

Herpes Zoster Vaccine (ZOSTAVAX™)

What is Zostavax™? ^{1,2,3,4,5,6,9}

- **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 immunocompromized; not reported to public health; ~ 1 million cases/ yr 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 wks) 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
 - ↑**risk of PHN with ↑age**: (incidence of PHN in 3.1yr study: age <60yrs = <2%, 60-69yrs = 7%, >70yrs 19%)^{7,8}, ↑**acute pain**, ↑**rash severity**.
 - Higher risk: immunosuppressed pts^{HIV, Lupus}, female, severe rash & pain; Lower risk: if African American, infected with wild type virus.
 - 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** ^{FDA≥50yr}. **Not** for treating shingles, PHN or preventing 1° varicella infection. [Advisory Committee on Immunization Practices (ACIP) in the USA recommends routine vaccination for those ≥60 years old regardless of previous chicken pox history. Patients with a history of zoster can be vaccinated (not studied; ? prior episodes of shingles ↑ immunity making recurrences uncommon.) <http://www.cdc.gov/mmwr/preview/mmwrhtml/nr560515a1.htm> [NACI also recommends for age 60+.] <http://www.phac.aspc.gc.ca/neci-cni/index-eng.php>

Is Zostavax™ effective? ^{7,8} {Shingles Prevention Study, SPS}

Shingles Prevention Study: double blind RCT, n = 38,546, ~69yr ^{59-99yr} , 3.1yr follow-up, hx of shingles not included ⁷					
Clinical Outcomes	Vaccine n = 19,270	Placebo n = 19,276	RRR	ARR	NNT/NNH / 3.1yr
Incidence of shingles	1.6% n=315	3.3% n=642	51%	1.7%	59 (95% CI: 50-72)
Incidence of PHN pain*	0.14 % n=27	0.42 % n=80	67%	0.27%	364 (95% CI: 263-589)
≥1 serious adverse event	1.3 % n=255	1.3 % n=254	NS	NS	-
≥1 serious adverse event AE substudy	1.9 % n=64 (3345)	1.3% n=41 (3271)	↑53%	↑0.66%	152 (95% CI: 79-1692)

AE=adverse event ARR=absolute risk reduction Dx=diagnosis NNT=number needed to treat NNH=number needed to harm RRR=relative risk reduction * 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

- Patients had hx of varicella or ≥30 yr's residence in USA

- Burden of illness score ↓61%; ≥47% was considered significant

- Concern: No information on nature of "serious adverse events" although increased in substudy (RR↑=46%)

- Efficacy for prevention was highest in age 60-69 yrs & decreases as age increases.

- Unaddressed ?'s: ♦efficacy in immunocompromised ♦duration of protection ♦optimal age of administration

How is Zostavax™ supplied? What is the dosage and how is it administered? ^{1,2,3,5}

- 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 degrees 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 minutes**. Contains no preservatives (thimerosal free).
- Individuals should receive a single dose of the entire vial contents, **subcutaneously** ^{deltoid region}. No booster dose is recommended at present!

What are potential adverse effects and drug interactions with Zostavax™? ^{1,5}

- **Common side effects** 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** with other meds or vaccines are not known, since not studied in clinical trials. (Space other live vaccines 4 weeks apart)
 - Must **not** be mixed with any other products in the same syringe. Must be given as separate injections and at different body sites.
 - **Not** to be given together with **Pneumovax[®] 23** (pneumococcal vaccine). Resulted in reduced immunogenicity of Zostavax™.

What are other potential cautions regarding the use of Zostavax™? ^{1,2,3,5}

- **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 ≥1 month before 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 ^{ACIP08}
 - 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 <60 yrs not adequately studied; however **antibody data for age 50-59 support use** in this age group. ¹³ {NACI also supports; Jan 2010} {Zostavax™ is not recommended in pregnancy due to lack of trials. Pregnancy to be avoided for **3 months** following vaccination. Breast feeding is not a contraindication.}

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.

Is administration of Zostavax™ cost effective? ^{2,3,5}

- Zostavax™ costs approximately \$175+ 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}

Bottom Line...

- Zostavax™ is a new vaccine indicated for the **prevention of shingles in immunocompetent patients age ≥60**. ^{Vaccine efficacy is only about 50-60%.}
- Zostavax™ reduces the risk of shingles by 50% (ARR=1.7%, NNT=59) and PHN by 67% (ARR=0.27%, NNT=364) over 3.1years. {NNT: Eg. for every 364 patients vaccinated with Zostavax, 1 case of PHN was prevented & 6 shingles cases were prevented over ~ 3 years.}
- Efficacy for prevention of shingles is highest in patients **60-69 years old** & decreases with increasing age. {Lack outcome data for age <60yrs.}
- Zostavax™ is **not** indicated for treating shingles or post-herpetic neuralgia (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 will have greatly boosted immunity.}
- Cost effectiveness remains to be established. **Cost per single dose = \$ 175 – 195 given SC.**

Shingles Extras:

- **antivirals** (e.g. valacyclovir 1g TID or acyclovir 800mg 5x/day) x7 days ^{S125}; effective in shingles tx for age >50 if used within 24-72hrs of rash onset
- **PHN pain tx:** see RxFiles CNMP chart (7th Ed pg 56).
⇒e.g. nortriptyline, gabapentin, opioid, capsaicin ...

On the horizon: non-freezer version & non-live vaccine formulations in development.

References: see page 2 online to www.RxFiles.ca

NACI Update ^{Jan 2010}: <http://www.phac.aspc.gc.ca/publicat/ccdr-mrc/10vol36/ccs-1/index-eng.php>

Zostavax: in Canada, September 22nd, 2009
{Health Canada approval 2008; USA FDA approval May 2006.}
See www.Zostavax.ca for a list of clinics with vaccine supply.
FDA Update: Mar 2011: add indication for age 50+

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