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Non-Live Recombinant Herpes Zoster Vaccine (SHINGRIX)

Bottom Line…

- **SHINGRIX** is indicated for the **prevention of herpes zoster (HZ or shingles) in adults age ≥ 50**
- **SHINGRIX** reduces the risk of shingles by 91% (ARR=3.1%, **NNT=32**) & postherpetic neuralgia (PHN) by ~90% (ARR=0.30%, **NNT=333**) in 3 yrs.

NNT: Eg. *for every **333** vaccinated with **SHINGRIX**, 10 shingle cases (age ≥50 years) and **1 PHN** cases (**age ≥50** years) were prevented over **~ 3 yrs**.*

- **SHINGRIX** demonstrated efficacy for prevention of shingles effective in all age groups 50-80+. **ZOSTAVAX** less effective with increasing age.
- **SHINGRIX** use in patients with a history of shingles has been studied {open-label, non-randomized trial (n=93 patients, age 50-89 yr) for 3 months}.[ZOSTER-033] Vaccine can be given after shingles symptoms/rash resolved [CDC] or ≥1 yr [CDN]
- **Cost ~ $ 300 for 2 doses given intramuscularly (IM) 2-6 months apart** [(can give up to 12 months apart if needed to increase compliance)]**. (Refrigerate 2 to 8°C; Discard if frozen)**
- **Canadian NACI'18 recommends SHINGRIX should be offered to individuals ≥50 yrs without contraindications** including:
  - -Individuals previously vaccinated with **ZOSTAVAX**; Re-vaccinate with two doses of RZV at least one year after receiving Zostavax
  - -Individuals with a previous episode of herpes zoster disease. Provide two doses of **SHINGRIX** at least one year after herpes zoster episode.[expert opinion]
  - -Immunocompromised individuals, may be considered on a case-by-case assessment of the benefits vs risks [expert opinion]

  ZOSTAVAX may be considered for immunocompetent individuals ≥50 yrs of age without contraindications when **SHINGRIX** is contraindicated, unavailable or inaccessible.
- **Advisory Committee on Immunization Practices (ACIP [USA]) recommends SHINGRIX as the preferred vaccine for preventing shingles and related complications. ACIP also recommends SHINGRIX (give both of the 2 doses) for adults who previously received ZOSTAVAX.**
  - Administer **SHINGRIX** as early as 8 weeks after **ZOSTAVAX**, but especially after 5 years (as **ZOSTAVAX** efficacy declines over time).
- **Outstanding Questions:** What is the long-term effectiveness?

What is SHINGRIX? [1,2,3,4,5,6,7,8]

- **Herpes Zoster (shingles) vaccine** contains NON-live, recombinant, AS01B adjuvanted herpes zoster vaccine. This vaccine contains antigen glycoprotein E, which is the most abundant antigen in varicella zoster vaccine (VZV) infected cells and the main target for VZV-specific CD4+ T-cell response. This vaccine also includes adjuvant AS01 that helps to elicit an early, high and long-lasting response with less antigen.
- Indicated for prevention of shingles in **patients ≥50yrs**. **Not** for treating shingles, PHN or preventing primary varicella infection.

Is SHINGRIX effective? Two Studies: Efficacy of the Herpes Zoster Subunit Vaccine: in Adults 70 years of age or older (ZOE-70) [2016] & in Older Adults (ZOE-50) [2015]

ZOE-70: n = 13,900, **mean age ~76 yr,** 62-96yr, 22.1% ≥ 80 yr, 0.5% ≥ 90 yr, 45.1% ♂, 19% North American, 51% European, 77% white, ~95% received both doses, **3.7 yr follow-up**.
ZOE-50: n=15,411, **mean age = 62 yr**, 61.2% ♂, 51% European, 19% North American, 72% white, **3.2 yr follow-up**
Both studies: Blinded investigators, participants and those responsible for the evaluation of any study endpoint (study staff who prepared injection were not blinded), RCT, excluded history of shingles, previously vaccinated against varicella or herpes zoster or immunosuppressed, significant underlying illness or other condition that may interfere with study assessments (e.g. cognitive impairment, chronic pain syndrome); no intention to treat analysis was performed.

Clinical Outcomes (Pooled ZOE-70 & ZOE-50)*	Vaccine %, n = 8250		Placebo %, n = 8346		RRR		ARR		NNT over ~3yrs NNH within 7 days	
Incidence of shingles **(overall)**	0.30%, n=25		3.40%, n=284		91.3%		3.10%		**NNT = 32**	
Age 70-79 yr	0.29% (n=19/6468)		3.30% (n=284/8346)		91.3%		3.01%		33 / 3 yrs	
Age ≥ 80 yr	0.34% (n=6/1782)		3.79% (n=68/1792)		91.4%		3.45%		29 / 3 yrs	
Year 1	0.02% (n=2/8250)		0.99% (n=83/8346)		97.6%		0.97%		103@1yr	
Year 2	0.09% (n=7/8039)		1.08% (n=87/8024)		92.0%		0.99%		156@2yr	
Year 3	0.12% (n=9/7736)		0.76% (n=58/7661)		84.7%		0.64%		172@3yr	
Year 4	0.09% (n=7/7426)		0.77% (n=56/7267)		87.9%		0.68%		147@4yr	
Incidence of PHN									**NNT over 3.8y**	
≥ 70 yr	0.05%, (n=4/8250)		0.43% (n=36/8346)		88.8%		0.38%		**263**	
≥ 50 yr	0.03% (n=4/13881)		0.33% (n=46/14035)		91.2%		0.30%		**333**	
Age 50-59 yr	0.00% (n=0/3491)		0.23% (n=8/3523)		100.0%		0.23%		435	
Age 60-69 yr	0.00% (n=0/2140)		0.09% (n=2/2166)		100.0%		0.09%		1111	
Age 70-79 yr	0.03% (n=2/6468)		0.44% (n=29/6554)		93.0%		0.41%		244	
Age ≥ 80 yr	0.11% (n=2/1782)		0.39% (n=7/1792)		71.2%		0.28%		357	
Injection-site **Reaction ≤ 7 days**	ZOE-50 N=4382	ZOE-70 N=505	ZOE-50 N=4382	ZOE-70 N=505	ZOE-50	ZOE-70	ZOE-50	ZOE-70	ZOE-50 **NNH**	ZOE-70 **NNH**
Pain	79.1%	68.7%	11.2%	8.5%	85.8%	87.6%	67.9%	60.2%	1	2
Redness	38.0%	39.2%	1.3%	1.0%	96.6%	97.4%	36.7%	38.2%	3	3
Swelling	26.3%	22.6%	1.1%	0.4%	95.8%	98.2%	25.2%	22.2%	4	5
Grade 3 reaction#	9.5%	8.5%	0.4%	0.2%	95.8%	97.6%	9.1%	8.3%	11	12
Systemic Reaction **within 7 days**	ZOE-50 N=4375	ZOE-70 N=504	ZOE-50 N=4378	ZOE-70 N=505	ZOE-50	ZOE-70	ZOE-50	ZOE-70	ZOE-50 **NNH**	ZOE-70 **NNH**
Fatigue	45.9%	32.9%	16.6%	15.2%	63.8%	53.8%	29.3%	17.7%	3	6
Myalgia	46.3%	31.2%	12.1%	8.1%	73.9%	74.0%	34.2%	23.1%	3	4
Headache	39.2%	24.6%	16.0	10.9%	59.2%	55.7%	23.2%	13.7%	4	7
Shivering	28.2%	14.9%	5.9%	4.4%	79.1%	70.5%77	22.3%	10.5%	4	10
Fever	21.5%	12.3%	3.0%	2.6%	86.0%	8.9%	18.5%	9.7%	5	10
GI symptoms	18.0%	10.9%	8.8%	7.9%	51.1%	27.5%	9.2%	3.0%	11	33
Grade 3 reaction^	11.4%	6.0%	2.4%	2.0%	78.9%	66.7%	9.0%	4.0%	11	25

Efficacy:
- Efficacy for prevention of shingles decreases over time (97.6% → 87.9% over 4 years)
- Optimal age for benefit in incidence of PHN: Age > 69

SHINGRIX vs **ZOSTAVAX** studies:
- **ZOSTAVAX** - higher incidence of Shingles in 3.1year study (n=38,546):[9]
  - Overall Age ≥ 60 yrs: 1.64% vs 3.33% placebo
  - Age 60-69yrs: 1.18% vs 3.22% placebo
  - Age >70yrs: 2.17% vs. 3.46% placebo
- **ZOSTAVAX** - higher incidence of PHN in 3.1year study:
  - Overall Age ≥ 60 yrs: 0.14% vs 0.42% placebo
  - Age 60-69yrs: 0.08% vs 0.22% placebo
  - Age >70yrs: 0.21% vs. 0.64% placebo
- **ZOSTAVAX** - More frail, more active surveillance, and/or the use of a more sensitive case definition?

Adverse reactions:
- More pain, redness & swelling x 2-3days
- More Grade 3 injection site reaction = redness & swelling > 100mm (NNH=11-12 in 7 days)
- More systemic reactions x 1-2 days
- Grade 3 solicited systemic reactions (prevents normal activity) were more frequent after 2nd dose (8.5%, 95% CI, 7.7 to 9.4) than after 1st dose (5.9%, 95% CI, 5.2 to 6.6)[ZOE-50]

*Modified Vaccinated Cohort = excluded participants who did not receive the second dose of the herpes zoster subunit vaccine or placebo or who had a confirmed episode of herpes zoster within 1 month after the second dose. #Grade 3 injection site reaction = redness & swelling in the affected area > 100mm ^Grade 3 systemic reaction = prevents normal activity

What are potential adverse events and drug interactions with SHINGRIX? [1-3,5,10,11,12,13]

- **Common adverse events include** (compared to placebo):
  - Reactions were transient, with median durations of 2 to 3 days for injection-site reactions, 1 to 2 days for systemic reactions, and 1 to 2 days for grade 3 reactions. Most reactions were considered mild to moderate in intensity.
  - More redness and swelling > 100mm to affected area lasting 1-2 days (NNH=11-12 in 7 days).
  - More systemic reactions that prevented normal activity for 1-2 days (NNH=11 to 25 in 7 days).
  - Injection site reactions: pain, redness, swelling; and systemic reactions: myalgia, fatigue, headache, shivering, fever, GI symptoms.
  - For age > 70, the overall frequency and severity of the reactions did not increase significantly after 2nd dose[ZOE-70].
  - For ages 50-70, systemic reactions that prevented normal activity were more frequent after 2nd dose (8.5%) than after the first dose (5.9%)[ZOE-50].
- **Interactions:** Can be administered with other live vaccines & inactivated vaccines.
  - Can be given concomitantly with unadjuvanted seasonal influenza vaccine at different injection sites.[14]
  - Must **not** be mixed with any other products in the same syringe.

What are other potential cautions regarding the use of SHINGRIX? [1-3,5]

- **SHINGRIX is contraindicated if**: ***Consider deferring in acute illness/fever!***
  - Patients have a known hypersensitivity to the active substances or to any component of the vaccine.
- **Can SHINGRIX be used in immunocompromised patients?**
  - Yes, limited data in patients with autologous Haematopoietic Cell Transplant (HCT) & HIV indicate no safety concerns 1-yr post-vaccination.
- Pregnancy or Breastfeeding is not a contraindication.

Is administration of SHINGRIX cost effective?[15]

- SHINGRIX costs ~ $300 for 2 doses.
- SHINGRIX was more effective and less expensive than the live attenuated herpes zoster vaccine at all ages and had an incremental cost-effectiveness ratio from $20,038 to $30,084 per quality-adjusted life year compared to no vaccination (US study, non-pharmaceutical funding).

What are the Current Vaccination Recommendations for Herpes Zoster Vaccine (SHINGRIX)?[16,17,18,19] NACI & ACIP = national advisory committees

- NACI [2018] : Canadian NACI recommends **SHINGRIX** should be offered to individuals ≥50 yrs without contraindications.
- **USA** – ACIP [2017]: preferred vaccine for preventing shingles & related complications for all ≥50 yrs, including those who previously received **ZOSTAVAX.**
- **History of chicken pox**: HZV can be administered (not studied).

How long after a shingles episode can the Herpes Zoster Vaccine be given?

- No official or specific recommendation for **SHINGRIX.**
- **Canada:** It is recommended that at least 1 year elapse between the last shingles episode and zoster vaccination. Herpes ophthalmicus has recurred following **ZOSTAVAX II** but causality was not established.
- **CDC:** Vaccine can be administered after the acute stage and symptoms/rash have subsided, no specific time frame.
- **History of HZ**: patients can be vaccinated. In theory, prior episodes of HZ ↑ immunity & ↓ likelihood of recurrences, but observational evidence is contradictory.[20,21] A recent study reports the risk of recurrence is ↓ for 12 to 18 months after having HZ so vaccination could be delayed by ≥1 year to take advantage of this natural immunity.[20] {Persons with a history of herpes zoster or had herpes zoster vaccination were excluded from ZOE-50 and ZOE-70 trials.}

How is SHINGRIX supplied? What is the dosage and how is it administered? [1-3,5]

- Supplied as 2 vials: (1) single dose lyophilized gE powder and (2) adjuvant suspension vials both refrigerated (2-8°C) and protected from light.
- Reconstitute prior to administration: **Administer vaccine promptly.** If this is not possible, store in refrigerator (2-8°C) and use within 6 hours. Discard if not used within 6 hours. The reconstituted vaccine is an opalescent, colourless to pale brownish liquid. Discard if frozen.
- Before administration: withdraw the reconstituted vaccine into a sterile syringe and attach a new needle to use for the injection.
- 2 doses of 0.5mL each; an initial dose at Month 0 followed by a second dose administered between 2 and 6 month later.
- **Intramuscular (IM) injection only**, preferably in the deltoid muscle.

Uncertainties

- Can the non-live herpes zoster vaccine be effective and safe in frail elderly or immunocompromised patients over the long term? expert opinion says "yes"
- Of those in the vaccinated group who do get shingles, are severity and complications reduced? Is efficacy retained over longer term?
- As more severe PHN is likely the most important issue, to what extent were the more severe/persistent PHN cases prevented?

What are the advantages and disadvantages of SHINGRIX vs. ZOSTAVAX?

Advantages of SHINGRIX	Disadvantages of SHINGRIX
Non-live vaccine – option for immunocompromised persons expert opinion	Higher reactogenicity, more injection site reactions (pain, redness, swelling), systemic reactions (fatigue, myalgia, headache, shivering, fever, GI symptoms)
Higher efficacy rate (91% vs. 51%), although different patient population studied	More local redness and swelling (>100mm) & Grade 3 systemic reactions (prevents normal activity) that last for an average median of 1-2 days.
Easier storage requirements (refrigerate, can last up to 6 hours in refrigerator after reconstituted). If inadvertently left out of fridge & then put back in fridge, it is stable at room temperature for up to 72hr.	2-dose schedule
More cost-effective	
ZOSTAVAX contains gelatin & neomycin, which may induce reaction	
ZOSTAVAX is administered SC, SHINGRIX is administered IM – this could be an advantage or disadvantage, depending on personal preference	

Shingles Extras [27,22]:

- Antivirals (e.g. valcyclovir 1g TID or acyclovir 800mg 5x/day) x 7 days $70; effective in shingles treatment for age >50 if used within 24-72hrs of rash onset.
- See RxFiles ZOSTAVAX Q&A.
- See RxFiles Chronic Non-Cancer Pain chart for PHN pain treatment (11th Ed, pg 99) → e.g. nortriptyline, gabapentin, opioid, capsaicin.
- See RxFiles Adult Vaccines Chart (11th ed, pg 77).

ACIP=Advisory Committee on Immunization Practices **ARR**=absolute risk reduction **CDC**=Center for Disease Control and Prevention **HIV**=Human immunodeficiency virus **NACI**=National Advisory Committee on Immunization **NNT**=number needed to treat **NNH**=number needed to harm **RCT**=randomized controlled trial **RRR**=relative risk reduction **yr(s)**=year(s)

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