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.

**What is SHINGRIX?**
- SHINGRIX, 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.

<table>
<thead>
<tr>
<th>Clinical Outcomes (Pooled ZOE-70 &amp; ZOE-50)*</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT over ~3yrs</th>
<th>Efficacy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of shingles (overall)</td>
<td>0.30%, n=25</td>
<td>3.40%, n=284</td>
<td>91.3%</td>
<td>3.10%</td>
<td>NNT=32</td>
<td>33/3yrs</td>
</tr>
<tr>
<td>Age 70-79 yr</td>
<td>0.29% (n=19/6468)</td>
<td>3.30% (n=284/8346)</td>
<td>91.3%</td>
<td>3.01%</td>
<td>29/3yrs</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80 yr</td>
<td>0.34% (n=61782)</td>
<td>3.79% (n=681792)</td>
<td>91.4%</td>
<td>3.45%</td>
<td>103/1yr</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.02% (n=2/28250)</td>
<td>0.99% (n=83346)</td>
<td>97.6%</td>
<td>0.97%</td>
<td>136/2yr</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>0.09% (n=70393)</td>
<td>1.08% (n=870024)</td>
<td>92.0%</td>
<td>0.84%</td>
<td>72/3yr</td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>0.12% (n=97796)</td>
<td>0.76% (n=587691)</td>
<td>84.7%</td>
<td>0.64%</td>
<td>147/4yr</td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>0.09% (n=77426)</td>
<td>0.77% (n=567267)</td>
<td>87.9%</td>
<td>0.68%</td>
<td>147/4yr</td>
<td></td>
</tr>
</tbody>
</table>

**What is Herpes Zoster (shingles) vaccine?**
- SHINGRIX 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 reactogenicity.
- SHINGRIX is contraindicated, unavailable or inaccessible.

**What is the long-term effectiveness?**
- 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 herpes zoster, ZOE-50, but especially after 5 yrs (as ZOVE efficacy declinate over time).

**Outstanding Questions:**
- What is the long-term effectiveness?

**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) (Prevents normal activity) were more effective:
  - 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 II - 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 0.84% placebo

**SHINGRIX** - 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 in the affected area > 100mm

**What is the long-term effectiveness?**
- 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 herpes zoster, ZOE-50, but especially after 5 yrs (as ZOVE efficacy declinate over time).

**Outstanding Questions:**
- What is the long-term effectiveness?

**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) (Prevents normal activity) were more effective:
  - 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 II - 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 0.84% placebo

**SHINGRIX** - More frail, more active surveillance, and/or the use of a more sensitive case definition?
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 (O6-J0).
  - For ages 50-70, systemic reactions that prevented normal activity were more frequent after 2nd dose (8.3%) than after the first dose (5.9%) (O0-E-O).

- **Interactions:** Can be administered with other live vaccines & inactivated vaccines.
  - Can be given concomitantly with unadjuvanted seasonal influenza vaccine at different injection sites.
  - Must not be mixed with any other products in the same syringe.

What are other potential concerns regarding the use of **SHINGRIX**? 1-3,5

- **SHINGRIX is contraindicated if**:
  - Patients have a known hypersensitivity to the active substances or to any component of the vaccine.
  - 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.** (New Jan/2023 NIHBI covers for those ≥65 years of age)

- **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 (study, non-pharmaceutical funding).**

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

- **Canadian 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** 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 are a risk factor. 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. (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 at Month 2.**

- **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 II?**

<table>
<thead>
<tr>
<th>Advantages of <strong>SHINGRIX</strong></th>
<th>Disadvantages of <strong>SHINGRIX</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-live vaccine – option for immunocompromised persons</td>
<td>Higher reactogenicity, more injection site reactions (pain, redness, swelling), systemic reactions (fatigue, myalgia, headache, shivering, fever, GI symptoms)</td>
</tr>
<tr>
<td>Higher efficacy rate (91% vs. 51%), although different patient population studied</td>
<td>More local redness and swelling (&gt;100mm) &amp; Grade 3 systemic reactions (prevents normal activity) that last for an average median of 1-2 days.</td>
</tr>
<tr>
<td><strong>SHINGRIX</strong> = Refrigerate (2-8°C), can last up to 6 hrs in refrigerator after reconstituted</td>
<td>2-dose schedule</td>
</tr>
<tr>
<td><strong>ZOSTAVAX II</strong> = Refrigerate (2-8°C), discard if reconstituted vaccine is not used within 30 minutes.</td>
<td></td>
</tr>
<tr>
<td><strong>SHINGRIX</strong> is more cost-effective</td>
<td></td>
</tr>
<tr>
<td><strong>ZOSTAVAX II</strong> contains gelatin &amp; neomycin, which may induce reaction</td>
<td></td>
</tr>
<tr>
<td><strong>ZOSTAVAX II</strong> is administered SC, <strong>SHINGRIX</strong> is administered IM – this could be an advantage or disadvantage, depending on personal preference</td>
<td></td>
</tr>
</tbody>
</table>

Shingles Extras 27,22:

- **Antivirals** (e.g. valacyclovir 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. ZOSTAVAX discontinued and replaced with ZOSTAVAX II which has also been discontinued.

- 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).
Additional articles:


Le P, Rothenberg M. Herpes zoster infection. BMJ. 2019 Jan;364:k6905.


References: Inactivated Herpes Zoster Vaccine (SHINGRIX)


2. Shingrix Monograph, RxTx, accessed December 28, 2017


