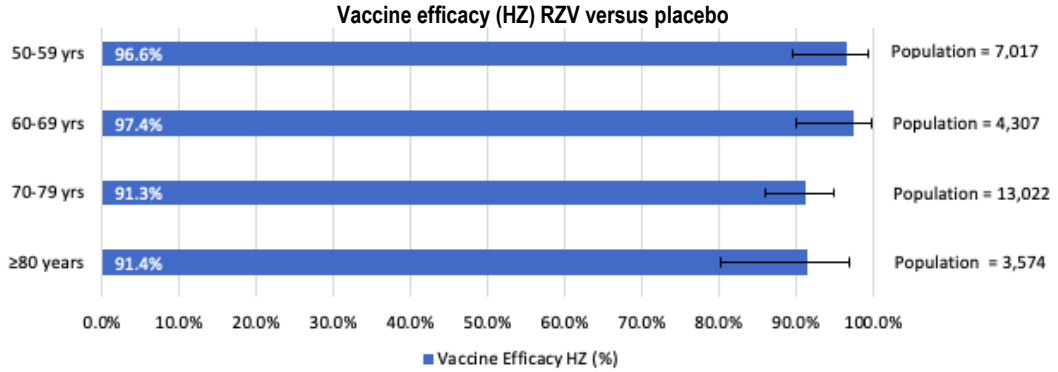
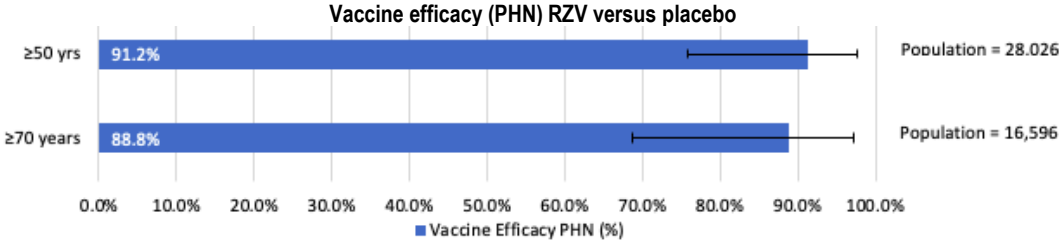
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the ATAGI statement on the clinical use of zoster vaccine for older adults in Australia.

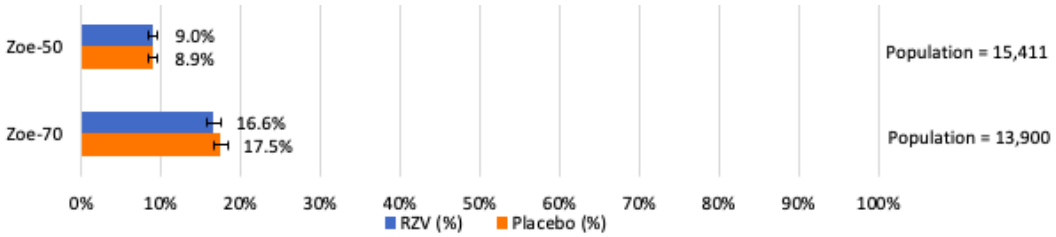
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompetent older adults

Patient or population: Immunocompetent older adults ≥50 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV versus Placebo) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with RZV				
CRITICAL OUTCOMES						
Vaccine efficacy against confirmed herpes zoster (HZ) Assessed with: PCR/blinded ascertainment committee confirmed [VE = (1-RR)x100] follow up: range 3.2 years to 3.7 patient years № of participants: 27922 (2 RCTs)				⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) results in a large reduction in confirmed herpes zoster cases compared with placebo. Note: 70–79 years and ≥80 years figures reflects pooled data from ZOE-50+ZOE-70 Refs: (1, 2)
Vaccine efficacy against post-herpetic neuralgia (PHN) Assessed with: Worst pain score ≥3 on ZBPI for pain developing / persisting >90 days post rash onset [VE = (1-RR)x100] follow up: mean 3.8 years № of participants: 27,916 (2 RCTs)				⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) results in a large reduction in post-herpetic neuralgia compared with placebo. Note: Estimates reflect pooled ZOE-50/ZOE-70 data (≥70 years are subset of ≥50 years analysis) Refs: (1)

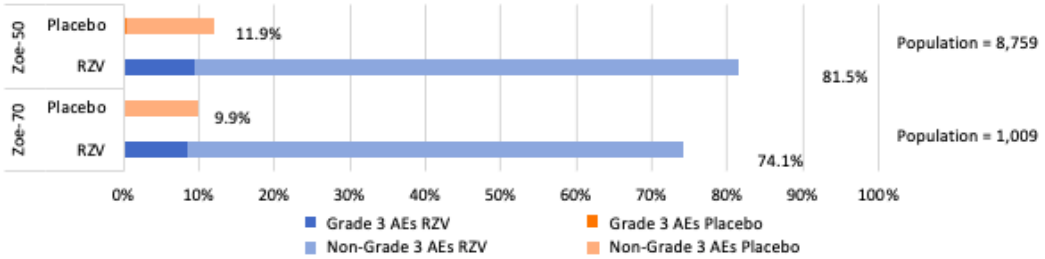
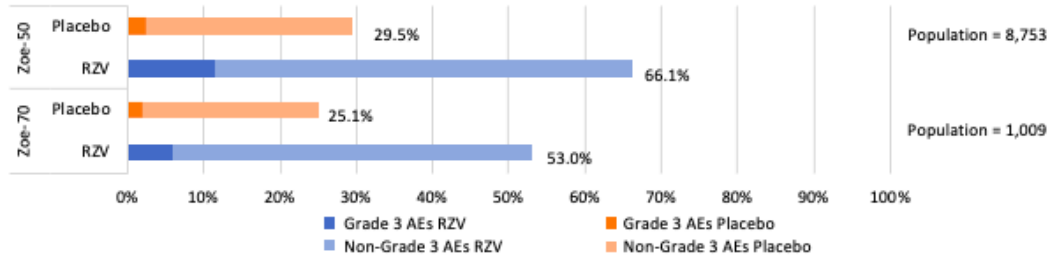
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompetent older adults

Patient or population: Immunocompetent older adults ≥50 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV vs Placebo) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with RZV				
Herpes zoster (HZ)–related hospitalisations [VE = (1-RR)x100] follow up: mean 3.9 years № participants: 27,916 (2 RCTs)	Vaccine efficacy (HZ-related hospitalisation): calculated for ZOE-70 modified vaccinated cohort only 100% (-9.9 to 100) p=0.064 There were no HZ-related hospitalisations in the ZOE-50 study in either arm (0/14,759) 5 placebo recipients in ZOE-70 had HZ-related hospitalisation (5/6,622). 0/6541 ZOE-70 vaccine recipients had HZ-related hospitalisation.			27,916 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	Recombinant herpes zoster vaccine (Shingrix) may result in a decrease in herpes zoster–related hospitalisation compared with placebo. Note: VE calculated for ZOE-70 only. No hospitalisations in either arm of ZOE-50 Ref: (3)
HZ-related mortality follow up: range 3.7 years to 3.9 years № participants: 27916 (2 RCTs)	No HZ-related deaths in ZOE-50 or ZOE-70 (0/27916 participants total)			27,916 (2 RCTs)	N/A	Unable to be GRADED – excluded as zero-event studies Ref: (3)
Serious adverse events (SAEs) defined as: events that resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalization, resulted in disability, incapacity, congenital anomaly, or birth defect in participant's child Follow-up: Mean 3.2 years and 3.7 years No. participants: 29311 (2 RCTs)	**Any SAE (not limited to vaccine-related)**  In ZOE-50 and ZOE-70, 13/14648 (0% to 0.2%) of SAEs were deemed ***vaccine-related*** by investigators in the vaccine recipients, compared with 11/14,663 (0% to 0.1%) in placebo recipients.				⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) results in little to no difference in serious adverse events compared with placebo. Note: All SAEs recorded for 12 months post final dose, plus fatal AEs, potential immune-mediated disease and vaccine-related SAEs recorded for entire study period Refs: (1, 2, 4)

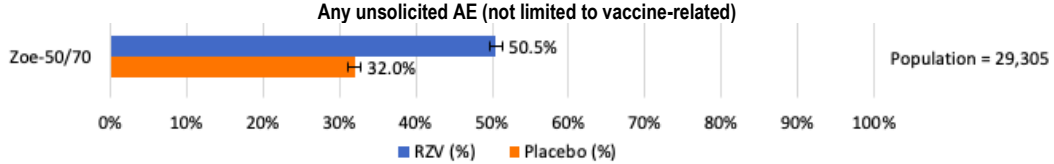
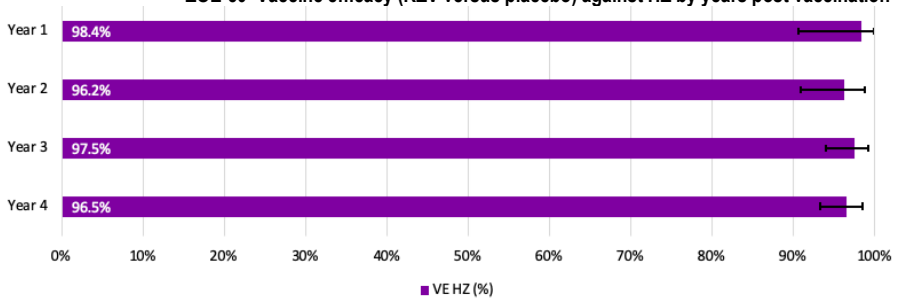
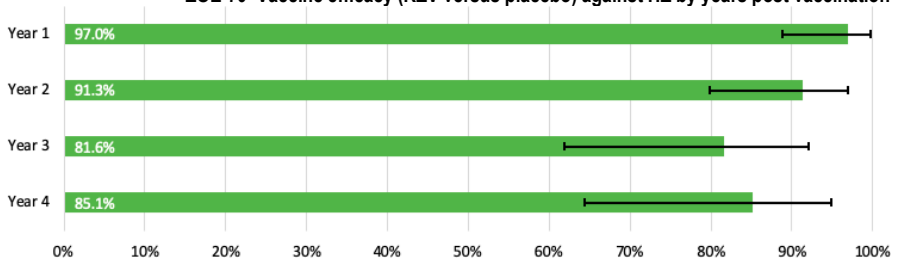
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompetent older adults

Patient or population: Immunocompetent older adults ≥50 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV versus Placebo) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with RZV				
IMPORTANT OUTCOMES						
Solicited local adverse events (AEs) Recorded using diary cards post vaccination (Local solicited AEs include pain, redness, swelling) follow up: 7 days No. participants: 9769 (2 RCTs)				⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) results in a large increase in solicited local AEs compared with placebo. Note: Solicited AEs recorded only in reactogenicity sub-group: ZOE-50: included all participants aged ≥70 years, and a random selection of participants aged 50–59 years and 60–69 years as part of reactogenicity sub-group ZOE-70: randomly selected reactogenicity sub-group Grade 3 = preventing normal functioning Refs: (1, 2)
Solicited general/systemic AEs Recorded using diary cards post vaccination. General solicited AEs include: fever, fatigue, gastrointestinal (GI) symptoms, headache, shivering, myalgia follow up: 7 days No. participants: 9762 (2 RCTs)				⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) results in a large increase in solicited general/systemic AEs compared with placebo. Note: Solicited AEs recorded only in reactogenicity sub-group: ZOE-50: included all participants aged ≥70 years, and a random selection of participants aged 50–59 years and 60-69 years as part of reactogenicity subgroup ZOE-70: randomly selected reactogenicity sub-group Grade 3 = preventing normal functioning Refs: (1, 2)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompetent older adults

Patient or population: Immunocompetent older adults ≥50 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV versus Placebo) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with RZV				
Unsolicited AEs Recorded for 30 days after each dose by participants follow up: 30 days No. participants: 29305 (2 RCTs)			**Any unsolicited AE (not limited to vaccine-related)**  34.5% (95%CI 33.7-35.3) of unsolicited AEs were considered ***vaccine-related*** in the RZV arm, versus 6.6% (95% CI: 6.2–7.0) in placebo.		⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) increases unsolicited AEs compared with placebo. Note: Pooled ZOE-50/ZOE-70 data Refs: (4)
Duration of protection assessed with: PCR/blinded ascertainment committee confirmed [VE = (1-RR)x100] follow up: range mean 3.2 years to mean 3.7 patient years № of participants: 27,922 (2 RCTs)			**ZOE-50 Vaccine efficacy (RZV versus placebo) against HZ by years post vaccination**  **ZOE-70 Vaccine efficacy (RZV versus placebo) against HZ by years post vaccination** 		⊕⊕⊕⊕ HIGH	Recombinant herpes zoster vaccine (Shingrix) maintains a large reduction in confirmed herpes zoster compared with placebo for up to 4 years post vaccination. Note: ZOE-50: ≥50 years; ZOE-70 ≥70 years Note: Longer follow-up reported for persistence of immune response measures (10 years post vaccination) Refs: (1, 2, 5)

Grade 3 = preventing normal functioning
a. Risk of bias - some concerns due to potential for selective reporting (post hoc pooled analysis due to low event numbers), however not downgraded as outcome was a prespecified outcome prospectively measured according to study protocol
b. Wide confidence interval crosses null due to small number of hospitalised cases

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence	
⊕⊕⊕⊕ **High certainty**	We are very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ **Moderate certainty**	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ **Low certainty**	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ **Very low certainty**	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016;375(11):1019-32.
2. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087-96.
3. Kovac M, Lal H, Cunningham AL, Levin MJ, Johnson RW, Campora L, et al. Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials. Vaccine. 2018;36(12):1537-41.
4. López-Fauqued M, Campora L, Delannois F, El Idrissi M, Oostvogels L, De Looze FJ, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-93.
5. GSK. Clinical Study Report: Study to evaluate efficacy, safety and immunogenicity of GSK Biologicals' Herpes Zoster (HZ) vaccine GSK1437173A in adults aged 50 years and older. 2016. Contract No.: NCT01165177.

Evidence profile: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompetent older adults

Certainty assessment							№ of patients[1]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV (Shingrix)	placebo	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOMES											
Vaccine efficacy (VE) against confirmed herpes zoster (HZ) (follow up: range 3.2 years to 3.7 patient years; assessed with: PCR or blinded ascertainment committee confirmed; VE = (1- RR) x 100)											
2	Randomised trials	not serious	not serious	not serious	not serious	very strong association	29/13,885 (0.2%)	443/14,037 (3.2%)	VE against HZ was >90% for all age-stratified groups, but trended slightly lower among older age groups. **Overall vaccine efficacy against HZ:** % (95% CI) ≥50 years: 97.2% (93.7–99.0) p<0.001 (ZOE-50 only) ≥70 years: 91.3% (86.8–94.5) p<0.001 (Pooled ZOE-50/70) Refs: (1, 2)		⊕⊕⊕⊕ HIGH
Vaccine efficacy against post-herpetic neuralgia (PHN) (follow up: mean 3.8 years; assessed with: Worst pain score ≥3 on ZBPI for pain developing/persisting >90 days post rash onset)											
2	Randomised trials	not serious	not serious	not serious	not serious	strong association	4/13,881 (0.0%)	46/14,035 (0.3%)	VE against PHN was 91.2% in the ≥50 years age group and 88.8% in the ≥70 years age group. **Age-stratified VE:** 50–59 years: 100% (40.8 – 100.0) p=0.008 60–69 years: 100% (-442.9 – 100; p=0.51 70–79 years: 93.0% (72.4 – 99.2) p<0.001 ≥80 years: 71.2% (-51.6 – 97.1) p=0.18 Refs: (1)		⊕⊕⊕⊕ HIGH
Herpes zoster–related hospitalisation (follow up: mean 3.9 years)											
2	Randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	0/13,881 (0.0%)	5/14,035 (0.0%)	There were no HZ-related hospitalisations in the ZOE-50 study in either arm (0/14,759) 5 placebo recipients in ZOE-70 had HZ-related hospitalisation (5/6,622). No ZOE-70 vaccine recipients had HZ-related hospitalisation. Ref: (3)		⊕⊕◯◯ LOW [a b]

[1] Manually calculated pooling data from all included studies

Certainty assessment							№ of patients[1]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV (Shingrix)	placebo	Relative (95% CI)	Absolute (95% CI)	
Serious adverse events (follow up: range 12 months to 4.4 years; assessed with: SAEs recorded for 12 months post final dose, plus Fatal AEs, pIMD and vaccine-related SAEs recorded for entire study period)											
2	Randomised trials	not serious	not serious	not serious	not serious	none	1842/14648 (12.6%)	1900/14663 (13.0%)	Both studies reported similar rates of SAEs in intervention and control arms. 9% ≥50 years and 17–18% ≥70 years in both arms reported SAEs. In ZOE-50 and ZOE-70, 13/14,648 (0% to 0.2%) of SAEs were deemed ***vaccine-related*** by investigators in the vaccine recipients, compared with 11/14,663 (0% to 0.1%) in placebo recipients. Refs: (1, 2, 4)		⊕⊕⊕⊕ HIGH
IMPORTANT OUTCOMES											
Solicited AEs (Local) (follow up: mean 7 days; assessed with: Recorded using diary cards for 7 days post vaccination (Local solicited AEs include pain, redness, swelling))											
2	Randomised trials	not serious	not serious	not serious	not serious	strong association	3945/4887 (80.7%)	572/4882 (11.7%)	Both studies reported higher local reactogenicity in the vaccine arm compared with placebo (range 74–82% in vaccine arm compared with 10–12% placebo). ***Grade 3*** solicited local AEs (preventing normal functioning) were reported in 8.5–9.5% of vaccine recipients compared to <1% placebo recipients. Refs: (1, 2)		⊕⊕⊕⊕ HIGH
Solicited AEs (General/Systemic) (follow up: mean 7 days; assessed with: Recorded using diary cards for 7 days post vaccination. General solicited AEs include: fever, fatigue, GI symptoms, headache, shivering, myalgia)											
2	Randomised trials	not serious	not serious	not serious	not serious	strong association	3161/4879 (64.8%)	1420/4883 (29.1%)	Both studies reported higher systemic reactogenicity in the vaccine arm compared with placebo (range 53–66% with vaccine compared with 18–30% placebo). ***Grade 3*** solicited systemic AEs (preventing normal functioning) were reported in 6–11.4% of vaccine recipients compared to 2–2.4% placebo. Refs: (1, 2)		⊕⊕⊕⊕ HIGH
Unsolicited AEs (follow up: mean 30 days; assessed with: Recorded for 30 days after each dose by participants)											
2	Randomised trials	not serious	not serious	not serious	not serious	strong association	7393/14645 (50.5%)	4689/14660 (32.0%)	Pooled results from both RCTs indicated a higher rate of unsolicited AEs in the vaccine arm compared with placebo (range 50.5% in the vaccine arm compared with 32% placebo arm) 34.5% (95% CI: 33.7–35.3) of unsolicited AEs were considered ***vaccine-related*** in the HZ/Su arm versus 6.6% (95% CI: 6.2–7.0) in the placebo arm. Refs: (4)		⊕⊕⊕⊕ HIGH
Duration of protection (VE HZ) (follow up: range 3.2 years to 3.7 years; assessed with: PCR/blinded ascertainment committee confirmed [VE = (1-RR)x100])											

Certainty assessment							№ of patients[1]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV (Shingrix)	placebo	Relative (95% CI)	Absolute (95% CI)	
2	Randomised trials	not serious	not serious	not serious	not serious	strong association	29/13885 (0.2%)	443/14037 (3.2%)	Duration of protection of clinical efficacy against confirmed HZ reported for up to 4 years post vaccination Vaccine efficacy remained >80% in the first 4 years following vaccination in two large RCTs, trending slightly lower in the older age group across all time points. Refs: (1, 2)		⨁⨁⨁⨁ HIGH

Explanations

a. Risk of bias - some concerns due to potential for selective reporting (post hoc pooled analysis due to low event numbers); however, not downgraded as outcome was a prespecified outcome prospectively measured according to study protocol

b. Wide confidence interval crosses null due to small number of hospitalised cases

Evidence to Decision Framework: Individual Perspective

SHOULD RECOMBINANT HERPES ZOSTER VACCINE (SHINGRIX) VERSUS PLACEBO BE USED FOR IMMUNOCOMPETENT OLDER ADULTS?	
Population	Immunocompetent older adults (aged ≥50 years)
Intervention	Recombinant herpes zoster vaccine (Shingrix)
Comparison	Placebo
Main outcomes	Vaccine efficacy against confirmed herpes zoster Vaccine efficacy against post-herpetic neuralgia Herpes zoster–related hospitalisation Herpes zoster–related mortality Serious adverse events Local solicited adverse events General/systemic solicited adverse events Unsolicited adverse events Duration of protection (VE HZ)
Setting	US, Europe, Latin America, Asia, Australia
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- The lifetime risk of shingles is 20–30%, particularly from 50 years of age. Incidence increases with age, from 6.5 per 1,000 population in persons aged 50–59 years to over 14 per 1,000 population in those over 70 years of age. (6)
- Post-herpetic neuralgia causes significant disease burden (6)

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Point estimates for VE against HZ in 2 large RCTs were >90% in all age groups across 3.2–3.7 years follow-up (1, 2)
- Vaccine efficacy remained >80% in the first 4 years following vaccination in two large RCTs (longest follow-up to date), trending slightly lower in the older age group across all time points. Immunogenicity data suggest protection may persist for at least 10 years post vaccination. (7)
- Point estimate for VE against PHN was 91.2% in the ≥50 years age group, and 88.8% in the ≥70 years age group.

Undesirable effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Higher frequency of local and systemic adverse events, including Grade 3 (preventing normal functioning) was observed in the vaccine arm compared with placebo (1, 2)
- However, frequency of serious adverse events appear similar between RZV and placebo recipients (1, 2, 4)

Certainty of evidence
What is the overall certainty of the evidence of effects?

No. included studies	Very low	Low	Moderate	High

- Certainty of evidence against HZ-related hospitalisation downgraded due to imprecision (low event numbers)
- Certainty of evidence against HZ-related mortality unable to be assessed due to zero events in the included trials
- Other efficacy and safety outcomes were of high certainty

Values
I*s there important uncertainty about or variability in how much people value the main outcomes?*

Important uncertainty		Possibly important uncertainty or variability		Probably no important uncertainty or variability		No important uncertainty or variability
• Unlikely to be important uncertainty in how people value protection against shingles and post-herpetic neuralgia						
Balance of effects *Does the balance between desirable and undesirable effects favour the intervention or the comparison?*						
Don't know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention
• The overall high protection against HZ provided by RZV is likely to outweigh the additional frequency of non-serious adverse events/reactogenicity						
Acceptability *Is the intervention acceptable to key stakeholders?*						
Don't know	Varies	No	Probably no	Probably yes	Yes	
• Vaccination to prevent herpes zoster appears to be acceptable in the Australian setting, with estimates of up to 47% of eligible Australians aged 70–79 years receiving a single dose of the NIP-funded live vaccine in approximately the first 2 years of the program. (8-10) • Shingrix has not been administered in a non-trial setting in Australia; however, the majority (>94% in all arms) of vaccine recipients in two large RCTs completed the two-dose schedule.						
Feasibility *Is the intervention feasible to implement?*						
Don't know	Varies	No	Probably no	Probably yes	Yes	
• Vaccine delivery system already exists						

Note: The Australian Technical Advisory Group on Immunisation takes an individual perspective when using the GRADE framework and does not consider resources or cost-effectiveness, with agreement from the National Health and Medical Research Council.

References

1. National Centre for Immunisation Research and Surveillance. Zoster vaccine for Australian adults.; 2020.
2. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016;375(11):1019-32.
3. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087-96.
4. Hastie A, Catteau G, Enemuo A, Mrkvan T, Salaun B, Volpe S, et al. Immunogenicity of the Adjuvanted Recombinant Zoster Vaccine: Persistence and Anamnestic Response to Additional Doses Administered 10 Years After Primary Vaccination. The Journal of infectious diseases. 2020.
5. López-Fauqued M, Campora L, Delannois F, El Idrissi M, Oostvogels L, De Looze FJ, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-93.
6. National Centre for Immunisation Research and Surveillance. Evaluation of the National Shingles Vaccination Program: process and early impact evaluation.; 2019.
7. Jayasinghe S, Sheridan S, Macartney K. Herpes zoster vaccination in Australia: what's available and who benefits? Aust Prescr. 2020;43(1):2-6.
8. Lin J, Wood JG, Bernardo C, Stocks NP, Liu B. Herpes zoster vaccine coverage in Australia before and after introduction of a national vaccination program. Vaccine. 2020;38(20):3646-52.