Shingrix use immunocompromised adults (PICO 2): GRADE tables and study characteristics

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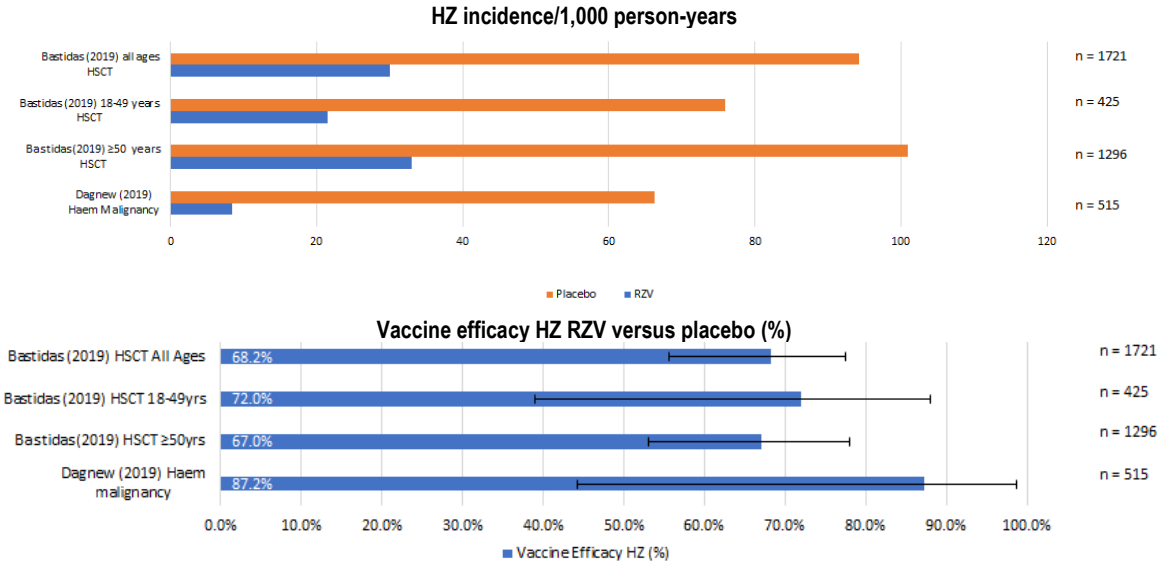
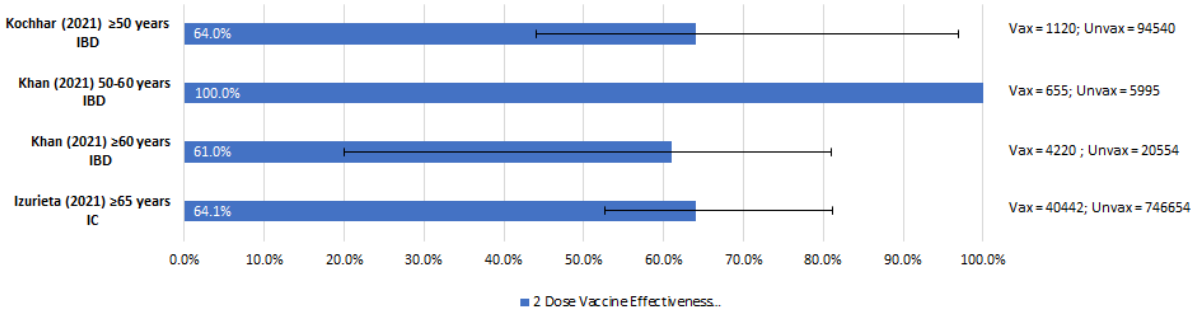
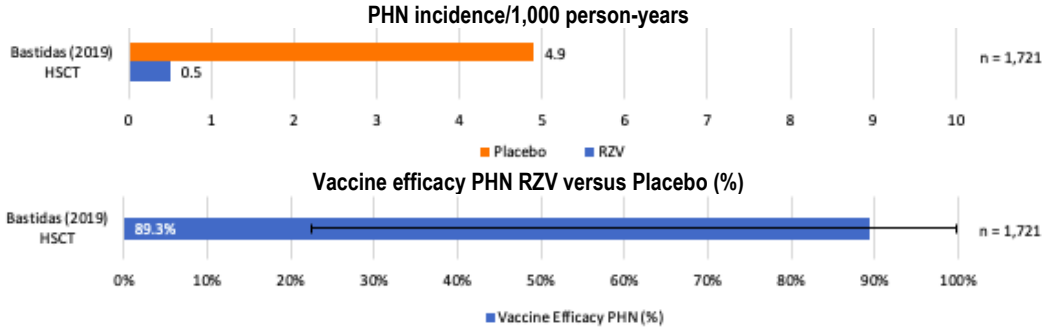
Summary of Findings (SoF) Table

Summary of findings: Recombinant herpes zoster vaccine (Shingrix, RZV) compared with placebo or unvaccinated for immunocompromised adults

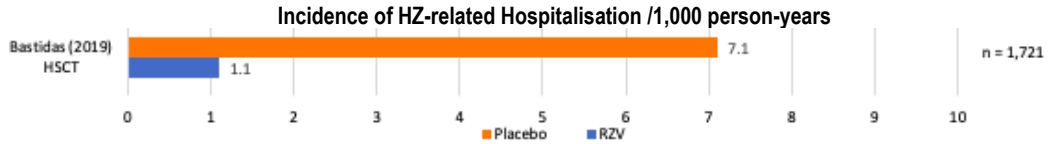
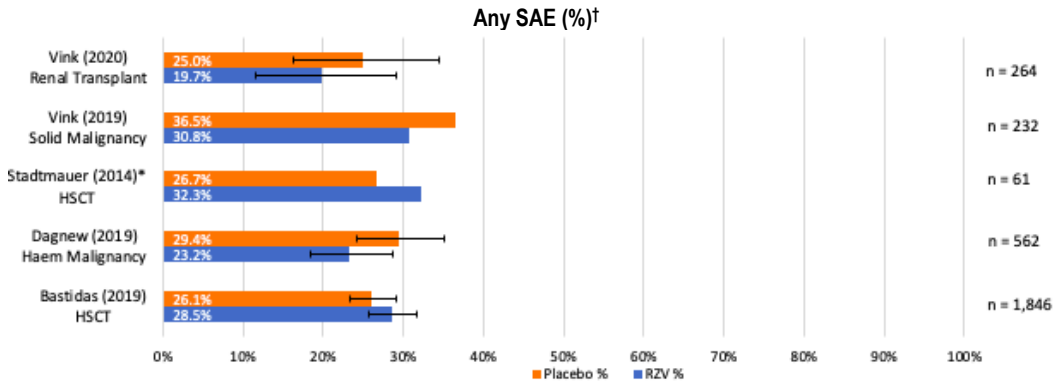
Patient or population: Immunocompromised adults aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (placebo) or unvaccinated

Outcomes (No. studies)	Anticipated absolute effects* (95% CI)		Relative effect (RZV versus Placebo or Unvaccinated) (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with RZV				
CRITICAL OUTCOMES						
Confirmed herpes zoster (HZ) Assessed with: PCR or blinded ascertainment committee Follow-up: 11.1–21 months Participants: 2,236 (2 RCTs)			⊕⊕⊕◯ MODERATE [a]	Recombinant zoster vaccine (Shingrix) probably results in a large reduction in confirmed HZ. Note: Immunocompromised populations represented in data: Bastidas 2019: Recent haematopoietic stem cell transplant Dagnew 2019: Haematological malignancy receiving or recently received immunosuppressive therapy Ref: (1, 2)

Herpes zoster (HZ) Assessed with: ICD-9, ICD-10 or SNOMED-CT coding from administrative or electronic medical record data Follow-up: 9-23 months Participants: 914,180 (3 Observational Studies)		⊕⊕⊕◯ MODERATE [b]	Recombinant zoster vaccine (Shingrix) probably results in a large reduction in confirmed HZ Note: Vaccine effectiveness was calculated: Kochhar 2021: VE = 1-Odds Ratio Khan 2021: VE = 1-Hazard Ratio Izurieta 2021: VE = 1-Hazard Ratio Khan and Izurieta assessed HZ with diagnostic codes from International Classification of Diseases, Ninth and/or Tenth Revision, Clinical Modification (ICD-9-CM & ICD-10-CM) and Kochhar used SNOMED-CT diagnostic coding IBD = Inflammatory Bowel Disease IC = General Immunocompromise Ref: (3-5)
Post-herpetic neuralgia (PHN) Assessed with: HZ-associated worst pain (ZBPI ≥3) persisting or appearing more than 90 days post HZ rash onset Follow-up: 11.1–21 months Participants: 1,721 (1 RCT)		⊕⊕⊕◯ MODERATE [c,d,e]	Recombinant zoster vaccine (Shingrix) probably results in a large reduction in PHN. Note: Immunocompromised populations represented in data: Bastidas 2019: Recent haematopoietic stem cell transplant Ref: (1)

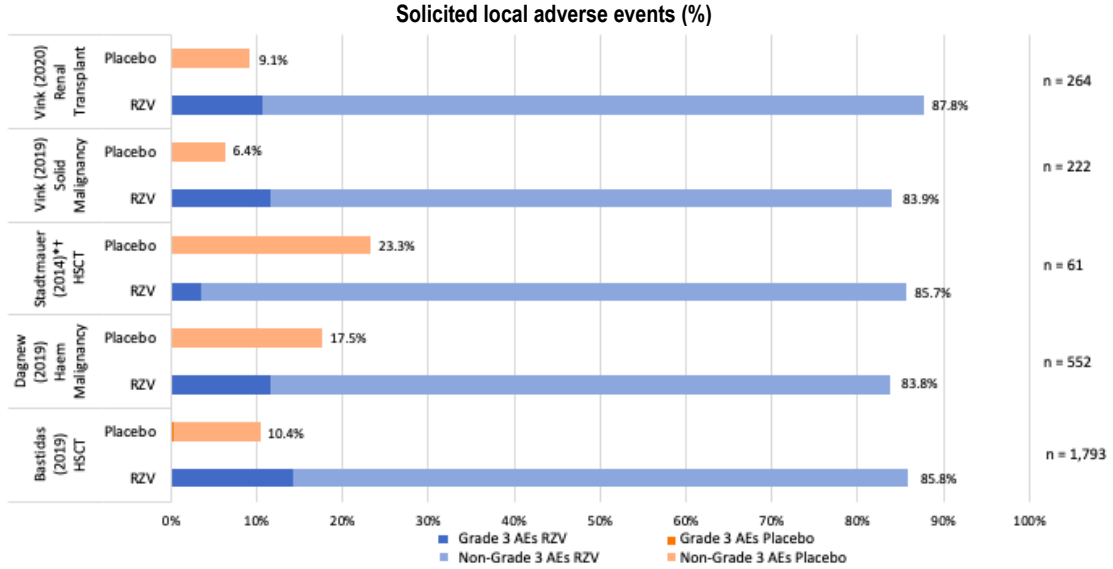
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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				
HZ-related hospitalisation Follow-up: 21 months Participants: 1,721 (1 RCT)			 Hazard ratio (HR) of HZ-related hospitalisation in the vaccine arm compared with placebo was 0.15 (95% CI, 0.03-0.68; P = .01)		⊕⊕⊕◯ MODERATE c,d,h	Recombinant zoster vaccine (Shingrix) probably results in a large reduction in HZ-related hospitalisation. Note: Immunocompromised populations represented in data: Bastidas 2019: Recent haematopoietic stem cell transplant Ref: (1)
Serious adverse events (SAEs) defined as: events that resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in disability, incapacity, congenital anomaly, or birth defect in participant's child Follow-up: 12 months post 2nd dose Participants: 3,088 (6 RCTs)			 † Not limited to SAEs deemed vaccine-related * Participants received 3 injections - vaccine arm received 1 dose placebo followed by 2 doses vaccine		⊕⊕⊕⊕ HIGH f,g	Recombinant zoster vaccine (Shingrix) results in little to no difference in SAEs. Note: Rates of ***vaccine-related*** SAEs were low (<0.5%) and similar between intervention arms across studies. One small RCT (Stadtmauer 2014) reported a rate of vaccine-related SAEs of 3.2% in the vaccine arm (n=1) compared with 0% in placebo. Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy Ref: (1, 2, 6-8)

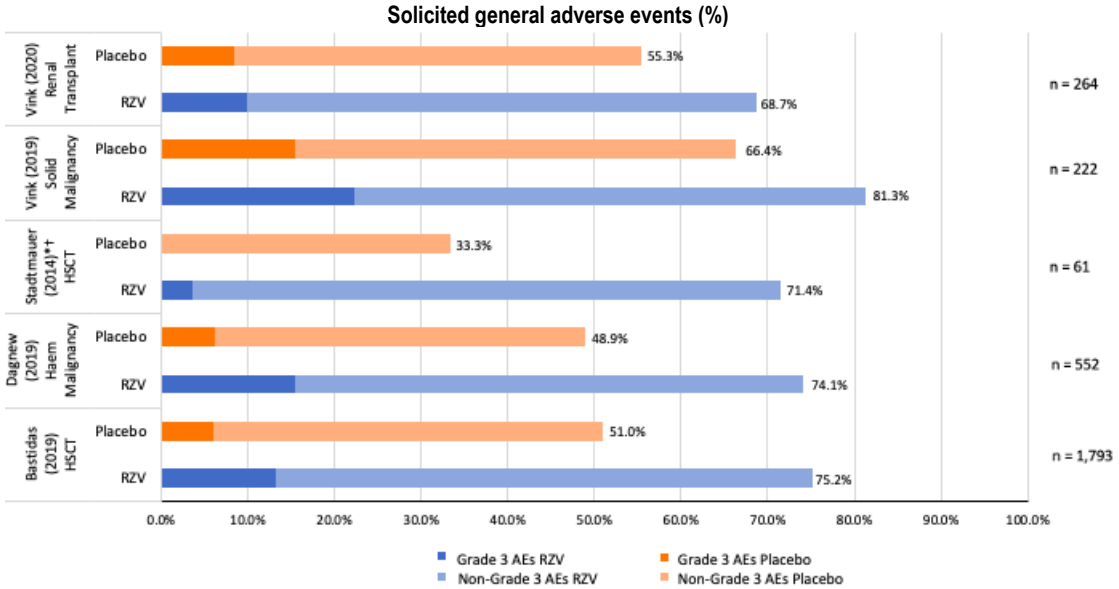
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo for immunocompromised adults

Patient or population: Immunocompromised adults aged ≥18 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				
IMPORTANT OUTCOMES						
Solicited local adverse events Assessed with: Diary card Follow-up: 7 days post vaccination Participants: 2,892 (5 RCTs)	 * Participants received 3 injections - vaccine arm received 1 dose placebo followed by 2 doses vaccine † Total local AEs NR – Figures reflect the most frequently reported local solicited AE – pain			⊕⊕⊕⊕ HIGH [i]	Recombinant zoster vaccine (Shingrix) results in large increase in solicited local adverse events. Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy Ref: (1, 2, 6-8)

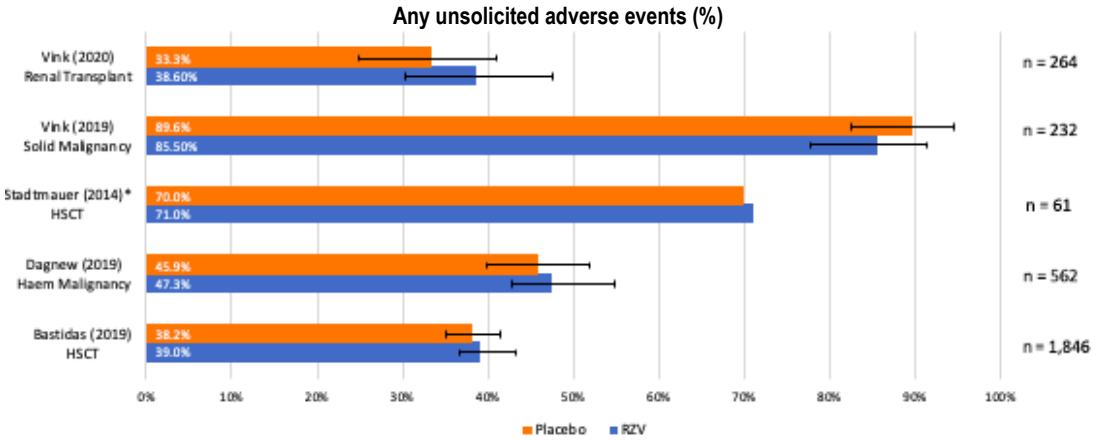
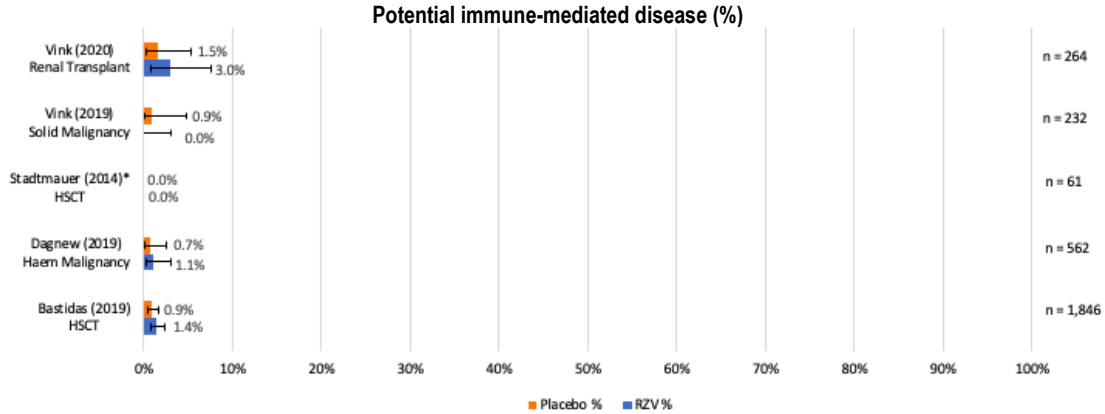
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised adults aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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				
Solicited general adverse events Assessed with: Diary card Follow-up: 7 days post vaccination Participants: 2,892 (5 RCTs)	 * Participants received 3 injections - vaccine arm received 1 dose placebo followed by 2 doses vaccine † Total Solicited General AEs NR – Figures reflect the most frequently reported general solicited AE – fatigue			⊕⊕⊕⊕ HIGH [i]	Recombinant zoster vaccine (Shingrix) results in an increase in solicited general adverse events. Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy Ref: (1, 2, 6-8)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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 adverse events Follow-up: 30 days post vaccination Participants: 2,965 (5 RCTs)			 * Participants received 3 injections - vaccine arm received 1 dose placebo followed by 2 doses vaccine	⊕⊕⊕⊕ HIGH [i]	Recombinant zoster vaccine (Shingrix) results in little to no difference in unsolicited adverse events. Note: Rates of **Grade 3** and **vaccine-related** events were similar between arms. Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy Ref: (1, 2, 6-8)
Potential immune-mediated disease (adverse event of special interest) Follow-up: 11–25 months Participants: 2,904 (4 RCTs)			 * Participants received 3 injections - vaccine arm received 1 dose placebo followed by 2 doses vaccine	⊕⊕⊕⊕ HIGH [i,j]	Recombinant zoster vaccine (Shingrix) results in little to no difference in potential immune-mediated disease. Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy Ref: (1, 2, 6-8)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised adults aged ≥18 years
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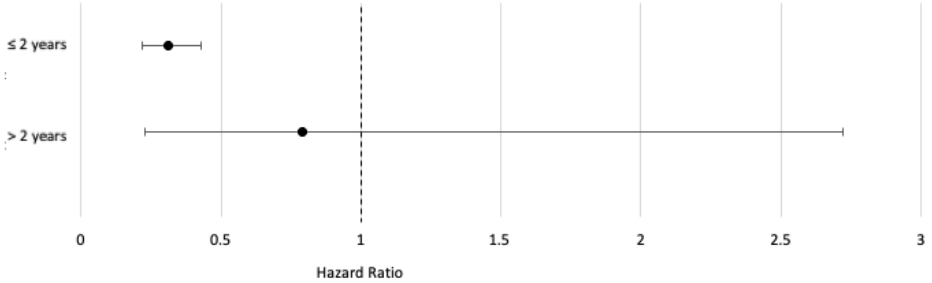
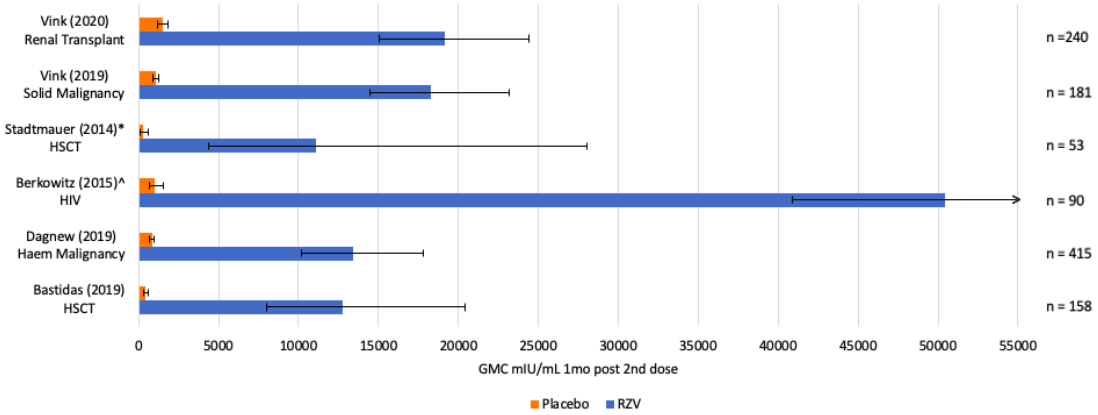
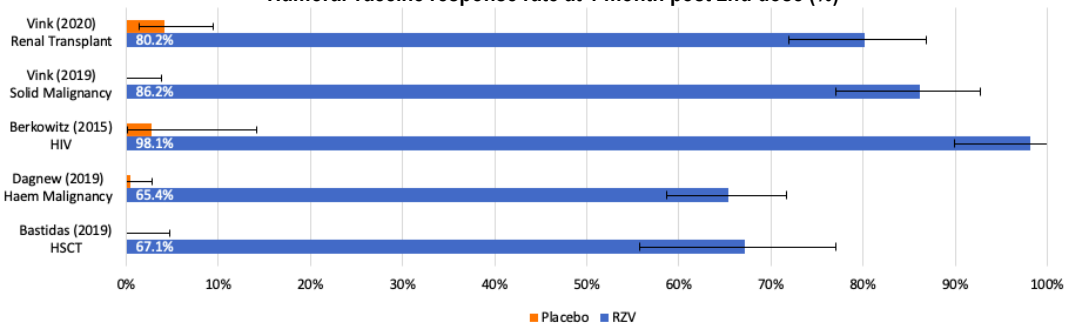
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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				
Duration of protection (clinical outcomes) Assessed with: PCR or blinded ascertainment committee Follow-up: 21 months Participants: 1,721 (1 RCT)			**Duration of protection: Hazard ratio for first HZ episode by time since vaccination**  **First HZ episode: (time since the first month after dose 2)** (Bastidas 2019 – HSCT patients) ≤ 2 years: HR = 0.31 (95% CI: 0.22–0.43; P < 0.001) >2 years: HR = 0.79 (95% CI: 0.23–2.72; P < 0.71)		⊕⊕⊕◯ MODERATE [c,d] ⊕◯◯◯ VERY LOW [c,d,j,n]	Recombinant zoster vaccine (Shingrix) probably reduces HZ to 2 years post vaccination but the evidence for protection beyond 2 years is very uncertain. Note: Post-hoc analysis - insufficient follow-up to determine duration of protection beyond 2 years Ref: (1)

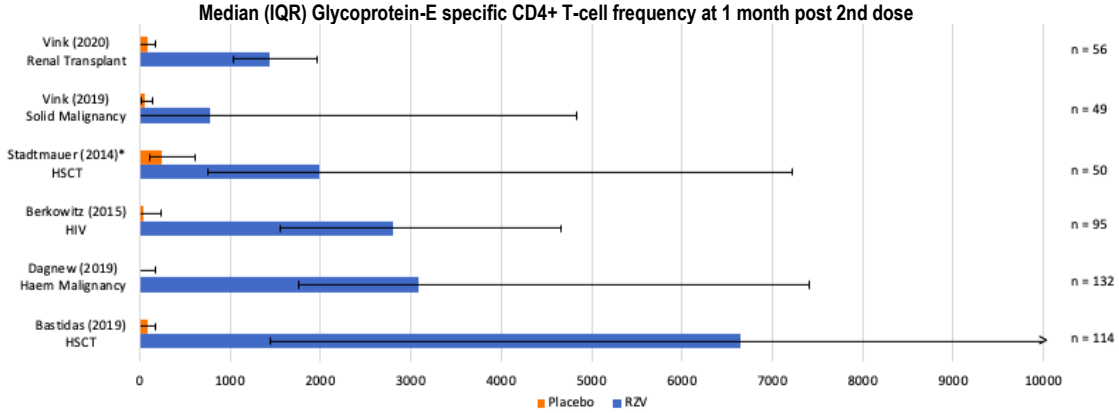
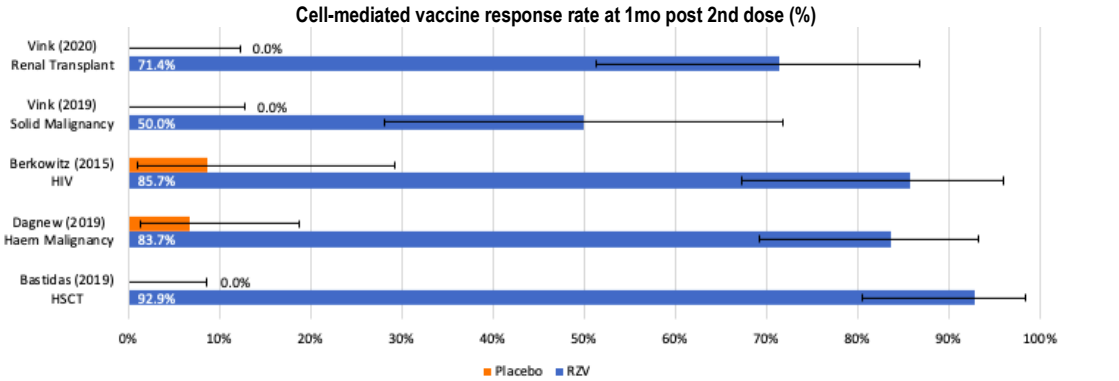
Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised adults aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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				
Humoral immune response assessed with: Anti-glycoprotein E GMC (VRR = post-vaccination anti-glycoprotein E at least 4-fold the cut-off (for participants initially below the cut-off) or 4-fold the pre-vaccination concentration (for participants initially above the cut-off): ELISA cut-off range 18-97 mIU/mL) follow up: 1 months Participants: 1,137 (6 RCTs)			**Anti-glycoprotein E geometric mean concentration (95% CI) at 1 month post 2nd dose (mIU/mL)**  **Humoral vaccine response rate at 1 month post 2nd dose (%)**  		⨁⨁⨁⨁ HIGH [g]	Recombinant zoster vaccine (Shingrix) results in a large increase in humoral immunogenicity measured by anti-glycoprotein E levels/response. Note: Stadtmauer (2104) does not report VRR % - presented in in-text figure only (approx. 78% vaccine arm, 0% placebo arm) – not included in GRADE for VRR Note: Immunocompromised populations represented: recent hematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy; HIV on stable ART, CD4 T cell count ≥50 cells/mm3 and viral load ≤ 40 copies/mL Ref: (1, 2, 6-9)

Summary of findings: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Patient or population: Immunocompromised adults aged ≥18 years
Intervention: Recombinant herpes zoster vaccine (Shingrix) IM at 0, 2 mo (RZV)
Comparison: Placebo IM at 0, 2 mo (Placebo) or unvaccinated

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				
Cell-mediated immune response assessed with: Median Glycoprotein-E specific CD4+ T-cell frequency and vaccine response rate (VRR = % of participants with post vaccination frequency of CD4 T cells expressing at least 2 activation markers of ≥ 2-fold the threshold of 320 per 10^6 total CD4 T cells (for participants initially below this threshold) or at least 2-fold the pre-vaccination CD4 T-cell frequencies (for participants initially above this threshold) follow up: 1 months Participants: 375 (6 RCTs)			 		⊕⊕⊕◯ MODERATE g,h,l	Recombinant zoster vaccine (Shingrix) probably results in a large increase in cell-mediated immunogenicity measured by glycoprotein-E specific CD4 T cell response. Note: Vink 2019 = CMI analysed in subgroup of according to protocol pre-chemo solid malignancy cohort only Note: Stadtmauer does not report VRR % - presented in in-text figure only (approx. 76% vaccine arm, 20% placebo arm) – not included in GRADE for VRR Note: Berkowitz VRR = frequency of CD4 T cells expressing at least 2 activation markers on intracellular cytokine staining ≥2 fold pre-vaccination level (not relative to seropositive threshold as per other studies) Note: Immunocompromised populations represented: recent haematopoietic stem cell transplant; haematological malignancy receiving or recently received immunosuppressive therapy; solid tumour receiving immunosuppressive therapy; post renal transplant on immunosuppressive therapy; HIV on stable ART, CD4 T cell count ≥50 cells/mm3 and viral load ≤ 40 copies/mL Ref: (1, 2, 6-9)

RZV: recombinant zoster vaccine; VE – vaccine efficacy; HZ – herpes zoster; PHN – post-herpetic neuralgia; ZBPI – Zoster brief pain inventory; Grade 3 – preventing normal functioning

Explanations:

a. Only HSCT recipients and patients with haematological malignancy represented
b. Risk of bias judgement = serious- due to confounding
c. Inconsistency not able to be rated - single study
d. Only HSCT recipients represented
e. Based on a single RCT, low case numbers
f. 3/6 RCTs some concerns for outcome measurement - unblinded
g. Evidence reflects data from the following immunocompromised groups: HSCT recipients, haematological malignancy, HIV patients, people with solid malignancy receiving chemotherapy, post renal transplant patients
h. Based on a single RCT, low case numbers
i. Evidence reflects data from the following immunocompromised groups: HSCT recipients, haematological malignancy, people with solid malignancy receiving chemotherapy, post renal transplant patients
j. 2/4 RCTs some concerns for outcome measurement - unblinded
k. 2/4 RCTs some concerns for randomisation - non-randomised sample form randomised cohort
l. Wide CIs, small sample size/case numbers
m. Post-hoc analysis, insufficient follow-up planned to facilitate comparison of different time periods
n. Insufficient follow-up and low case numbers in >2 years cohort. 95% CI indicates imprecision (HR = 0.79; 95% CI: 0.23–2.72)

* 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. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, López-Jiménez J, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. Jama. 2019;322(2):123-33.
2. Dagnew AF, Ilhan O, Lee WS, Woszczyk D, Kwak JY, Bowcock S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019;19(9):988-1000.
3. Kochhar GS, Desai A, Caldera DF, et al. Effectiveness of recombinant zoster vaccine (RZV) in patients with inflammatory bowel disease. Vaccine 2021;39:4199-202.
4. Khan N, Wang L, Trivedi C, et al. Efficacy of Recombinant Zoster Vaccine in Patients With Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology 2021.
5. Izurieta HS, Wu X, Forshee R, et al. Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. Clinical Infectious Diseases 2021;73:941-8.
6. Vink P, Delgado Mingorance I, Maximiano Alonso C, Rubio-Viqueira B, Jung KH, Rodriguez Moreno JF, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: A randomized trial. Cancer. 2019;125(8):1301-12.
7. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, Kim SJ, Kim SI, Zaltzman J, et al. Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial. Clin Infect Dis. 2020;70(2):181-90.
8. Stadtmauer EA, Sullivan KM, Marty FM, Dadwal SS, Papanicolaou GA, Shea TC, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood. 2014;124(19):2921-9.
9. Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015;211(8):1279-87.

Evidence Profile Table

Evidence Profile: Recombinant herpes zoster vaccine (Shingrix) compared with placebo or unvaccinated for immunocompromised adults

Certainty assessment							№ of patients[1]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV (Shingrix)	Placebo/ unvaccinated	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOMES											
Confirmed herpes zoster (HZ) (Assessed with: PCR or blinded ascertainment committee; follow up: range 11 months to 21 months)											
2	Randomised trial	not serious	not serious	serious [a]	not serious	none	55/1,129 (4.9%)	154/1,107 (13.9%)	Vaccine efficacy against HZ in patients who recently underwent haematopoietic stem cell transplant was observed to be 68.2% (95% CI: 55.6–77.5%) An additional post-hoc analysis of RCT data in people with haematological malignancy observed VE against HZ to be 87.2% (95% CI: 44.3–98.6%)	⊕⊕⊕◯ MODERATE [a]
Herpes zoster (HZ) (Assessed with: ICD-9, ICD-10 or SNOMED-CT coding from administrative or electronic medical record data; follow up: range 9 months to 23 months)											
3	Observational studies	serious [b]	not serious	not serious	not serious	none	Khan & Izurieta: 151/46437 (0.3%) Kochhar: 1120 (No numerator available)	Khan & Izurieta: 18841/773203 (2.4%) Kochhar: 94540 (No numerator available)	Vaccine effectiveness against HZ in patients ≥65 years with general immunocompromise was observed to be 64.1% (95% CI: 52.7-69.8%). In those patients with inflammatory bowel disease, vaccine effectiveness was observed to be 61.0% (95% CI: 20.0-81.0%) for those aged 60 and over, and 64.0% (95% CI: 44.0-77.0%) for those aged 50 and over.	⊕⊕⊕◯ MODERATE [b]
Postherpetic neuralgia (PHN) (Assessed with: HZ-associated worst pain (ZBPI ≥3) persisting or appearing more than 90 days post HZ rash onset; Follow up: range 11 months to 21 months)											
1	Randomised trial	not serious	not able to be rated [c]	serious [d]	not serious [e]	none	1/870 (0.0%)	9/851 (1.1%)	Vaccine efficacy against PHN in patients who recently underwent haematopoietic stem cell transplant was 89.3% (95% CI: 22.5–99.8%).		⊕⊕⊕◯ MODERATE [c,d,e]

[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/ unvaccinated	Relative (95% CI)	Absolute (95% CI)	
Serious Adverse Events (SAEs) (Assessed with: Recorded for 12 months post 2nd dose)											
6	Randomised trial	not serious [f]	not serious	not serious [g]	not serious	none	407/1,559 (26.1%)	408 /1,529 (26.7%)	All studies reported similar rates of SAE between arms (range 20–32% in the vaccine arm compared with range 25–37% in placebo). Rates of vaccine-related SAEs were low and similar between intervention arms across most studies.		⊕⊕⊕⊕ HIGH [f,g]
Herpes Zoster related hospitalisation (HZ-related hospitalisation) (Follow up: mean 21 months)											
1	Randomised trial	not serious	not able to be rated [c]	serious [d]	serious [h]	none	2/870 (0.2%)	13/851 (1.5%)	The incidence of HZ-related hospitalisation among HSCT patients in the vaccine arm was 1.1/1,000 person-years compared with 7.1/1,000 person-years in the placebo arm. HR of HZ-related hospitalisation in the vaccine arm compared with placebo was 0.15 (95% CI: 0.03-0.68; P = 0.01)		⊕⊕⊕◯ MODERATE [c,d,h]
IMPORTANT OUTCOMES											
Solicited AEs (Local) (follow up: 7 days; assessed with: Diary Card)											
5	Randomised trial	not serious	not serious	not serious [i]	not serious	none	1242/1454 (85.4%)	167 /1438 (11.6%)	All studies reported significantly higher local reactogenicity in the vaccine arm compared with placebo (range 84–99% in vaccine arm compared with 6–23% placebo). Grade 3 solicited local AEs (preventing normal functioning) were reported in 11–14% of vaccine recipients compared with <1% placebo recipients.		⊕⊕⊕⊕ HIGH [i]
Solicited AEs (General/Systemic) (follow up: 7 days; assessed with: Diary Card)											
5	Randomised trial	not serious	not serious	not serious [i]	not serious	none	1087 /1454 (74.8%)	745 /1438 (51.8%)	All studies reported higher local reactogenicity in the vaccine arm compared with placebo (range 69–81% in vaccine arm compared with 30–66% placebo) (95% CI: overlapping in 2/5 RCTs: Bastidas, Dagnew) Grade 3 solicited general AEs (preventing normal functioning) were reported in 4–22% of vaccine recipients compared with 0–16% placebo recipients.		⊕⊕⊕⊕ HIGH [i]
Unsolicited AEs (follow up: 30 days; assessed with: diary card)											
5	Randomised trial	not serious	not serious	not serious [i]	not serious	none	667 /1485 (44.9%)	649 /1480 (43.9%)	All studies reported similar rates of unsolicited AEs in the vaccine arm compared with placebo. Rates of unsolicited AEs considered vaccine-related by investigators were similar in both arms (range 3–15% of vaccine recipients versus 2–13% in the placebo arm).		⊕⊕⊕⊕ HIGH [i]

Certainty assessment							№ of patients[1]		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV (Shingrix)	Placebo/ unvaccinated	Relative (95% CI)	Absolute (95% CI)	
Potential immune-mediated disease (follow up: range 11 months to 25 months)											
4	Randomised trial	not serious [j]	not serious	not serious [i]	not serious	none	20 /1454 (1.4%)	13 /1450 (0.9%)	All studies reported similar rates of potential immune-mediated disease (pIMD) in the vaccine arm compared with placebo (range 0-3% of vaccine recipients, versus 0–1.5% in the placebo arm).		⊕⊕⊕⊕ HIGH [i,j]
Humoral Immunogenicity (follow up: 1 month post 2nd dose; assessed with: Anti-glycoprotein E GMC and Response Rate)											
6	Randomised trial	not serious	not serious	not serious [g]	not serious	none	421 /560[2] (75.2%)	7 /524[2] (1.3%)	Significantly higher anti-glycoprotein E response rate was observed in the vaccine arm compared with placebo (range of vaccine response rate 65–98% in the vaccine arm compared with 0–4% in the placebo arm). Higher levels of anti- glycoprotein-E antibodies were achieved 1 month after second dose compared with placebo.		⊕⊕⊕⊕ HIGH [g]
Cell-mediated immunogenicity (follow up: 1 month post 2nd dose; assessed with: Median Glycoprotein-E specific CD4+ T-cell frequency and cell-mediated vaccine response rate)											
6	Randomised trial	serious [k]	not serious	not serious [g]	not serious [l]	none	130 /163[2] (77.3%)	5 /162[2] (3.1%)	Significantly higher CD4 T-cell response rate was observed in the vaccine arm compared with placebo at 1 month post second dose (range of vaccine response rate 50-93% in the vaccine arm compared with 0-9% in the placebo arm). Higher levels of glycoprotein-E specific T cells were achieved 1 month after second dose compared with placebo.		⊕⊕⊕◯ MODERATE [g,k,l]
Duration of protection ≤ 2 years (VE HZ) (Assessed with: PCR or blinded ascertainment committee; follow up mean 21 months)											
1	Randomised trial	Not serious	not able to be rated [c]	serious [d]	not serious	none	870 (events NR)	851 (events NR)	First herpes zoster episode: (time since the first month after dose 2) ≤ 2 years: HR = 0.31 (95% CI, 0.22-0.43; P < .001)		⊕⊕⊕◯ MODERATE [c,d]
Duration of protection > 2 yrs (VE HZ) (Assessed with: PCR or blinded ascertainment committee; follow up mean 21 months)											
1	Randomised trial	very serious [m]	not able to be rated [c]	serious [d]	serious [n]	none	870 (events NR)	851 (events NR)	First herpes zoster episode: (time since the first month after dose 2) >2 years: HR = 0.79 (95% CI, 0.23-2.72; P < .71)		⊕◯◯◯ VERY LOW [c,d,m,n]

HZ: Herpes Zoster; PHN: Post-herpetic neuralgia; VE: Vaccine Efficacy; AEs: Adverse Events; NR: Not reported: RR: Relative Risk; HR: Hazard Ratio; CI: Confidence Interval

[2] Figure reflects the 5/6 RCTs reporting VRR %, despite all 6 RCTs reporting GMC

Explanations

a. Only HSCT recipients and patients with haematological malignancy represented
b. Risk of bias judgement = serious- due to confounding
c. Inconsistency not able to be rated - single study
d. Only HSCT recipients represented
e. Based on a single RCT, low case numbers
f. 3/6 RCTs some concerns for outcome measurement - unblinded
g. Evidence reflects data from the following immunocompromised groups: HSCT recipients, haematological malignancy, HIV patients, people with solid malignancy receiving chemotherapy, post renal transplant patients
h. Based on a single RCT, low case numbers
i. Evidence reflects data from the following immunocompromised groups: HSCT recipients, haematological malignancy, people with solid malignancy receiving chemotherapy, post renal transplant patients
j. 2/4 RCTs some concerns for outcome measurement - unblinded
k. 2/6 RCTs some concerns for randomisation - non-randomised sample form randomised cohort
l. Wide CIs, small sample size/case numbers
m. Post-hoc analysis, insufficient follow-up planned to facilitate comparison of different time periods
n. Insufficient follow-up and low case numbers in >2 years cohort. 95%CI indicates imprecision (HR = 0.79; 95% CI, 0.23-2.72)

Evidence to Decision (EtD) Framework: Individual Perspective

SHOULD RECOMBINANT HERPES ZOSTER VACCINE (SHINGRIX) BE USED FOR IMMUNOCOMPROMISED ADULTS?	
Population	Immunocompromised adults (aged ≥18 years)
Intervention	Recombinant herpes zoster vaccine (Shingrix)
Comparison	Placebo or unvaccinated
Main outcomes	Vaccine efficacy against confirmed herpes zoster Vaccine effectiveness against herpes zoster Vaccine efficacy against post-herpetic neuralgia Herpes zoster related hospitalisation Serious adverse events Local solicited adverse events General/systemic solicited adverse events Unsolicited adverse events Duration of protection (against HZ) Humoral immune response Cell-mediated immune response Potential immune-mediated disease
Setting	Global middle- to higher-income countries
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Incidence of herpes zoster is significantly higher among people with immunocompromise compared with the general population (10-14). A large 2014 Australian cohort study reported that recent immunosuppressive condition was associated with a greater than 50% increase in the risk of herpes zoster compared with that in the general population. (10) In populations with severe immunocompromise, such as those with haematological malignancy, the risk can be up to four times higher. (11)
- Immunocompromised individuals are also significantly more likely to experience severe herpes zoster disease/complications requiring hospitalisation compared with the general population. (10-14)
- Incidence of HZ and HZ-related complications increases with age from 50 years, causing significant burden of disease. (15-18)
- The existing NIP-funded live zoster vaccine in Australia is contraindicated in individuals with significant immunocompromise due to medication or disease. (19)

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Estimated vaccine efficacy against herpes zoster was 68% in patients post haematopoietic stem-cell transplant and 87% in patients with haematological malignancy receiving or who have recently received immunosuppressive therapy, based on two moderately sized RCTs.
- Vaccine effectiveness from observational studies against herpes zoster was estimated to be 64% in those with general immunocompromise and for those with inflammatory bowel disease it ranged from 61% to 64%.
- Estimated vaccine efficacy against PHN in patients post haematopoietic stem-cell transplant was 89%, based on a single RCT.
- HZ-related hospitalisations among patients post haematopoietic stem-cell transplant were significantly reduced in the vaccine arm compared with placebo (HR = 0.15).
- Protection against HZ was observed to 2 years post vaccination, but the certainty of evidence for protection beyond this time is very low due to insufficient follow-up in the included studies.

- A robust humoral and cell-mediated immunogenic response was observed in the vaccine arm compared with placebo in the following populations:
  - recent haematopoietic stem cell transplant
  - haematological malignancy receiving or who have recently received immunosuppressive therapy
  - HIV (low viral RNA, and either anti-retroviral (ART) naïve with high CD4 count, or ART stable with CD4 count >50)
  - solid malignancy receiving/scheduled to receive immunosuppressive/cytotoxic therapy
  - recent renal transplant (receiving immunosuppressive therapy and with stable renal function).

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. These adverse events, in particular fever, may have greater significance in an immunocompromised population compared with an immunocompetent population, in terms of potential implications for investigation/intervention.
- However, frequency of serious adverse events, potentially immune-mediated disease and unsolicited adverse events appear similar between vaccine and placebo recipients
- Overall, the panel considered the undesirable effects to be small.
- Populations in which comparable safety, in terms of the critical safety outcome (SAEs), was observed were:
  - recent haematopoietic stem cell transplant
  - haematological malignancy receiving or who have recently received immunosuppressive therapy
  - HIV (low viral RNA, and either ART naïve with high CD4 count, or ART stable with CD4 count >50)
  - solid malignancy receiving/scheduled to receive immunosuppressive/cytotoxic therapy
  - recent renal transplant (receiving immunosuppressive therapy and stable renal function).

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

No. included studies	Very low	Low	Moderate	High

- Overall certainty of evidence for the beneficial effects of vaccination is moderate. One large study assessed effectiveness in a generalised immunocompromised population. All other efficacy and effectiveness estimates were only available in specific populations with immunocompromising conditions (recent haematopoietic stem cell transplant, haematological malignancy and inflammatory bowel disease).
- Certainty of evidence for the safety of the vaccine in this population was high.
- Uncertainty remains regarding the duration of protection against HZ after vaccination, as well as efficacy / effectiveness in other immunocompromising conditions and younger age cohorts.

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 and associated complications provided by Shingrix is likely to outweigh the significantly higher local and systemic reactions from the vaccine, particularly in the context that individuals who are immunocompromised have a higher risk of severe disease and do not have an alternative zoster vaccine available to them.

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 70-79 years receiving a single dose of the NIP-funded live vaccine in approximately the first two years of the program. (20-22)
- The NIP-funded live vaccine is contraindicated in immunocompromised people, making Shingrix the only safe vaccine for prevention of HZ and associated complications in this population
- 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.

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