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Originally prepared by: J Kielly BScPharm, L Regier BSP BA, B Jensen BSP, K Jensen MSc BSP, D Bunka BScPharm, L Kosar MSc BSP, J Bareham BSP BSc

Herpes Zoster Vaccine ZOSTAVAX discontinued 2015 & replaced by Zostavax II discontinued 2022

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 3.1yrs.

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

- **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/ 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.** [9,10]
  - 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 primary varicella infection.

Is ZOSTAVAX effective? Two Studies: Shingles Prevention Study (SPS) [2005] & Zostavax Efficacy& Safety Trial (ZEST) [2012]

Shingles Prevention Study (SPS) [9,10]: 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 = 19276	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 AE substudy [11]	1.9 % n=64 (3345)	1.3% n=41 (3271)	↑53%	↑0.66%	**NNH = 152** (95% CI: 79-1692)

- Patients had hx of varicella or ≥30 yrs 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

For every 364 patients vaccinated, 6 cases of shingles & 1 case of PHN is prevented over 3 years.

Zostavax Efficacy & Safety Trial (ZEST) [12,13]: 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	-	-

- North America & Europe
- History of varicella or ≥ 30 yrs residence in VZV-endemic area
- Burden of Illness (acute symptoms) not significantly decreased
- Efficacy to ↓incidence of shingles was 70 %
- Incidence of shingles lower than in SPS trial
- Limitations: Short follow up time; Trial did not assess incidence of PHN pain

* 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[14]:** n=14,270 subjects: 7320 vaccine & 6950 placebo followed for an additional 5 years ~8yr follow-up. Efficacy ↓ yearly, losing statistical significance in the 3rd year post-vaccination for PHN & the 6th 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[15].** 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. SPS 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.

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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.[Tseng]) 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[20].
  - 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. PL

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[25,26]. 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].

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)[27] & 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. valcyclovir 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 (9th Ed, pg 67) → e.g. nortriptyline, gabapentin, opioid, capsaicin.
- See RxFiles Adult Vaccines Chart (9th ed, pg 50).

AE=adverse event AIDS=acquired immunodeficiency syndrome **ARR**=absolute risk reduction **DB**=double blind **Dx**=diagnosis **HIV**=Human immunodeficiency virus **hx**=history **NNT**=number needed to treat **NNH**=number needed to harm **NNV**=number needed to vaccinate **RCT**=randomized controlled trial **RR**=relative risk **RRR**=relative risk reduction **TNF**=tumour necrosis factor **wk**=week **yr**=year

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