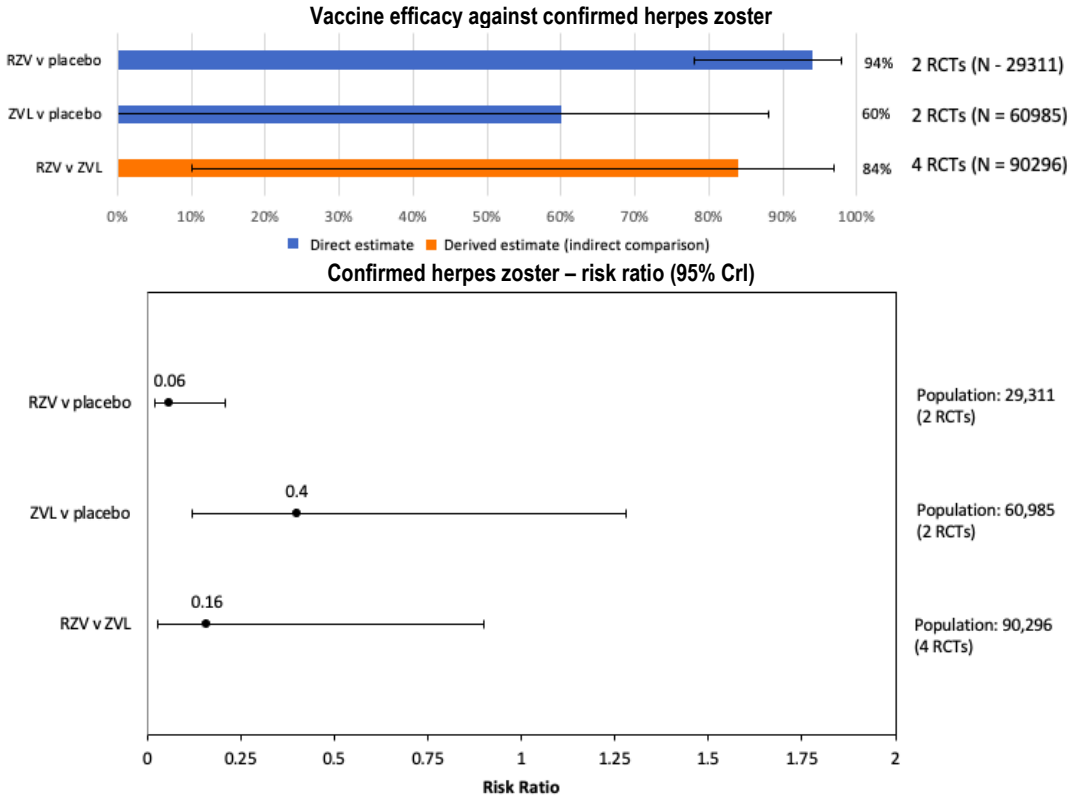
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the ATAGI statement on the clinical use of zoster vaccines in older adults in Australia.

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with live zoster vaccine (Zostavax) 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: Live zoster vaccine (Zostavax) SC at 0 mo (ZVL)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV vs ZVL) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with ZVL	Risk with RZV				
CRITICAL OUTCOMES						
Confirmed herpes zoster assessed with: PCR or blinded ascertainment committee confirmed Follow-up range: 1.3 years to 3.7 years 4 RCTs		⊕⊕⊕◯ MODERATE [a,b]	Recombinant zoster vaccine (Shingrix) probably results in a large reduction in confirmed herpes zoster compared with Zostavax. Note: Informative prior sensitivity analysis obtained from researchers[i] suggests less serious imprecision and inconsistency: RR = 0.16 (95% CrI: 0.05–0.53) (95% PrI: 0.03–0.82) Refs: (1-5)

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

Patient or population: Immunocompetent older adults ≥50 years
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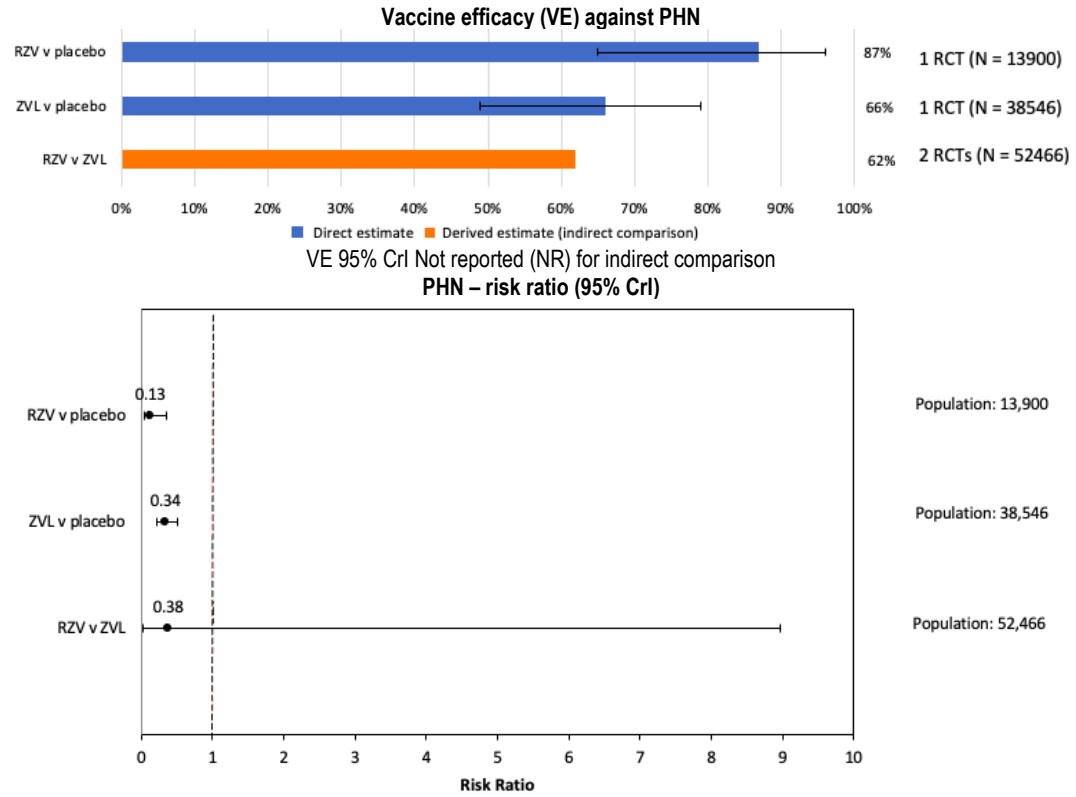
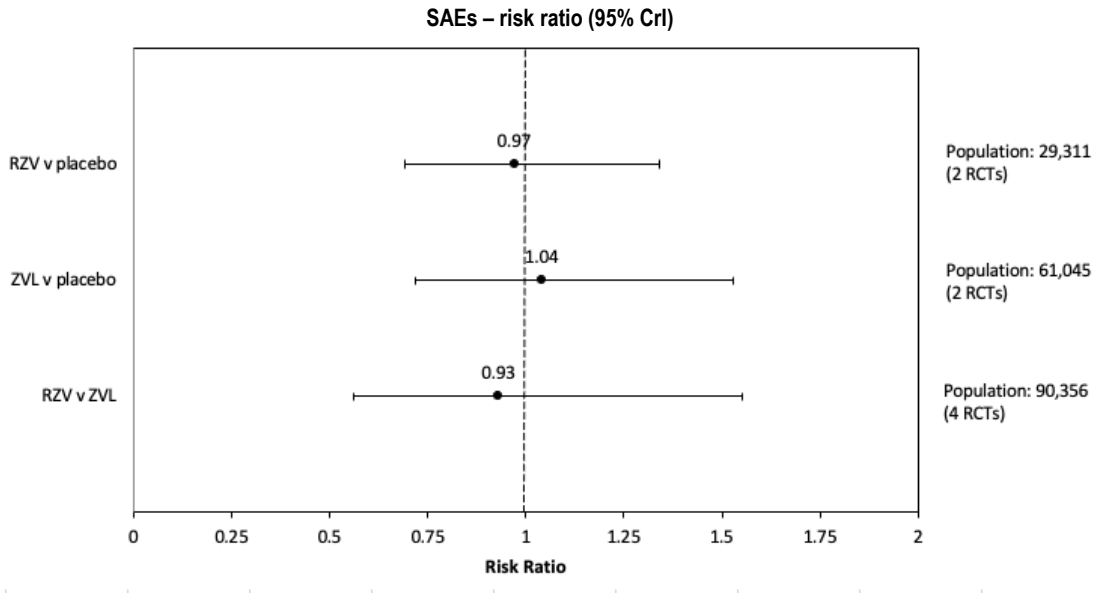
Comparison: Live zoster vaccine (Zostavax) SC at 0 mo (ZVL)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV vs ZVL) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with ZVL	Risk with RZV				
Post-herpetic neuralgia (PHN) assessed with: HZ-associated pain score ≥ 3 persisting or appearing >90 days after onset of HZ rash on Zoster brief pain inventory (ZBPI) Follow-up range: 3.1 years to 3.7 years 2 RCTs				⨁◯◯◯ VERY LOW b,c,d,e	Recombinant zoster vaccine (Shingrix) may reduce PHN compared with Zostavax, but the evidence is very uncertain. Note: Informative prior sensitivity analysis obtained from researchers[i] indicates persistent imprecision and inconsistency (RR = 0.39 (95% CrI: 0.05–3.17) (95% PrI: 0.03–4.88). Estimated VE = 61% (-216% to 95%) Note: Zoe-50 VE against PHN not included in meta-analysis for RZV versus placebo. The ZOE-50 VE estimates is higher than Zoe-70 – inclusion of this study likely to increase the RZV versus placebo estimate for VE against PHN Refs: (2, 3, 5)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with live zoster vaccine (Zostavax) 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: Live zoster vaccine (Zostavax) SC at 0 mo (ZVL)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV vs ZVL) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with ZVL	Risk with RZV				
Serious adverse events (SAEs) assessed with: Any events requiring hospitalisation (initial or prolonged) or medical intervention to prevent permanent damage/impairment, resulting in birth defect, disability/permanent damage, death or life-threatening condition Follow-up: 182 days to 12 months 4 RCTs				⊕◯◯◯ VERY LOW b,f,	Recombinant zoster vaccine (Shingrix) may have little to no effect on SAEs compared with Zostavax, but the evidence is very uncertain. Note: Informative prior sensitivity analysis obtained from researchers[i] indicates persistent imprecision and inconsistency RR = 0.93 (95% CrI: 0.56–1.53) (95% PrI: 0.47–1.86) Refs: (1-6)

[i] Analysis performed by Areti-Angeliki Veroniki (AV) to inform recommendations in the Australian Immunisation Handbook (Received in an email). Data were from a published network MA for which AV conducted the original analysis (BMJ 2018;363:k4029 http://dx.doi.org/10.1136/bmj.k4029).

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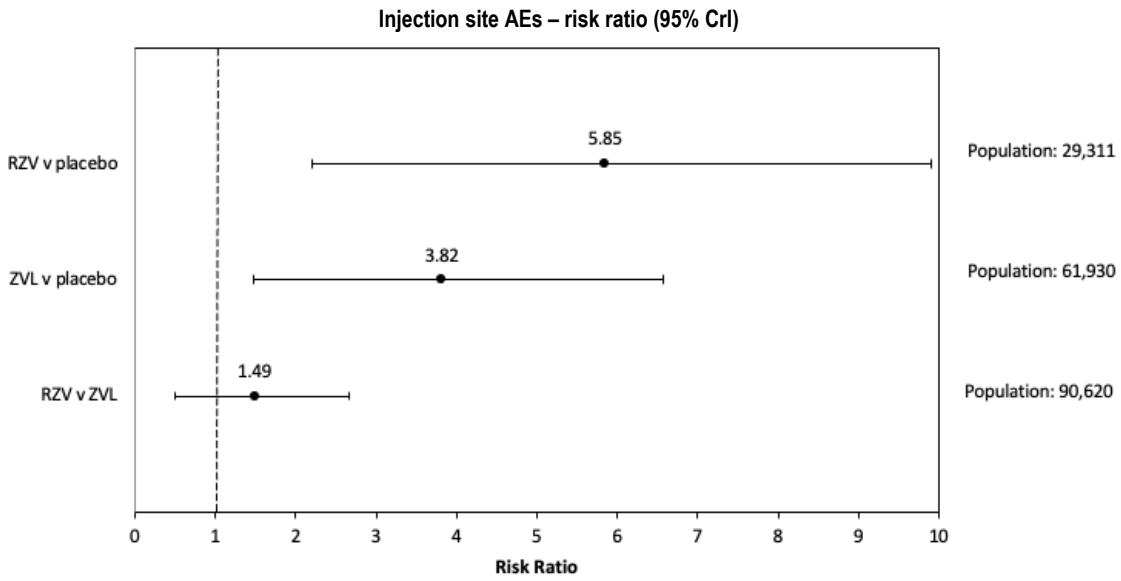
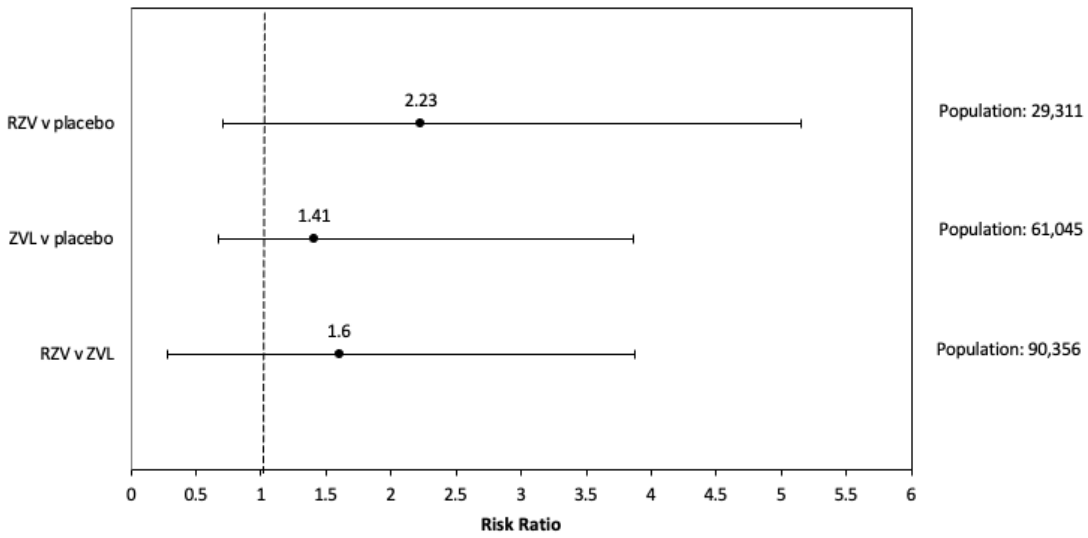
Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV versus ZVL) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with ZVL	Risk with RZV				
IMPORTANT OUTCOMES						
Injection site adverse events (AEs) Assessed with: Diary card: Local reactions such as pain, redness, swelling, induration, pruritus, etc at the injection site. Follow up: range 7 days to 42 days 6 RCTs					⨁◯◯◯ VERY LOW b,g,i,j,k	Recombinant zoster vaccine (Shingrix) may increase injection site AEs, but the evidence is very uncertain. Note: ZVL versus placebo includes study (Hata 2016 (7)) of BIKEN vaccine in immunocompetent diabetics (n=54) and study administering two doses of Zostavax (Vermeluen 2012 (8), n=209) Refs: (1-8)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared to Live zoster vaccine (Zostavax) 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: Live zoster vaccine (Zostavax) SC at 0 mo (ZVL)

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV vs ZVL) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with ZVL	Risk with RZV				
Systemic adverse events (AEs) Assessed with: Diary Card: Generalised reactions such as headache, myalgia, fever, fatigue, etc. Follow up: range 7 days to 42 days 6 RCTs			**Systemic AEs – risk ratio (95% CrI)** 	Population: 29,311 Population: 61,045 Population: 90,356	⊕◯◯◯ VERY LOW b,g,i,l,m	Recombinant zoster vaccine (Shingrix) may increase systemic AEs but the evidence is very uncertain. Note: ZVL vs placebo includes study (Hata 2016 (7)) of BIKEN vaccine in immunocompetent diabetics (n=54) and study administering two doses of Zostavax (Vermeluen 2012 (8), n=209) Refs: (1-8)

95% CrI: 95% credible interval; **95% PrI**: prediction interval. Figures reflect sensitivity analysis limited to RCTs in immunocompetent participants only (excluding observational studies and studies potentially including immunocompromised participants)
Follow-up for outcome measurement extracted from original studies – reflects combined range for RZV and ZVL studies

* 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

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

Certainty assessment							№ of patients[i]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency[ii]	Indirectness[iii]	Imprecision[iv]	Other considerations	RZV	ZVL	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOMES											
Confirmed herpes zoster (HZ)											
1	Network meta-analysis	not serious	not serious[a]	serious[b]	not serious	none	2 RCTs 29,311	2 RCTs 60,985	Estimated vaccine efficacy of RZV versus ZVL against HZ (indirect) was 84% (95% CrI: 10–97%). The RR of confirmed HZ with receipt of RZV compared with ZVL was 00.16 (95% CrI: 0.03–0.90) (95% PrI: 0.01–1.73) Informative prior sensitivity analysis[v] obtained from researchers suggests less inconsistency (RR = 0.16 [95% CrI: 0.05–0.53] [95% PrI: 0.03–0.82])		⊕⊕⊕◯ MODERATE a,b
Post-herpetic neuralgia (PHN)											
1	Network meta-analysis	not serious[c]	unable to rate[d]	serious[b]	very serious[e]	none	1 RCT 13,900	1 RCT 38,546	Estimated vaccine efficacy of RZV versus ZVL against PHN (indirect) was 62% (95% CrI NR for indirect comparison) The RR of PHN with receipt of RZV compared with ZVL was 0.38 (95% CrI: 0.02–8.96) Informative prior sensitivity analysis[v] obtained from researchers indicates persistent imprecision and inconsistency (RR = 0.39 [95% CrI: 0.05–3.17] [95% PrI: 0.03–4.88]). Estimated VE = 61% (-216% to 95%)		⊕◯◯◯ VERY LOW b,c,d,e
Serious adverse events (SAEs)											
1	Network meta-analysis	not serious	serious[f]	serious[b]	serious[h]	none	2 RCTs 29,311	2 RCTs 61,045	The RR of SAEs with receipt of RZV compared with ZVL was RR = 0.93 (95% CrI: 0.56–1.55) (95% PrI: 0.45–1.85) Informative prior sensitivity analysis[v] obtained from researchers indicates persistent imprecision and inconsistency (RR = 0.93 [95% CrI: 0.56–1.53] [95% PrI: 0.47–1.86])		⊕◯◯◯ VERY LOW b,f,h
IMPORTANT OUTCOMES											
Injection site adverse events (AEs)											
1	Network meta-analysis	not serious [i]	serious [j]	serious [b,g]	serious [k]	none	2 RCTs 29,311	4 RCTs 61,390	The RR of Injection site AEs with receipt of RZV compared with ZVL was RR = 1.49 (95% CrI: 0.49–2.66) (95% PrI: 0.23–2.91)		⊕◯◯◯ VERY LOW b,g,i,j,k
Systemic AEs											

Certainty assessment							№ of patients[i]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency[ii]	Indirectness[iii]	Imprecision[iv]	Other considerations	RZV	ZVL	Relative (95% CI)	Absolute (95% CI)	
1	Network meta-analysis	not serious [i]	serious [l]	serious [b,g]	serious [m]	none	2 RCTs 29,311	4 RCTs 61,390	The RR of systemic AEs with receipt of RZV compared with ZVL was RR = 1.60 (95%CrI: 0.28–3.88) (95% PrI: 0.12–5.19)		⨁◯◯◯ VERY LOW [b,g,i,l,m]

Notes

i Manually calculated pooling data from all included studies
ii 95% PrI = 95% prediction interval; this statistic predicts the interval within which the results of a future study may fall, and forms the basis of the assessment of inconsistency.
iii There is currently no head-to-head comparison of Shingrix and Zostavax. This GRADE Assessment is based on a network meta-analysis which provides an indirect comparison of two interventions compared with a common third intervention (in this case placebo). The validity of the network meta-analysis relies on both interventions having been administered to similar populations with similar outcome measurement. Indirectness has been downgraded once for all outcomes because of the lack of direct comparison of the two interventions.
iv 95% CrI = 95% credible interval; this statistic is from Bayesian analysis, but can be interpreted in the same way as a 95% CI from a frequentist analysis, and forms the basis of the assessment of imprecision.
v Informative prior analysis uses externally acquired data (from Cochrane database of systematic reviews) to assess expected heterogeneity across particular outcomes, and so may give a more accurate assessment of heterogeneity/inconsistency (reflected in a narrower prediction interval) in the context of network meta-analyses based on a very small number of studies.

Explanations

a 95% PrI includes potential harm and benefit: RR = 0.16 (95% CrI: 0.03–0.90; 95% PrI: 0.01–1.73). Informative prior sensitivity analysis obtained from researchers) suggests less inconsistency (RR = 0.16 (95% CrI: 0.05–0.53) (95% PrI: 0.03–0.82).
b Indirect comparison via network meta-analysis. ZVL population younger than RZV population. Downgraded once only.
c Relevant pivotal study excluded (Zoe-50) - no justification provided. Not downgraded.
d. Inconsistency not able to be assessed - only 2 RCTs (1 direct comparison of each intervention against placebo) included for this outcome.
e 95% CrI includes potential harm and benefit: RR = 0.38 (0.02 – 8.96). Informative prior sensitivity analysis obtained from researchers indicates persistent imprecision and inconsistency (RR = 0.39 (95% CrI 0.05–3.17) (95% PrI: 0.03–4.88). Low event numbers in Zoe-70 (Vaccine arm = 4/6950; Placebo = 28/6950).
f Wide 95% PrI, upper limit 1.85, includes potential harm and benefit: RR = 0.93 (0.45–1.85).
g Small study (n=54) of BIKEN live vaccine in immunocompetent diabetic patients, and study administering two doses (n-209) included - not downgraded a second time because of small proportion of total participants in this comparison it represents.
h 95% CrI includes potential harm and benefit: RR = 0.93 (0.56–1.55). Informative prior sensitivity analysis obtained from researchers indicates persistent imprecision and inconsistency (RR = 0.93 (95% CrI: 0.56–1.53) (95% PrI: 0.47–1.86).
i Not downgraded despite Shingles Prevention Study (largest ZVL versus placebo study) recording/analysing Solicited AEs in non-randomised voluntary subcohort (n=6,616) only – not downgraded because of these being expected AEs measured by diary card in blinded cohort, large number of participants.
j Wide 95% PrI, upper limit 2.91, includes potential harm and benefit: RR = 1.49 (0.23–2.91).
k 95% CrI includes potential harm and benefit: RR = 1.49 (95% CrI: 0.49–2.66).
l Wide 95% PrI, upper limit 5.19, includes potential harm and benefit: RR = 1.60 (0.12–5.19).
m 95% CrI includes potential harm and benefit: RR = 1.60 (0.28–3.88).

Evidence to Decision Framework: Individual Perspective

SHOULD RECOMBINANT HERPES ZOSTER VACCINE (SHINGRIX) VERSUS ZOSTAVAX BE USED FOR IMMUNOCOMPETENT OLDER ADULTS?	
Population	Immunocompetent older adults (≥50 years)
Intervention	Recombinant herpes zoster vaccine (RZV; Shingrix)
Comparison	Live zoster vaccine (ZVL; Zostavax)
Main outcomes	Vaccine efficacy against confirmed herpes zoster Vaccine efficacy against post-herpetic neuralgia Serious adverse events Local solicited adverse events General/systemic solicited adverse events
Setting	Global middle- to high-income countries
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Lifetime risk of shingles 20–30%, primarily in older adults (9)
- Post-herpetic neuralgia causes significant disease burden (9)
- Live zoster vaccine has vaccine efficacy against herpes zoster of 51%, and 67% against post-herpetic neuralgia (9, 10)

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Shingrix probably results in a large reduction in herpes zoster compared with Zostavax.
  - Estimated vaccine efficacy of RZV versus ZVL against HZ (indirect) was 84% (95% CrI: 10%–97%).
  - The RR of confirmed HZ with receipt of RZV compared with ZVL was 0.16 (95% CrI: 0.05%–0.53%) (95% PrI: 0.03%–0.82%)
  - Informative prior sensitivity analysis obtained from researchers suggests less inconsistency (RR = 0.16 (95% CrI: 0.05%–0.53%) (95% PrI: 0.03%–0.82%)
- Shingrix may reduce post-herpetic neuralgia compared with Zostavax but the evidence is very uncertain.
  - Estimated vaccine efficacy of RZV versus ZVL against PHN (indirect) was 62% (95% CrI: NR for indirect comparison). The RR of PHN with receipt of RZV compared with ZVL was 0.38 (95% CrI: 0.02% – 8.96%).

Undesirable Effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Shingrix may be associated with a higher incidence of local and systemic solicited reactions but the evidence is very uncertain.
  - The RR of injection site AEs with receipt of RZV compared with ZVL was 1.49 (95%CrI: 0.49–2.66) (95% PrI: 0.23–2.91)
  - The RR of systemic AEs with receipt of RZV compared with ZVL was 1.60 (95% CrI: 0.28–3.88) (95% PrI: 0.12–5.19)
- Shingrix may have little to no effect on SAEs compared with Zostavax but the evidence is very uncertain.
  - The RR of SAEs with receipt of RZV compared with ZVL was 0.93 (95% CrI: 0.56–1.55) (95% PrI: 0.45–1.85)
-

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

No. included studies	Very low	Low	Moderate	High

- Certainty of evidence for protection against HZ is moderate; however, certainty for remaining critical and important

outcomes is very low to low.

- There has been no head-to-head comparison of Shingrix and Zostavax – evidence for relative benefit/harm from future direct comparison may affect the nature/strength of this recommendation.
- Despite uncertainty of the relative efficacy and safety of Shingrix versus Zostavax, the certainty of high vaccine efficacy and acceptable safety of Shingrix compared with placebo in this population is high.
- Additional informative prior sensitivity analyses have been sought from the researchers for critical outcomes, which take into consideration the impact of low study numbers in the network meta-analysis.

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

- Shingrix probably results in a large reduction in herpes zoster compared with Zostavax, but evidence regarding relative protection against post-herpetic neuralgia and relative incidence of undesirable effects is very uncertain.

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 >30% of Australians aged >70 years receiving the NIP-funded live vaccine in the first 17 months of the program. (10, 11)
- Shingrix requires 2 doses of vaccine administered 2–6 months apart. This vaccine has not been administered in a non-trial settings 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
- Shingrix will be available in limited supply

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.

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