

a Source: reference 24.

b 95% confidence interval.

assessed in a small group of individuals only and was considerably lower, at 69.5% (95% CI: 24.9–89.1%) over 3.2 to 3.7 years,[24] hence a two-dose schedule is recommended. In immunocompromised people aged ≥ 18 years, efficacy following a two-dose schedule was 68.2% (95% CI: 55.6–77.5%) in recent haematopoietic stem cell transplant recipients and 87.2% (95% CI: 44.3–98.6%) in those with a haematological malignancy.[25,26]

A recent study showed RZV vaccine efficacy against HZ remained high at 84.1% (95% CI: 64.4–94.0%) at 8 years after vaccination in original trial participants aged ≥ 50 years (mean age at vaccination of 67.2 years).[27]

Clinical trials reported solicited local reactions in 74–82% of RZV recipients, with 8.5–9.5% grade 3 reactions, compared to 10–12% (< 1% grade 3) of placebo recipients.[28] Solicited systemic reactions occurred in 53–66% (grade 3: 6.0–11.4%) of RZV recipients compared to 18–30% (grade 3: 2.0–2.4%) placebo recipients.[28] There were no significant differences in serious adverse events between the trial arms.[24] Trials in immunocompromised groups showed similar types of local and systemic adverse events, but these occurred more frequently, with 84–99% reporting solicited local reactions and 69–81% reporting solicited systemic reactions.[29]

A possible association between RZV and Guillain-Barré syndrome (GBS) has emerged from US post-market surveillance data to March 2019, with an attributable risk estimated at 3.6–6.3 cases of GBS per million RZV doses administered.[30] However, modelling indicates that the overall benefits of RZV use outweighs the potential rare risk of GBS.[31]

Comparison between ZVL and RZV

No head-to-head clinical trials of ZVL and RZV efficacy have been performed to date.[32] However, a systematic review and network meta-analysis published in 2018 compared the two vaccines, in adults ≥ 50 years of age, for efficacy, effectiveness and safety outcomes, showing that RZV was likely to be more effective in preventing herpes zoster than ZVL, but more likely to be associated with local adverse effects.[33]

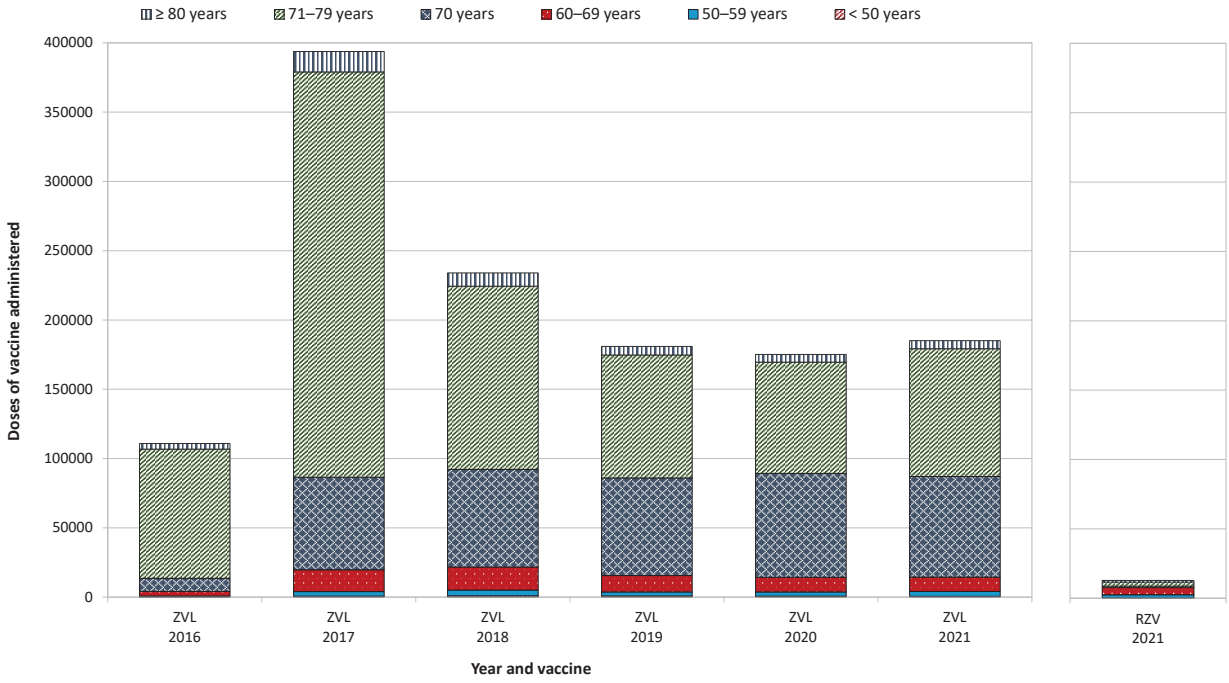
The Australian national herpes zoster vaccination program

ZVL was first registered for use in Australia in May 2007,[34] but had limited supply on the private market until its inclusion on the NIP from November 2016, for immunocompetent individuals aged 70 years, with an initial five-year catch-up program for immunocompetent individuals aged 71–79 years.[35] In October 2021, the catch-up program was extended to 31 October 2023.[36]

ZVL coverage estimates

In 2017, the first full calendar year of NIP funding, ZVL coverage as reported to the Australian

Figure 1: Doses of ZVL (2016–2021) and RZV (June–December 2021) administered by year and age group[a,b]



a Source: Australian Immunisation Register.

b Note that ZVL is a single-dose course whereas RZV is a two-dose course.

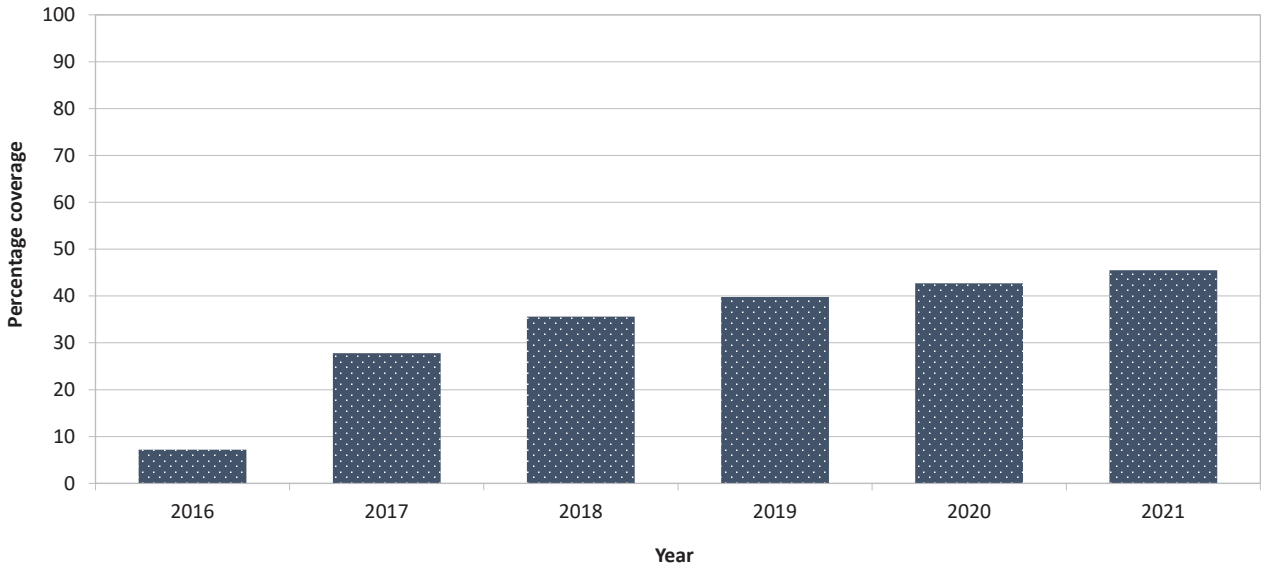
Immunisation Register (AIR) was 16.2% for people 70 years of age. Annual reported coverage has improved and stabilised at approximately 32% from 2018 to 2021,[37–39] with some variation between jurisdictions. For example, in 2020, recorded coverage was 19.7% in the Northern Territory, but 46.2% in Queensland.

ZVL uptake under the catch-up program was highest in 2017, with a decrease in the number of doses given annually thereafter to people aged 71–79 years (Figure 1). Single dose coverage in all individuals aged 70–79 years is calculated annually using all Medicare-eligible individuals in this age group each calendar year (Figure 2). The steeper initial rise in coverage reflected the surge in uptake early in the program among people in the targeted age range. Uptake has since plateaued among people aged 70 years, and has declined in the catch-up age group.

AIR data are likely to be an underestimate of the ZVL doses administered. A National Centre for Immunisation Research and Surveillance (NCIRS) report found that from October 2016 to November 2018, only 48.6% of doses of ZVL distributed to providers were reported as doses administered to AIR;[40] no data were available to assess how the remainder of doses were utilised. Another study, using electronic general practice records to assess uptake, estimated that at the end of 2018, ZVL coverage in those aged 70–79 years was 46.9%, higher than the 35.6% reported by AIR data at this time point.[41] ZVL coverage among the eligible immunocompetent population is also likely further underestimated because immunocompromised people ineligible for vaccine are included, but cannot be differentiated, in the AIR denominator. Mandatory reporting of all NIP vaccinations to the AIR commenced from 1 July 2021 and may improve issues of under-reporting.[42]

A 2021 study, using Australian general practice data, suggested ZVL uptake could be improved through offering the vaccine opportunistically during seasonal influenza vaccination or health assessment visits.[43] For individuals who had received ZVL, the adjusted odds ratio of having a health assessment at the same visit was 2.99

Figure 2: Cumulative proportion of individuals aged 70–79 years who have had a single dose of ZVL, as assessed by calendar year, 2016–2021[a]



a Source: Australian Immunisation Register.

(95% CI: 2.76–3.23) and for having an influenza vaccine at the same visit was 2.96 (95% CI: 2.80–3.14).

Australian zoster vaccination impact

Continual monitoring of HZ burden to assess program impact has been limited by the absence of a national surveillance plan and by challenges in measuring the incidence of HZ and PHN, which are largely managed in primary care by general practitioners. Despite this, a number of studies have suggested modest impact.

In the absence of a national surveillance plan for HZ, a study used data on the prescription of three antiviral agents used specifically (but not exclusively) for the treatment of HZ, obtained from a subset of national Pharmaceutical Benefits Scheme (PBS) data, as a surrogate marker to measure the impact of the vaccination program. In the first two years of the zoster vaccination program, there was a decrease in prescriptions of the antiviral agents by 13.6% (95% CI: 1.5–24.2%) per year in the target 70–79 year age group, but not in the 60–69 and ≥ 80 year age groups.[44]

Another study, using data from a sample of general practices across Australia, showed a decrease in the incidence of HZ in the target 70–79 year age group two years after the NIP addition of ZVL, by 2.3 presentations per 1,000 person-years (95% CI: 1.3–3.2) from the 2013–2016 period to the 2016–2018 period.[45] Reductions in the incidence of HZ in the age groups ineligible for NIP-funded ZVL vaccination were not seen. Early evidence suggesting waning vaccine effectiveness (VE) was also reported:[46] VE against HZ was in the first year of 63.5% (95% CI: 47.5–74.6%), decreasing to 48.2% (95% CI: 30.0–61.7%) in the second year.

No studies to date have assessed the impact of the Australian zoster vaccination program on PHN- or HZ-related hospitalisations. Several international studies have assessed the impact of ZVL on disease outcomes, as shown in Appendix A.

Vaccine program safety

Three deaths considered causally related to ZVL (Zostavax) administration and subsequent disseminated zoster have occurred in Australia (Figure 3). The first death in 2017 was in an immunocompromised individual in whom vaccine use was contraindicated.[47] In response, the TGA issued a safety advisory, and a pre-vaccination checklist for vaccine providers was developed by the ATAGI Special Risk Group Working Party and distributed to stakeholders.[48,49] The checklist was later incorporated onto the Australian Immunisation Handbook website in August 2020. The second death occurred in 2019, in a person on low doses of immunosuppressive agents in whom vaccine was not contraindicated.[50] This death highlighted the challenges in both identifying individuals who should potentially not receive ZVL and recognising and managing adverse events, such as vaccine virus-related rash, following immunisation. The third ZVL-related death occurred in late 2020 in a person contraindicated ZVL due to immunosuppression. Further TGA safety advisories were issued in July 2020, December 2020 and February 2022.[21] In addition, a letter from the Chief Medical Officer on the safe use of ZVL was issued in December 2020 to medical practitioners, pharmacists, nurses, and members of public health networks, and advice on seeking medical attention for rash following ZVL administration was added to consumer information.[50–52] In June 2021, the Zostavax product information and vaccine packaging were updated.

AusVaxSafety, an active surveillance system for adverse events following immunisation in Australia analysed ZVL data from November 2016 to November 2018, and did not find any additional safety signals of concern, although this study mainly targeted adverse events with a short onset time after vaccination.[53]

Introduction of RZV to the Australian market

RZV was registered by the TGA in July 2018, but due to global shortages in supply was not widely available in Australia until mid-2021.[34] Doses of RZV administered have been recorded in the AIR from this time onwards. However, as RZV is not funded under the NIP, it is recommended but not mandatory to report this vaccine to the AIR.

In 2018, the Pharmaceutical Benefits Advisory Committee (PBAC) considered a submission for NIP listing of RZV for adults 60 years of age with a five-year catch-up program[24] but did not grant a positive recommendation, with the rationale for the decision outlining significant uncertainties in the magnitude of clinical benefit, incremental cost-effectiveness ratios, and estimated financial impact.[24] Therefore, RZV is currently only available in Australia through private prescription.

From June to December 2021, there were 12,824 doses of RZV recorded in the AIR as administered (Figure 1), noting a two-dose course is recommended, and this dose count may include both doses of the primary RZV course in the one person. Uptake increased between June and November 2021, with age groups not yet eligible for NIP-funded ZVL, particularly the 60–69 and 50–59 years age groups, accounting for a large proportion of RZV administered (5,207 [40.6%] and 2,188 [17.1%] doses, respectively). There were fewer doses (1,019; 7.9%) given to people 70 years of age, with 3,909 (30.5%) given in the 71–79 years age group, and 1,257 doses (9.8%) recorded in people ≥ 80 years of age.

Data on RZV from AusVaxSafety from June to December 2021 did not demonstrate any safety concerns, with all adverse events occurring at rates lower than reported in clinical trials.[54]

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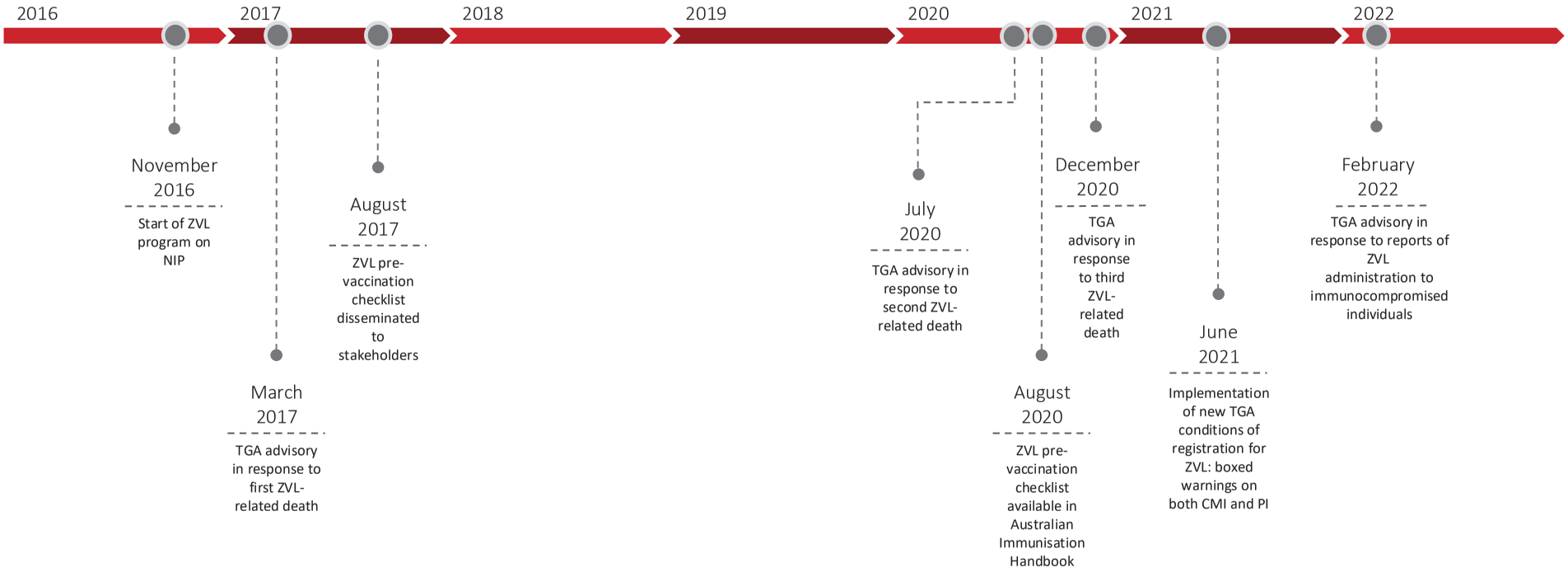
Figure 3: Timeline of significant safety events in the Australian ZVL program



Current ATAGI recommendations on zoster vaccines

In October 2021, ATAGI issued new clinical guidance that recommended RZV preferentially over ZVL for the prevention of herpes zoster and its complications in immunocompetent adults aged ≥ 50 years.[55] This is due to a higher efficacy demonstrated through clinical trials against both HZ and PHN, and evidence of slower waning of vaccine-induced immunity.[27,32,33]

ATAGI guidance was updated in April 2022 to recommend RZV for immunocompromised adults aged ≥ 18 years, for whom ZVL is contraindicated.[4] Where RZV is not accessible, for example due to issues of supply or cost to the individual, ZVL may be considered for people with mild immunocompromise aged ≥ 50 years, after careful assessment of benefits and risks. Serological confirmation of previous VZV infection may be considered in this group, to inform the evaluation of the risks and benefits of ZVL. Providers are also strongly recommended to complete a pre-administration risk-based screening assessment prior to use of ZVL in all patients.[48] For immunocompromised adults aged 18–49 years, RZV is the only vaccine registered and available to prevent HZ.

Unmet needs and challenges in zoster vaccination in Australia

Key data gaps, and limitations in the data sources available

Obtaining accurate data in Australia on the incidence and severity of HZ and its complications is an ongoing challenge. Only the Northern Territory and South Australia undertake routine public health follow-up of laboratory VZV notifications to confirm cases of HZ; other jurisdictions have reported trends in laboratory testing for VZV that are difficult to interpret.[5] Studies using primary health datasets are limited.[44] Data from a more detailed general practice research network, *Bettering the Evaluation and Care of Health* (BEACH), assessed the incidence of HZ and PHN, with a comprehensive and representative sample of GPs from 1998 to 2013 in two studies, but BEACH is no longer active.[6,56]

Under-reporting, to an unknown extent, of vaccine coverage data to the AIR is also a challenge. Mandatory reporting of NIP vaccines to the AIR from 1 July 2021 should improve the quality and completeness.[42] While this mandate does not include RZV administration, as it is not NIP funded, providers are still encouraged to report RZV doses administered to the AIR. Understanding uptake and impact of RZV in the immunocompromised population will require further analyses in linked datasets, as data on medical conditions are not recorded in AIR.[57]

Improving vaccination program coverage

Zoster vaccine coverage in Australia is lower than that achieved under a similar ZVL program in the UK.[58] ZVL uptake, from sentinel general practices in England in people aged 70, was 63% in the first year of the program but decreased to 46% by the fourth year.[59] Disparities in HZ vaccine and other vaccine uptake in Australia by sex, socioeconomic factors and area of residence are also evident and need to be addressed.[41]

Improving the safe use of ZVL

Despite the TGA, Commonwealth and jurisdictional health departments conducting a range of actions in response to reports of inadvertent administration of ZVL to immunocompromised individuals, an ongoing risk of similar incidents occurring remains, especially in older people where there may be multiple comorbidities and medication use. General practitioners have indicated that individual risk assessment is complex and a proportion have reduced knowledge and awareness of which patients may be suitable for vaccination.[60] The Advisory Committee on Vaccines to the TGA noted that "*the main area of difficulty (was) not a lack of awareness that this live-attenuated vaccine should not be given to immunocompromised persons, but the difficulty surrounding the assessment and definition of* '*immunocompromise*'." [61] Consideration could

also be given to the primary care software systems including an alert for immunosuppressed patients, reminding the clinician to review medications prior to considering ZVL. An additional challenge has been in clinicians recognising adverse events after vaccination, including the potential for disseminated vaccine (Oka) virus-related disease.

Preventing herpes zoster in the immunocompromised population

Immunocompromised people are at greatest risk of developing HZ and its complications, but until RZV became available, there was no safe and effective vaccine for disease prevention in this key group.[62] Extension of RZV registration in late 2021, to those aged ≥ 18 years, supports wider uptake, but equitable access will be very limited given the high vaccine cost on the private market.

Herpes zoster vaccination programs in other countries

Globally, there is a trend towards countries recommending RZV for the prevention of HZ in older adults, with or without a national vaccination program (Appendix A, Table A.2). Some countries that previously recommended against vaccination with ZVL, such as Germany and the Netherlands, now recommend RZV for older adults, due to RZV having the potential to protect individuals in immunocompromised and older age groups.[63–65]

In countries where ZVL was previously recommended, some have not changed recommendations (e.g. Greece, Switzerland);[66,67] others recommend either vaccine with no preference (e.g. Ireland, Sweden);[68,69] and some prefer RZV over ZVL (e.g. Canada, Spain).[70,71]

In the USA, preferential use of RZV over ZVL was recommended in 2018, and ZVL has been unavailable there since November 2020, due to a decision by the manufacturer to discontinue supply.[72] This may also impact the sustainability of the future ZVL vaccine supply in Australia.

The future of herpes zoster vaccination in Australia

Herpes zoster causes a significant burden of disease in the Australian population. Therefore, the introduction of ZVL to the NIP in 2016 was an important public health milestone in Australia. The ongoing burdens of HZ and PHN underpin the continuing value of a national vaccination program. However, while the current program using ZVL has demonstrated modest early impacts on disease, coverage continues to be lower than other vaccines administered to older people. Despite various mitigation measures, the inadvertent administration of ZVL to immunocompromised individuals continues to be a safety concern. Finally, there is significant unmet need and inequity in the current program, with immunocompromised populations—who have the highest burden of disease—unable to be vaccinated through the NIP due to contraindications to ZVL and the high cost of RZV.

As in other countries, use of RZV is now an option to facilitate achieving greater prevention of HZ and its associated burden through the NIP. However, as with any change to the NIP in Australia, a (re-)submission to the PBAC for evaluation for cost-effectiveness, and positive PBAC recommendation, would be required. Potential future vaccination strategies to achieve these aims could include continuation of ZVL, if available, in select (e.g. immunocompetent) individuals but use of RZV in immunocompromised individuals, or the replacement of ZVL on the NIP with RZV for all individuals, with options of either RZV revaccination of individuals who had already received ZVL, or no revaccination. Consideration of these options would require greater certainty on future vaccine supply, as well as demonstration to the PBAC of cost-effective provision of RZV under the NIP. ATAGI will continue to monitor the impact of HZ and PHN on the Australian community and will provide ongoing advice to government on utilising available vaccines safely and effectively.

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Appendix A: Supplementary material

Vaccine characteristics of ZVL and RZV

Table A.1: Characteristics of vaccines against herpes zoster currently registered for use in Australia

Vaccine	Live attenuated zoster vaccine (ZVL)	Recombinant zoster subunit vaccine (RZV)
Trade name and manufacturer	Zostavax (Merck)[1,11,34,73]	Shingrix (GlaxoSmithKline)[1,12,55]
Vaccine type	Live attenuated varicella zoster virus vaccine (Oka strain)	Recombinant varicella zoster virus glycoprotein E subunit vaccine with $AS01_B$ adjuvant
TGA approved indications	Prevention of herpes zoster in individuals ≥ 50 years of age Prevention of post-herpetic neuralgia and for reduction of acute and chronic zoster-associated pain in individuals ≥ 60 years of age	Prevention of herpes zoster and post-herpetic neuralgia in: Adults ≥ 50 years of age Adults ≥ 18 years of age at increased risk of herpes zoster
First TGA registration	March 2006 (frozen formulation) May 2007 (refrigerated formulation currently in use)	July 2018
Status on NIP	Funded for adults 70 years of age, with catch-up program for adults aged 71–79 years until October 2023	Not funded
Dose and route of administration	0.65 mL per dose; subcutaneous	0.5 mL per dose; intramuscular
Number of doses and interval	1	2, with a standard interval of 2–6 months, and an interval of 1–2 months acceptable for immunocompromised adults
Additional (booster) dose	Not recommended	Not recommended
Precautions and contraindications	Anaphylactic hypersensitivity Pregnancy Breastfeeding Immunocompromise Individuals with mild to moderate levels of immunocompromised may receive Zostavax following careful assessment of the level of immunocompromise using checklist[48]	Anaphylactic hypersensitivity

Table A.2: Herpes zoster vaccination recommendations in international jurisdictions

Country	Herpes zoster vaccination recommendation / program details
European Union (EU)	
EU overall[74,75]	2006: European Medicines Agency (EMA) granted marketing authorisation to ZVL 2018: EMA granted marketing authorisation to RZV
Austria[76]	RZV recommended for individuals 51–60 years of age (not funded) with catch-up administration recommended for adults 61 years and over (not funded)
Belgium[77]	July 2017: Recommendation to consider vaccinating against HZ in individuals aged 65–79 (not funded, vaccine not specified but at time of advice, only ZVL was available)
Czech Republic[78]	RZV recommended (not funded) for immunocompromised people ≥ 18 years of age Vaccination against HZ recommended (no vaccine preference) for immunocompetent adults ≥ 50 years of age (not funded)
Estonia[79]	Vaccination against HZ recommended for adults ≥ 65 years of age (not funded)
France[80,81]	ZVL recommended for individuals 65 to 74 years of age, with a co-funding arrangement with private providers
Germany[64,82]	2017: Decision against recommending vaccination using ZVL December 2018: Recommended for health insurance organisations to fund two doses RZV for individuals from age 60 years upwards, and individuals in specific risk groups ≥ 50 years of age
Greece[66]	ZVL funded for adults ≥ 60 years of age
Ireland[68]	Can consider vaccinating against HZ in individuals ≥ 50 years of age, with no vaccine preference stated, other than to use caution with ZVL in immunocompromised individuals
Italy[83,84]	2010: ZVL available on private market for individuals ≥ 50 years of age 2017: Recommendation to improve uptake in individuals ≥ 65 years of age, with a specific goal of 50% coverage by 2020; provinces responded to recommendations differently, with some offering funded ZVL programs to specific age cohorts 2021: RZV added to funded national immunisation program from age 50 years for immunocompromised adults and adults with high-risk comorbidities, and at age 65 years for all other adults
Netherlands[65]	2016: Decision against recommending vaccination using ZVL 2019: In principle, in favour of vaccination using RZV. However, did not meet cost-effectiveness criteria for inclusion in a funded national immunisation program
Spain[71]	2016–2017: ZVL programs commenced in three autonomous communities (regions), for specific groups of people at higher medical risk 2018: RZV recommended for individuals ≥ 18 years of age, with a specific list of immunocompromising conditions. However, there was a shortage in vaccine supply. March 2021: Specifically citing the shortage of vaccines, a decision was made to offer RZV to immunocompromised individuals ≥ 18 years of age in 2021. The population-wide vaccination program would commence in 2022, again pending vaccine supply. The program would target individuals aged 65 years, with a rolling catch-up program.
Sweden[69]	RZV recommended for immunocompromised people ≥ 18 years of age (not funded) Vaccination against HZ recommended, with either RZV or ZVL, for the general population > 50 years of age (not funded)
non-EU countries	
Canada[70,85,86]	Vaccination program decisions are made by individual provinces 2010: National Advisory Committee on Immunization (NACI) recommended ZVL for individuals ≥ 60 years of age 2016: Ontario started funded ZVL program targeting people 65 to 70 years of age 2018: NACI updated recommendation to preference RZV over ZVL 2020: Ontario program commences transition to use RZV exclusively
Israel[87]	ZVL registered for individuals ≥ 50 years of age 2014: Funded ZVL program commenced for individuals ≥ 60 years of age
Korea[88]	2015: Vaccination against HZ recommended for people at higher medical risk aged 50–59, and the general population ≥ 60 years of age (not funded)
Mexico[89]	2017: ZVL recommended for individuals ≥ 60 years of age (not funded)

Country	Herpes zoster vaccination recommendation / program details
New Zealand[90]	April 2018: Funded ZVL program commenced for immunocompetent adults 65 years of age, with catch-up program for individuals 66–80 years old until 31 December 2021 Individuals with certain high risk medical conditions (but immunocompetent) are recommended to receive ZVL between 50 and 64 years of age (not funded)
Switzerland[67]	2010: ZVL not recommended due to a lack of long-term efficacy data 2017: ZVL recommended (not funded) for immunocompetent adults 65 to 79 years of age, and for individuals at higher medical risk 50 to 79 years of age
United Kingdom[58,91]	2013: Funded zoster vaccination program commenced using ZVL for people aged 70, with a rolling catch-up program for people aged 71–79 2021: RZV added to the program for all immunocompromised people in age groups eligible for funded zoster vaccine
United States of America[15,72,92]	No publicly funded vaccination program against HZ 2008: Advisory Committee on Immunization Practices (ACIP) recommended zoster vaccination for immunocompetent adults ≥ 60 years of age 2018: ACIP updated advice to recommend RZV preferentially over ZVL for all adults ≥ 50 years of age 2022: ACIP advice expanded to recommend RZV for immunocompromised adults ≥ 19 years of age

Impact of herpes zoster vaccination programs in selected countries

United States of America

Several large studies have examined the impact of zoster vaccination in the US. Studies focusing on community populations ≥ 60 or ≥ 65 years of age, in the first three years after the introduction of ZVL, gave estimates of VEs against HZ of 33% to 55%.[27–29] In a study examining hospitalised groups ≥ 65 years of age only, the VE against HZ was estimated to be 74% (95% CI: 67–79%).[29] An industry-sponsored prospective cohort study following patients aged ≥ 50 years gave a VE against HZ of 49.1% (95% CI: 47.5–50.6%).[18] The VE against PHN in US studies ranged from 57% to 65%.[19,28,29]

Canada

Two studies were undertaken in the effectiveness of ZVL at the level of the province in Canada. Of note, the study from Ontario using administrative data showed that the publicly funded ZVL program contributed to a 19.1% reduction of the incidence of medically-attended HZ in the target age group between the 2009–2016 and 2016–2018 periods.[93] Concurrently in the same population, there was a 38.2% reduction in the incidence of HZ hospitalisations.

United Kingdom

The impact of the UK vaccination program has been assessed through four large studies, estimating the vaccine effectiveness to be 55.0–65.3% among general practice populations in eligible age groups within the first three to five years of the ZVL-only program.[59,94–96] In the same population, these studies estimated the vaccine effectiveness against PHN to be 71.6-88.0%.