

## Herpes Zoster Vaccine (ZOSTAVAX)

### Bottom Line...

- **ZOSTAVAX** is indicated for the **prevention of shingles in immunocompetent patients age ≥60** May be used for ≥50yr (FDA & NACI). Vaccine efficacy is only about 50-60%.
- **ZOSTAVAX** reduces the risk of **shingles** by 50% (ARR=1.7%, NNT=59) & post-herpetic neuralgia (PHN) by 67% (ARR=0.28%, NNT=364) over 3.1 yrs.

**NNT: Eg. for every 364 patients vaccinated with ZOSTAVAX, 1 PHN case was prevented & 6 shingles cases were prevented over ~ 3 yrs.**

- Efficacy for prevention of shingles is highest in patients **60-69 years old** & decreases with increasing age.
- **ZOSTAVAX** is **not indicated for treating** shingles or PHN, or for preventing primary varicella infection.
- **ZOSTAVAX** use in patients with a **history of shingles** has not been studied. The vaccine can be given, although the precise risk for and severity of shingles is unknown. (A recent episode of shingles may have boosted immunity).
- Cost effectiveness remains to be established. **Cost** per single dose = \$ 175 – 195 given subcutaneously. {Soon **ZOSTAVAX II** stored in fridge & more \$}
- **The risk of shingles ↑ with age, as does the risk for PHN, acute pain & severe rash, however the efficacy of the vaccine declines significantly for PHN after 3 years & 6 years for shingles – so when is the optimal time to vaccinate???** It may be in those 60 to 69 years old.
- **Outstanding Questions: Is ZOSTAVAX safe & effective in immunocompromised patients? Is it beneficial for patients with a history of shingles? What is the long-term effectiveness (will a booster be required)?**

### What is ZOSTAVAX? <sup>1,2,3,4,5,6,7,8</sup>

- **Herpes Zoster (shingles) vaccine** contains live, attenuated varicella-zoster virus (VZV) (Oka/Merck strain). It is 14 times more potent than **VARIVAX** chickenpox vaccine to induce an immune response to VZV in older adults. It is **not interchangeable** with **VARIVAX**.
- **Shingles** is a common problem (Lifetime incidence=10-30%; up to 50% in those surviving to age 85 & in immunocompromised; not reported to public health; ~ 1 million cases/ year in the USA)
  - It is due to a reactivation of the VZV within the sensory ganglia because of waning cell-mediated immunity. (Rare before age 50.)
  - Symptoms: painful, unilateral vesicular eruption, which usually occurs in restricted dermatomal distribution, rarely crosses the midline.
  - Rash red papules→ grouped vesicles→more pustular often around the trunk (lasts 2-3 weeks) gradually crusts over within 7-10day→not infectious; pain precedes the rash in many cases
  - ~ 20% of patients with shingles develop postherpetic neuralgia (PHN) often defined as pain persisting >3 months from the initial onset of the rash; varying severity
  - **Higher risk:** immunosuppressed pts (HIV, Lupus), female, severe rash & pain; **Lower risk:** if African American, infected with wild type virus.
  - Risk of recurrence is 4-7% after 8 years.
  - **↑risk of PHN with ↑age: ↑acute pain, ↑rash severity.** <sup>9,10</sup>
  - Shingles & PHN are rarely fatal, but PHN pain can be debilitating, persistent & diminish quality of life. (Differential DX: Herpes simplex, coxsackie, pyoderma)
- Indicated for prevention of shingles in **patients ≥60yrs** <sup>FDA≥50yr</sup>. **Not** for treating shingles, PHN or preventing primary varicella infection.

### Is ZOSTAVAX effective? Two Studies: Shingles Prevention Study (SPS) <sup>2005</sup> & Zostavax Efficacy & Safety Trial (ZEST) <sup>2012</sup>

Shingles Prevention Study (SPS) <sup>9,10</sup> : DB RCT, n = 38,546, immunocompetent pts, median age ~69 yr 59-99yr, 59% ♂, 3.1 yr follow-up, excluded those with history of shingles					
Clinical Outcomes at 3.1 years	Vaccine n = 19,270	Placebo n = 19,276	RRR	ARR	NNT/NNH Over 3.1yrs
Incidence of shingles	1.6% n=315	3.3% n=642	51%	1.7%	NNT = 59 (95% CI: 50-72)
Incidence of PHN pain*	0.14 % n=27	0.42 % n=80	67%	0.27%	NNT = 364 (95% CI: 263-589)
≥1 serious adverse event	1.3 % n=255	1.3 % n=254	NS	NS	-
≥1 serious adverse event <sup>AE substudy 11</sup>	1.9 % n=64 (3345)	1.3% n=41 (3271)	↑53%	↑0.66%	NNH = 152 (95% CI: 79-1692)
<b>For every 364 patients vaccinated, 6 cases of shingles &amp; 1 case of PHN is prevented over 3 years.</b>					
Zostavax Efficacy & Safety Trial (ZEST) <sup>12,13</sup> : DB RCT, n = 22,439, immunocompetent pts, mean age ~55 yr 50-59 yr, 62% ♀, 1.3 yr follow-up					
Clinical Outcomes at 1.3 years	Vaccine n=11,211	Placebo n=11,228	RRR	ARR	NNT/NNH Over 1.3 yrs
Incidence of shingles	0.27% n=30	0.88 % n=99	↓69.8 %	↓0.61 %	NNT = 164 (95% CI: 142 – 212) Conversion to 3 years NNT = 71
≥1 serious adverse event	0.6% n=69	0.5% n=61	NS	-	-


\* pain ≥3 on a scale of 0-10 (0 = no pain & 10 = pain as bad as you can imagine) persisting or appearing ≥90 days after rash onset

- **SPS Short-Term Persistence Substudy<sup>14</sup>:** n=14,270 subjects: 7320 vaccine & 6950 placebo followed for an additional 5 years ~8yr follow-up. Efficacy ↓ yearly, **losing statistical significance in the 3<sup>rd</sup> year post-vaccination for PHN & the 6<sup>th</sup> year post-vaccination for shingles.** Data from the **SPS Long-Term Persistence Substudy**, which followed subjects for 10 years, is not yet available.
- **Number Needed to Vaccinate (NNV)** is an estimate of the **lifetime risk** of shingles after vaccination. Using Canadian population-based data, assuming vaccination at 65 years of age, the **NNV for ZOSTAVAX is estimated at 11 to prevent one case of shingles & 43 to prevent one case of PHN over the remaining life span of vaccine recipients<sup>15</sup>.** Remember: NNT is for a specified time range e.g. vaccinate 59 people to prevent one shingles case & 364 people to prevent one PHN case over 3.1 yrs. <sup>SPS</sup> Note: NNV may vastly overestimate the benefit because it assumes that immunity does not wane, an assumption that conflicts with the **SPS** substudy. The most representative values for overall effectiveness are likely somewhere between the 3 year NNT & the lifetime NNV.

**What are potential adverse events and drug interactions with ZOSTAVAX? 1-3,5,16,17,18,19**

- **Common adverse events include** (compared to placebo):
  - Injection site reactions erythema, pain/tenderness, swelling, pruritis & headache. Most reactions were considered mild in intensity.
  - Post-market reports difficult to establish causal relationship; hypersensitivity incl. **anaphylactic reactions**; rash; pyrexia; lymphadenopathy injection-site
- **Interactions: Can be administered with other live vaccines** give on same day or separate by at least 4 weeks **& inactivated vaccines**
  - Must **not** be mixed with any other products in the same syringe. Must be given as separate injections and at different body sites.
  - Can **ZOSTAVAX** be given together with **PNEUMOVAX 23** (pneumococcal vaccine)? Manufacturer says “No”, CDC & PHAC says “Yes”. (An observational study suggests there is no problem with immune response when giving both together.<sup>Tseng</sup>) Likely give in separate injection sites.
    - **Co-administration of HZV & pneumococcal vaccine:** currently contraindicated by **ZOSTAVAX** manufacturer due to concerns about ↓ immunogenicity of HZV but a large observational study reported no difference in efficacy or safety when **ZOSTAVAX & PNEUMOVAX 23** were administered simultaneously. **Centers for Disease Control (CDC) & Prevention recommends concurrent administration of HZV & pneumococcal vaccines in patients who are eligible for both vaccinations.**


**What are other potential cautions regarding the use of ZOSTAVAX? 1-3,5**

- **ZOSTAVAX is contraindicated if:** *Consider deferring in acute illness/fever!*
  - Patients have had an anaphylactic or anaphylactoid reaction to gelatin or neomycin contact dermatitis to neomycin is not a contraindication
  - Active untreated tuberculosis or immunocompromised leukemia, lymphoma, neoplasms of the bone marrow/lymphatic system, AIDS/HIV.
  - Immunosuppressive therapy. **Vaccinate ≥14 days prior** (or at least 2 weeks) **starting treatment with immunosuppressives** anti-TNF agents, corticosteroids, etc. Delay administration for at least 1 month after high dose corticosteroids for ≥2 weeks (≥20 mg/day prednisone) or use of anti-TNF agents. Low dose methotrexate <0.4mg/kg/wk, azathioprine <3mg/kg/day or 6-mercaptopurine <1.5mg/kg/day are not CI since these are not considered sufficiently immunosuppressive ACIP'08
- **Can ZOSTAVAX be used in immunocompromised patients?** There is short-term evidence that HZV is safe & effective in patients with certain autoimmune diseases rheumatoid arthritis, psoriasis & inflammatory bowel disease, but there is no data on use patients who may be severely immunocompromised in e.g., HIV/AIDS, leukemia, lymphomas currently undergoing chemotherapy, etc.
  - A recently published retrospective study suggests that HZV in patients taking anti-TNF agents antagonists & other immunosuppressants are effective in ↓ the incidence of shingles & do not pose any additional safety risks<sup>20</sup>.
  - If post-chemo or post-immunosuppressant, no longer immunocompromised & WBC count ok, wait at least 3 months before giving Zostavax.
  - Acyclovir/famciclovir/valacyclovir should be stopped ≥24 h **before vaccination** & should not be started until 14 days afterward.
- Transmission of virus from vaccine to contacts (e.g. immunosuppressed) not reported, but a theoretical concern.
- Not recommend for patients who received **VARIVAX**. (Patients with hx of zoster can be vaccinated, but may consider **5+ yr delay** to ↑ immune boost effect.)
- Use in age <50 yrs or women of childbearing potential is not recommended. HZV is contraindicated in pregnancy (varicella infection a known fetal risk; no studies). Pregnancy should be avoided for at least 1 month following vaccination. Breast feeding is not a contraindication. 

**Is administration of ZOSTAVAX cost effective? 2,3,5**

- **ZOSTAVAX** costs \$175 - 195 for single dose. Given the many uncertainties, conclusions about cost-effectiveness remain to be definitively demonstrated. Estimate cost per quality adjusted life-year (QALY) gained \$27,000 - \$112,000 intermediate to high end of acceptable range.

**What are the Current Vaccination Recommendations for Herpes Zoster Vaccine (ZOSTAVAX)? 21,22,23,24 NACI & ACIP = national advisory committees**

-  **NACI 2010:** recommended for persons ≥60 years of age (Grade A) & may be used for persons 50 – 59 years of age (Grade B)
- **USA – ACIP 2008:** routine vaccination for all persons ≥60 yrs; No recommendation for persons <60 yrs
- **History of chicken pox:** HZV can be administered (NACI, Grade A)
- **History of HZ:** patients can be vaccinated. In theory, prior episodes of HZ ↑ immunity & ↓ likelihood of recurrences, but observational evidence is contradictory<sup>25,26</sup>. 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<sup>20</sup>.

**How is ZOSTAVAX supplied? What is the dosage and how is it administered? 1-3,5**

- Supplied in a single-dose vial. Diluent 0.7ml supplied separately. After reconstitution: is a semi-hazy to translucent, off-white to pale yellow liquid (0.65 mL) & contains VZV ≥19,400 PFU (plaque-forming units)
- Prior to reconstitution the vaccine **should be stored frozen** at an average temp of ≤ -15°C may be good for 72hr at up to 8°C, until reconstituted. The diluent should be stored at room temp (20-25°C) or refrigerated (2-8°C). **Administer vaccine immediately after reconstitution, to minimize loss of potency.** Discard if reconstituted vaccine is not used **within 30 mins**. Contains no preservatives (thimerosal free). **{ZOSTAVAX II stored in fridge & more \$}**
- Individuals should receive a single dose of the entire vial contents, **subcutaneously** deltoid region.
- Non-freezer version (**ZOSTAVAX II**)<sup>27</sup> & non-live vaccine formulations are in development.

**Uncertainties**

- 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?
  - **Duration of effect & boosters:** Persistence of **ZOSTAVAX** effect beyond 5 years is being studied. The results of this study should help determine the need for revaccination. **No booster dose is recommended at present.**
  - **Does ZOSTAVAX prevent recurrences of shingles after an initial episode?** There are no anticipated safety concerns but no studies have investigated efficacy.
  - **Will people who have received varicella vaccine be at risk of shingles as they age?** Currently, it is thought that varicella vaccination ↓ the risk of severe shingles but it is not known whether this effect will persist as people age.

**Shingles Extras 27,28:**

- Antivirals (e.g. valacyclovir 1g TID or acyclovir 800mg 5x/day) x7 days \$70; effective in shingles treatment for age >50 if used within 24-72hrs of rash onset.
- See RxFiles Chronic Non-Cancer Pain chart for PHN pain treatment (9<sup>th</sup> Ed, pg 67) → e.g. nortriptyline, gabapentin, opioid, capsaicin.
- See RxFiles Adult Vaccines Chart (9<sup>th</sup> ed, pg 50).

Additional articles:

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