Subunit adjuvanted zoster vaccine: why the fuss?

Soren Gantt, MD PhD MPH
Pediatric Infectious Diseases
Vaccine Evaluation Center
BC Children's Hospital
University of British Columbia







Disclosures

- Research support from:
 - -VBI for CMV and HBV vaccine trials
 - Meridian Biosciences for a CMV diagnostic trial
 - -GSK for a RSV vaccine trial
- Consulting fees from:
 - Omeros for antiviral drug development
- I will discuss potential off-label uses of Shingrix







Objectives

- Explain the differences in vaccine efficacy findings from clinical trials with the subunit adjuvanted zoster vaccine and the live attenuated zoster vaccine
- Appraise age-related differences in efficacy and duration of protection, as well as safety considerations in use of a live and non-live zoster vaccine







Varicella-Zoster Virus (VZV)

- Etiologic agent of chickenpox and shingles
- Enveloped DNA herpesvirus
- Only infects humans, single serotype
- Clinical presentations:
 - Acute infection: Varicella; "chickenpox"
 - Reactivation: Herpes zoster; "shingles"





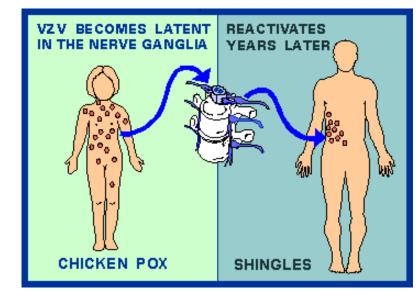


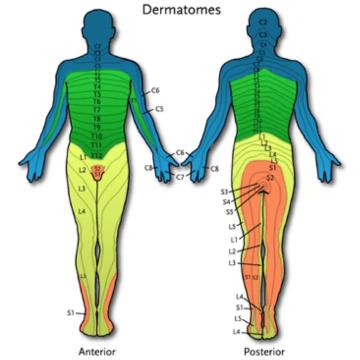




Herpes Zoster (HZ)

- Shingles is from the Latin for "girdle" (cingulum); zoster is Greek for "girdle"
- After primary infection, VZV goes latent in cerebral or dorsal root ganglia
- Virus reactivates, tracks down sensory nerve to infect the innervated skin in a dermatomal distribution
- Rash becomes vesicular and crust within 7-10 days
- Often associated with significant acute pain











Burden of HZ disease

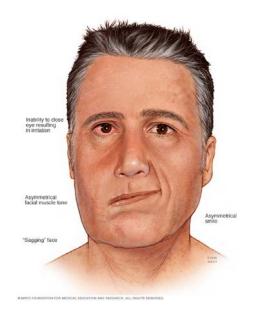
- HZ affects ~130,000 Canadians per year
- Incidence is increasing
- Age is the most important risk factor
- 99% of people >50 yrs old have had varicella and are at risk for HZ
 - 30% of Canadians will develop HZ
 - By age 85, 50% get >1 attack, and 1% get >2
- Post-herpetic neuralgia (PHN) is the most common complication of HZ
 - ≥ 90 days of pain
 - Occurs in ~15% of HZ cases
 - Risk is age-related, occurs in 5% of cases in those
 <60 yrs, and 20% in those
 >80 yrs old

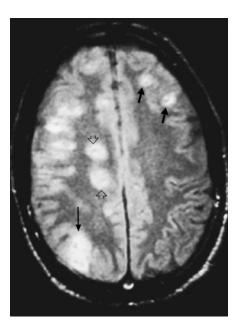




Other HZ Complications

- Bacterial superinfection
- Ramsay Hunt syndrome
 - HZ of the geniculate gangion
 - Pain/lesions in ear, facial droop
 - Hearing loss, tinnitus, vertigo
- Herpes zoster ophthalmicus
 - HZ of the trigeminal ganglion
 - Keratitis, vision loss
- Acute retinal necrosis
 - Vision loss, retinal detachment
- Encephalitis
 - Can occur before or long after rash
- Dissemination in immunocompromised











Management of HZ

- Early antiviral treatment with acyclovir, valacyclovir, or famciclovir
 - Viral replication ceases by ~72 hours
 - Reduces duration of acute symptoms
 - Might reduce risk of PHN?
- Analgesics for pain
- No role for steroids or other adjunctive treatment for uncomplicated cases
- Intravenous acyclovir for disseminated disease or other complication manifestations







Natural immunity to HZ

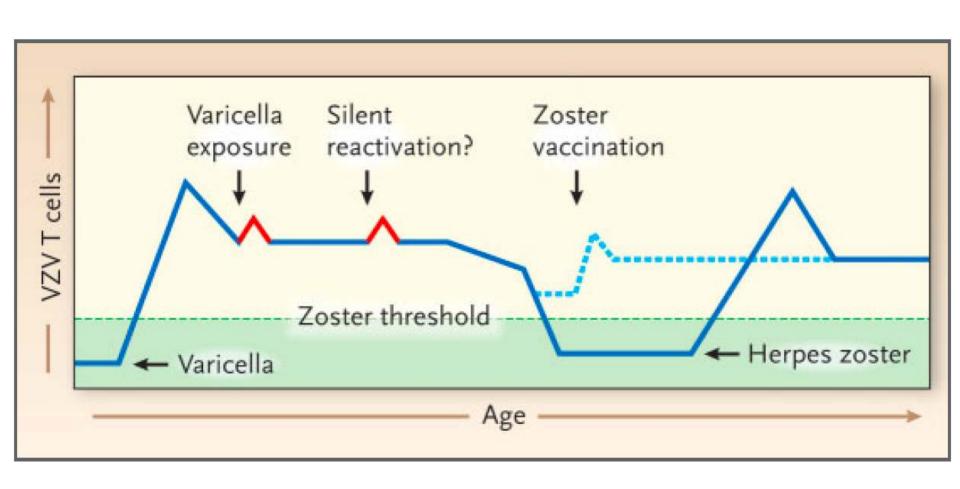
- T cell responses critical for preventing HZ and limiting disease severity
 - Defects in cell-mediated (not humoral) immunity associated with severe HZ
 - Lower VZV-specific T cell responses associated with higher risk of HZ and PHN
- HZ risk 10-100x in solid organ transplant
- >2x risk of HZ with rheumatologic diseases and HIV infection
- Disseminated HZ is potentially lifethreatening







T cell control of latent VZV



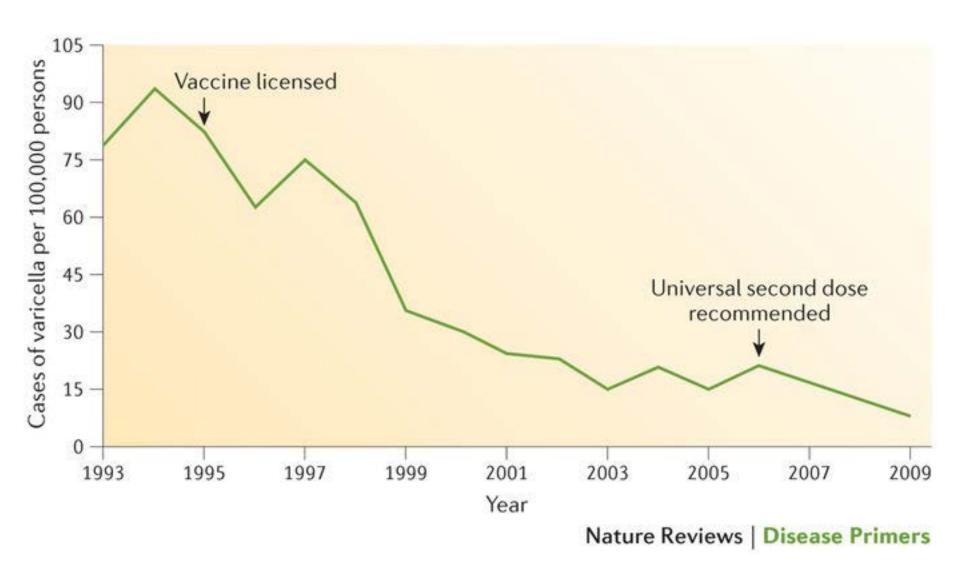
Varicella Vaccines

- Live attenuated VZV vaccine (Oka strain) developed in Japan in 1974 to prevent varicella
 - Licensed in US in 1995 and in 1998 in Canada
 - Varivax (Merck) and Varilrix (GSK)
 - Vaccine contains >1,350 PFU (plaque forming units)
 of Oka strain in each 0.5 ml dose
 - >97% effective against severe disease
- Varicella vaccination has not increased the incidence of HZ (a theoretical concern)
- HZ can result from the varicella vaccine, but occurs less often than from wild-type varicella





Impact of Immunization on Varicella









Zoster Vaccines

- Zostavax (Merck) contains ≥19,400 PFU of Oka strain in each 0.65 mL dose
 - Licensed in the US in 2006, in Canada in 2008
 - Given as a single dose SQ in deltoid region
 - Reduces HZ by 51% and PHN by 67%
 - Less effective for HZ in ≥70 yr olds (38%)
 - Efficacy wanes, no clear protection after 8 yrs









NOW APPROVED



Zoster Vaccines

- Zostavax (Merck) contains ≥19,400 PFU of Oka strain in each 0.65 mL dose
 - Licensed in the US in 2006, in Canada in 2008
 - Given as a single dose SQ in deltoid region
 - Reduces HZ by 51% and PHN by 67%
 - Less effective for HZ in \geq 70 yr olds (38%)
 - Efficacy wanes, no clear protection after 8 yrs
- Shingrix (HZ/su, GSK) recombinant gE + AS01B
 - Approved late last year in Canada, US and Europe
 - 2 doses, 2-6 months apart IM in deltoid region
 - Reduces HZ by >95% and PHN by 90%
 - >90% effective in people >70 yrs old
 - ≥85% effectiveness for 4 yrs; longer unknown

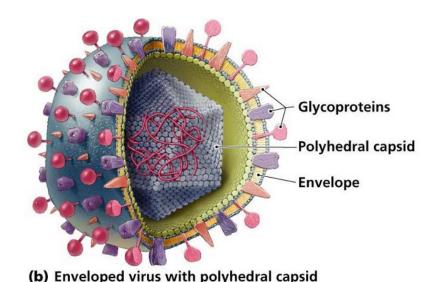






Shingrix adjuvanted gE subunit vaccine

- Glycoprotein E is abundant on VZV-infected cells
- Essential for neurotropism and virulence
- Varicella results in anti-gE antibodies and T cell responses
- Anti-gE antibody is neutralizing
 - No efficacy data for Shingrix to prevent varicella
- Shringrix recombinant gE made in CHO cells
- AS01B contains MPL and QS-21 in a liposomal formulation
 - Strong inducer of CMI











The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 28, 2015

VOL. 372 NO. 22

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D., Roman Chlibek, M.D., Ph.D., Javier Diez-Domingo, M.D., Ph.D., Shinn-Jang Hwang, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Airi Poder, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Timo Vesikari, M.D., Ph.D., Daisuke Watanabe, M.D., Ph.D., Lily Weckx, M.D., Ph.D., Toufik Zahaf, Ph.D., and Thomas C. Heineman, M.D., Ph.D., for the ZOE-50 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 15, 2016

VOL. 375 NO. 11

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C. Vanden Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S.A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, and T.C. Heineman, for the ZOE-70 Study Group*







Zoster Vaccine Comparison

Zostavax

- Given as a single dose
- Less effective, not very durable
- Well tolerated
 - Pain in 34%, ~no systemic AEs
- Cost ~\$260, covered by many insurance providers
- Cannot be given to immunocompromised patients

Shingrix

- 2 doses, 2 months apart
- More effective and appears more durable
- More reactogenic
 - Pain ~80%, ~20% fever, >10% grade 3 AEs (but no SAEs)
- Cost ~\$340, coverage likely similar to Zostavax
- Appears safe and effective in people who received Zostavax, and in immunocompromised patients



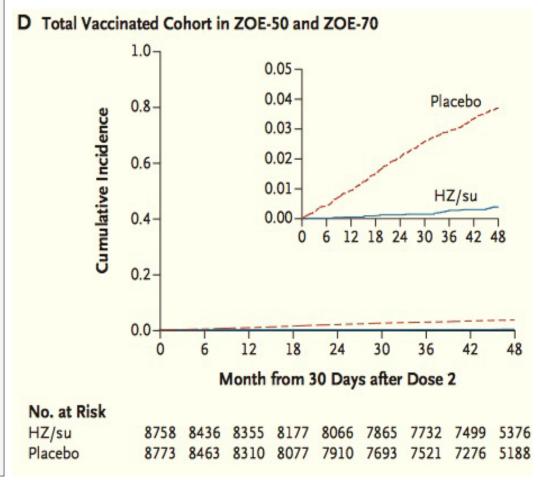




Zostavax (SPS)

В 6.0-Placebo 5.5-5.0-4.5-Cumulative Incidence of HZ (%) 4.0-3.5-3.0-Zoster vaccine 2.5-2.0-1.5-1.0-0.5 Years of Follow-up No. at Risk 19,247 18,915 18,422 Placebo 9806 1856 19,254 18,994 1906 18,626 9942 Vaccine

Shingrix (ZOE-70)









MAJOR ARTICLE







Im He Va

Katrijn Ilse Vas

Pennsylv

MAJOR ARTICLE

Safety and Immunogenicity of an Adjuvanted Herpes Zoster Subunit Candidate Vaccine in

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Elchone Moham

Pla

¹GlaxoSn Trafalgar Charité–l ⁷GlaxoSn

A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients

Edward A. Stadtmauer,¹ Keith M. Sullivan,² Francisco M. Marty,³ Sanjeet S. Dadwal,⁴ Genovefa A. Papanicolaou,⁵ Thomas C. Shea,⁶ Sherif B. Mossad,⁷ Charalambos Andreadis,⁸ Jo-Anne H. Young,⁹ Francis K. Buadi,¹⁰ Mohamed El Idrissi,¹¹ Thomas C. Heineman,¹² and Elchonon M. Berkowitz¹²

¹University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA; ²Duke University Medical Center, Durham, NC; ³Dana-Farber Cancer Institute and Brigham & Women's Hospital, Boston, MA; ⁴City of Hope, Duarte, CA; ⁵Memorial Sloan-Kettering Cancer Center, New York, NY; ⁶University of North Carolina Hospital, Chapel Hill, NC; ⁷Cleveland Clinic Foundation, Cleveland, OH; ⁸University of California Medical Center, San Francisco, CA; ⁹University of Minnesota, Minneapolis, MN; ¹⁰Mayo Clinic, Rochester, MN; ¹¹GlaxoSmithKline Vaccines, Wavre, Belgium; and ¹²GlaxoSmithKline Vaccines, King of Prussia, PA







HZ vaccine recommendations

- NACI recommended Zostavax for immunocompetent Canadians <u>></u>60 yrs old
 - 50-59 may also consider vaccination
- No NACI statement about Shingrix yet
- US Advisory Committee on Immunization Practices recommended Shingrix over Zostavax for all people >50 yrs old
 - Including those that already received Zostavax
 - Contentious vote because of lack of data in minorities and on long-term safety and efficacy
- Not (yet) recommended by ACIP for patients with moderate to severe immunocompromise







Potential uses of Shingrix in children

- No safety or efficacy data in children
- Prevention of HZ in high-risk children?
 - E.g. immunocompromised patients with a history of varicella (or varicella vaccine?)
- Prevention of varicella in immunocompromised children?
 - E.g. patients who could not be immunized with live vaccine prior to transplant
 - No data on efficacy of Shingrix to prevent varicella
- Prevention of varicella in healthy children?
 - Obviates any risk of vaccine strain HZ





FAQs

- Can Shingrix be given after HZ? Yes
- Can Shingrix be given after Zostavax? Yes
- Can Shingrix be co-administered with other vaccines? Yes
 - But only studied with QIV (Fluarix) so far
- What are contraindications to Shingrix?
 - Severe allergy to any component of Shingrix
 - A person known to be seronegative for varicella
 - Acute HZ
 - Pregnancy or breastfeeding
 - Moderate or severe acute illness (T≥38.5)
- When can I get Shingrix? "Soon"...









http://www.thisisyourconscience.com/