Emerging Issues in Reactivated Herpes Zoster Disease

Tim Hilderman, MD FRCPC

2018 Infection Prevention and Control
Across the Continuum

Friday, June 22nd, 2018

DISCLOSURE STATEMENT

Type of relationship	**Modest (less than 10K)** *Please specify organization name*	**Significant (greater than $10K)** *Please specify organization name*
A - Consulting Fees/Honoraria		
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F- Research Grants/Educational Grants		
G- Fellowship Support		
H – Salary		
I - Intellectual Property Rights		
J - Other Financial Benefit		

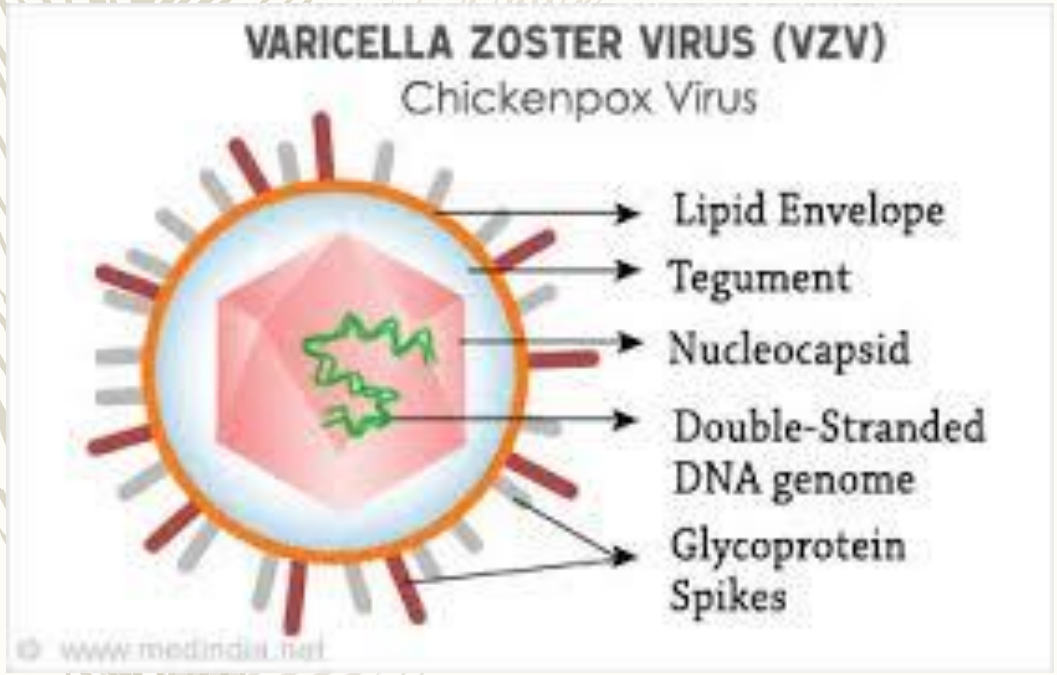
There are no relationships to disclose X

OBJECTIVES

1. Review the signs, symptoms and complications of Herpes Zoster
2. Understand the Epidemiology of Herpes Zoster
3. Describe how exposure occurs
4. Develop an approach to case and contact management
5. Compare and contrast the two currently approved Zoster Vaccines

VARICELLA VIRUS INFECTION

- Varicella-zoster virus (VZV) one of 8 herpes viruses known to cause human infection
- VZV is a double-stranded, DNA virus encoding approximately 75 proteins
- Possesses a lipid-containing envelope with glycoprotein spikes.
- VZV glycoprotein E is essential for viral replication and cell-to-cell spread
- It is a primary target of VZV-specific immune responses


VARICELLA ZOSTER VIRUS (VZV)
Chickenpox Virus
Lipid Envelope
Tegument
Nucleocapsid
Double-Stranded DNA genome
Glycoprotein Spikes
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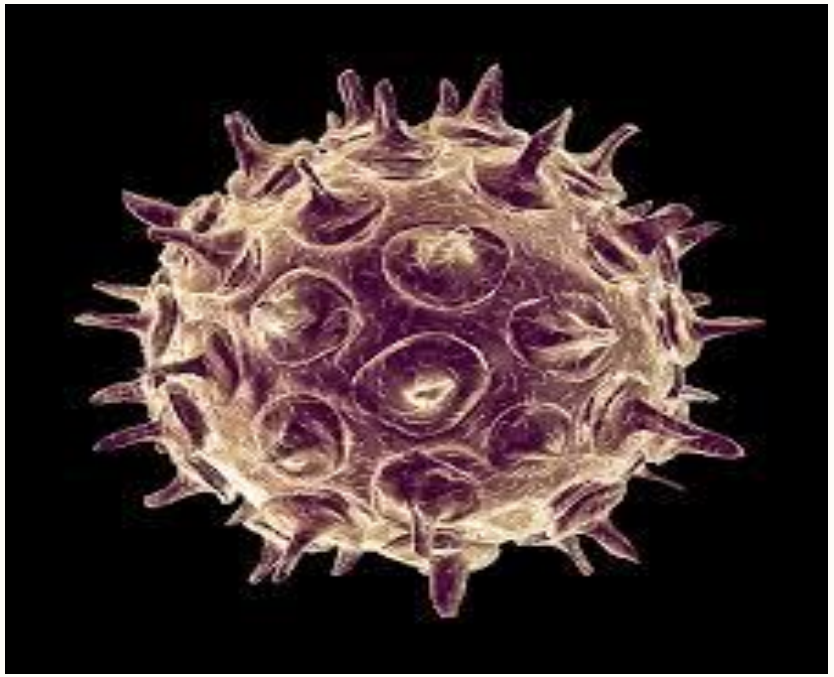
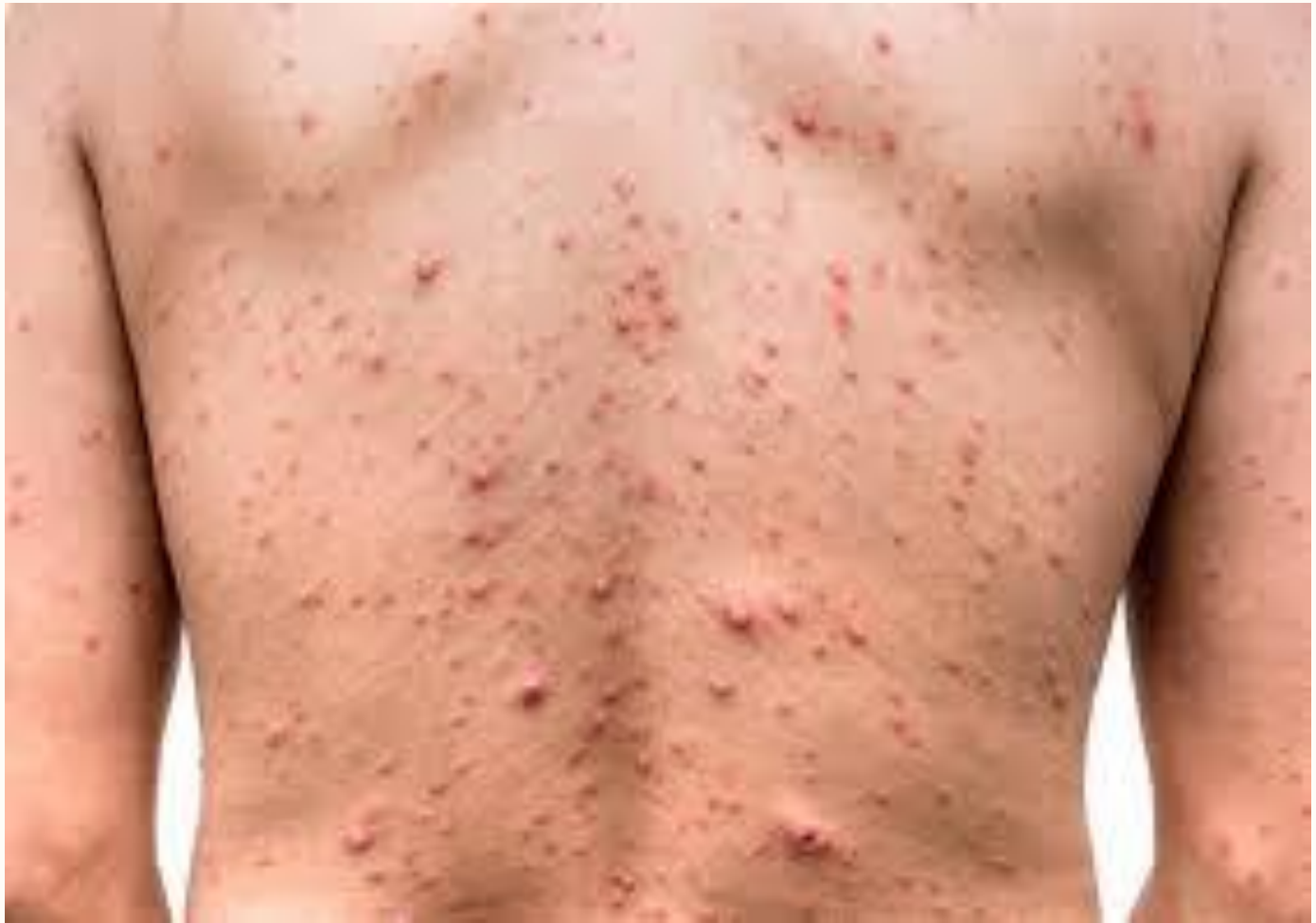
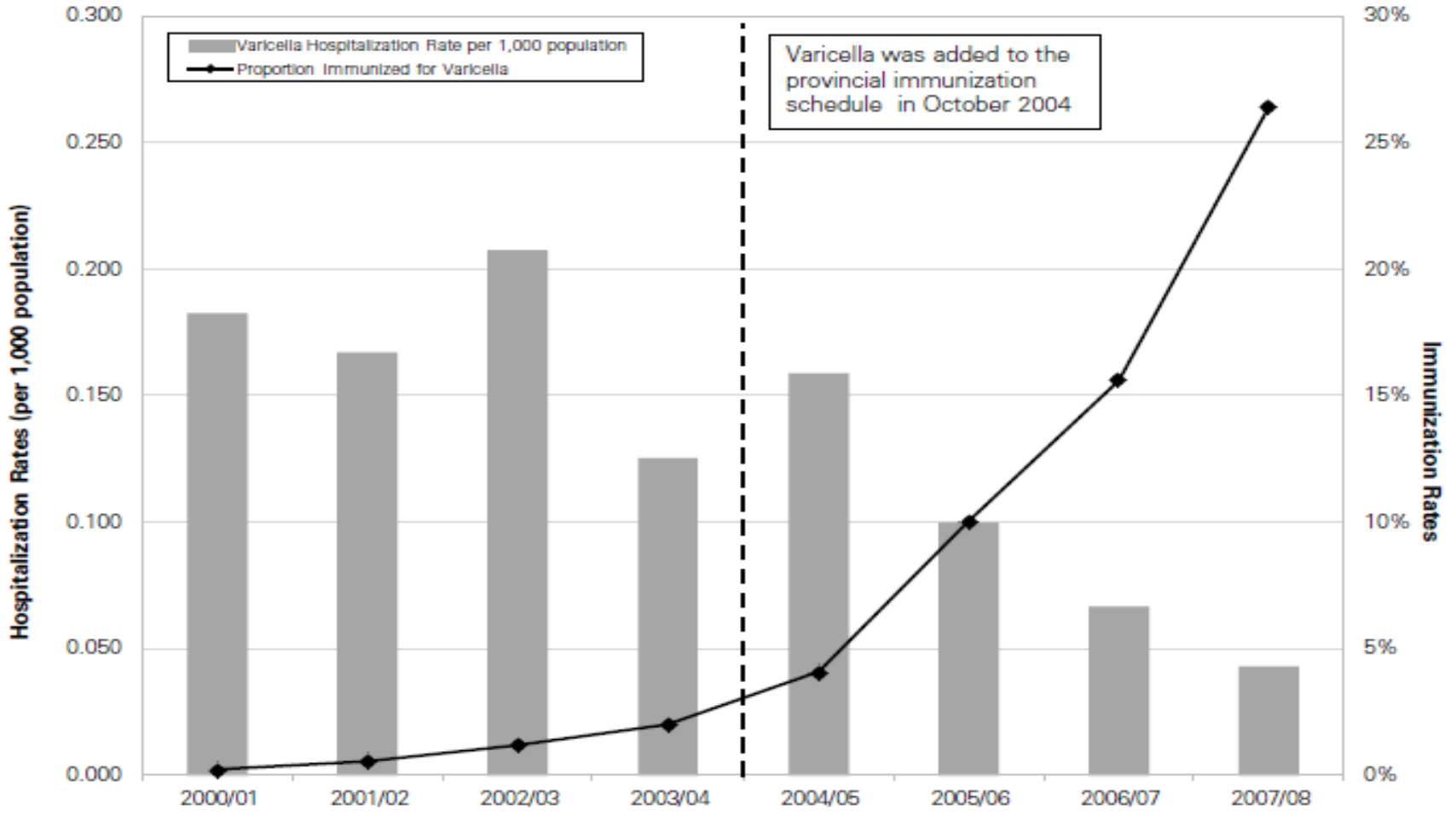


Two clinically distinct forms of disease: varicella (chicken pox) and herpes zoster (shingles)

- Primary *varicella zoster virus* (VZV) infection causes varicella (chickenpox),
- Reactivated infection results in herpes zoster (shingles). Herpes zoster (HZ) is characterized by neuropathic pain and dermatomal vesicular rash.

Primary Varicella(chickenpox)





Year	Population	Number of Children Hospitalized	Hospitalization Rate per 1,000 Population	Number of Children Immunized	Proportion Immunized
2000/01	306,832	56	0.183	642	0.21%
2001/02	305,141	51	0.167	1,697	0.56%
2002/03	303,738	63	0.207	3,607	1.19%
2003/04	303,345	38	0.125	6,059	2.00%
2004/05	302,399	48	0.159	12,356	4.09%
2005/06	300,363	30	0.100	30,160	10.04%
2006/07	299,587	20	0.067	46,725	15.60%
2007/08	301,787	13	0.043	79,772	26.43%

Source: Manitoba Centre for Health Policy, 2011

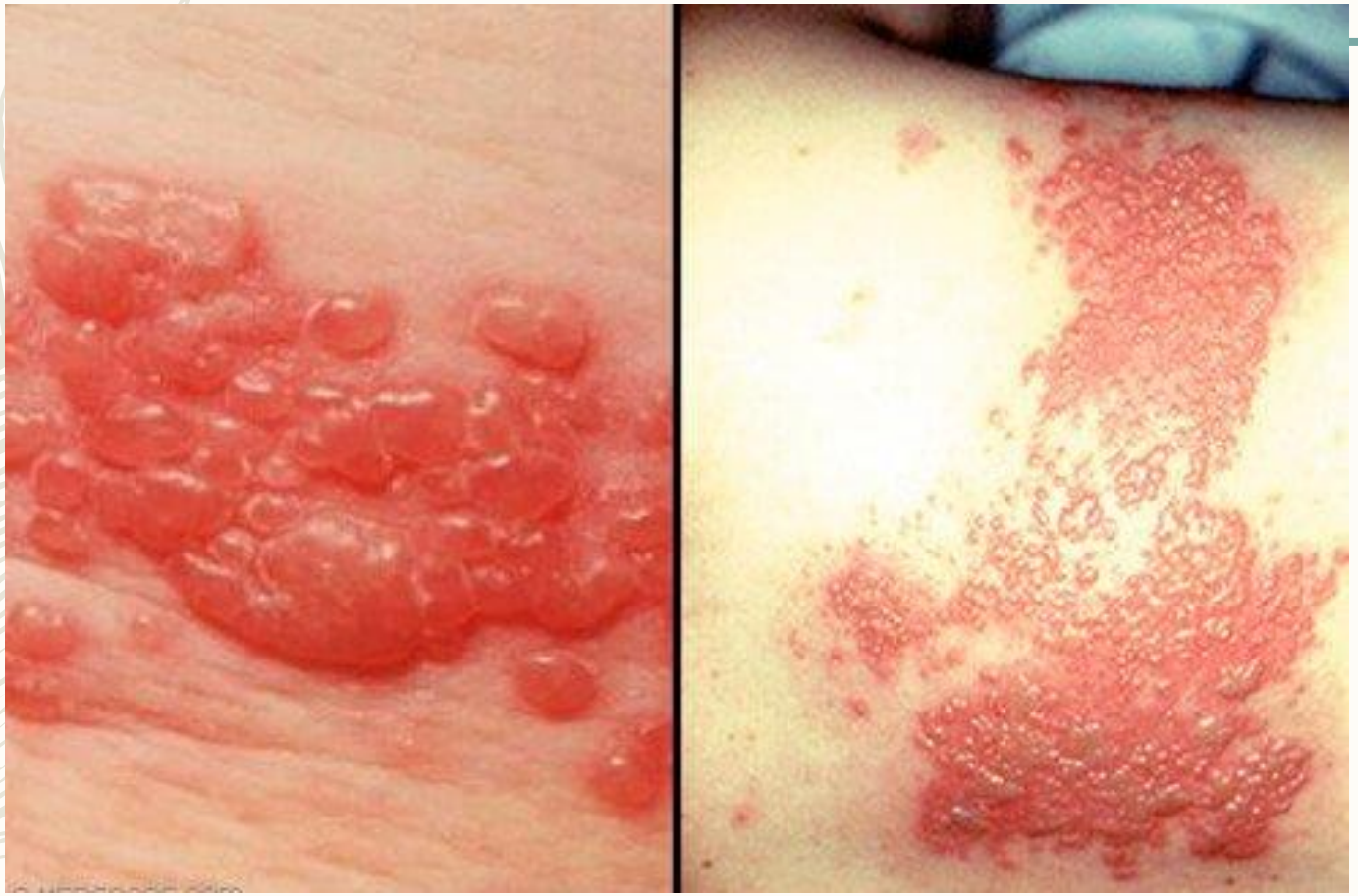
Latency

Cell-free virus, which is present only in skin vesicles, infects nerve endings in skin and migrates along sensory axons to establish latency in neurons within the regional ganglia.

VZV proteins accumulate preferentially in the cytoplasm of neurons during latency, but migrate to the nucleus during productive infection.

Once reactivation occurs, virus can spread to other cells within the ganglion to involve multiple sensory neurons and thereby establish infection of the skin

Herpes Zoster: Shingles



Reactivation

- Herpes Zoster results from reactivation of latent varicella-zoster virus in the dorsal-root or cranial nerve ganglia
- dorsal spinal ganglion show intense inflammation, hemorrhagic necrosis of nerve cells. The ganglion undergoes eventual neuronal loss with subsequent fibrosis of afferent nerve fibers, particularly type C nociceptors
- Risk Factors: Age, Age, Age…
- No definitive immunologic correlate of protection against herpes zoster has been identified
- CD4+ and CD8+ T cells play a role
- Effective vaccine needs to overcome immunosenescence

Clinical Manifestations

- Erythematous papules evolving quickly to grouped vesicles – become pustular
- Crust in 7-10 days = no longer infectious
- Usually limited to one dermatome- mainly thoracic or lumbar
- If ophthalmic branch of trigeminal cranial nerve involved – HZO
- 80% have no systemic symptoms
- Scarring and pigmentation changes may persist for years
- Recurrence can occur estimates vary

Clinical Manifestations

- Pain due to acute neuritis is most common symptom-75% prodromal pain
- Described as a burning, throbbing, and stabbing, allodynia
- 15-20% duration at least 30 days
- DDx: angina, cholecystitis, renal colic….

Complications

- Up to 40% of persons report at least one complication (increase with age/imm)
- Post Herpetic Neuralgia 20%
- HZO up to 10%
- CNS infections
- Nerve palsies
- Ramsay-Hunt Syndrome
- GBS
- Secondary Bacterial Infections

Post Herpetic Neuralgia

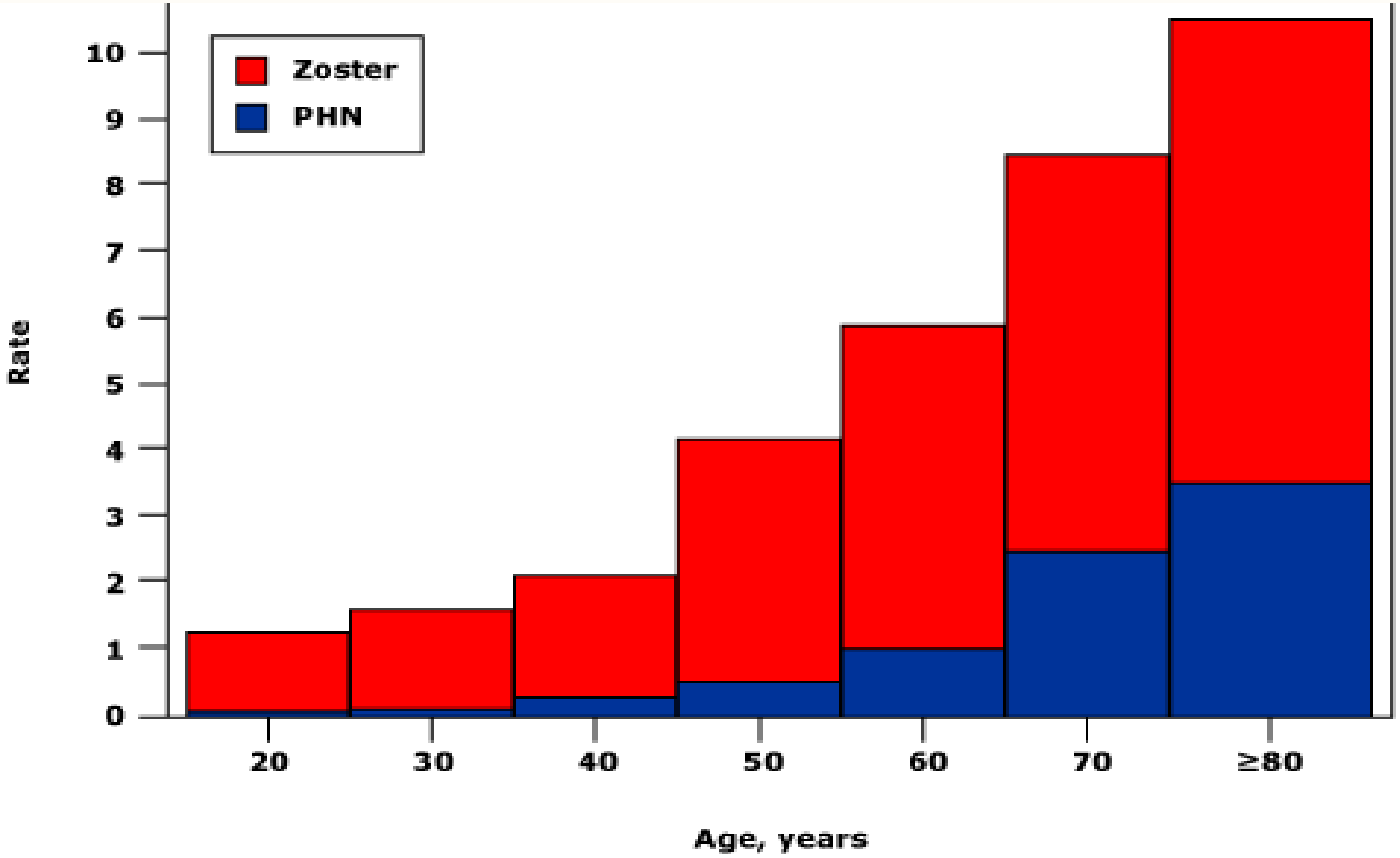
- Three phases of pain
- Acute herpetic neuralgia: persists up to 30 days
- Subacute herpetic neuralgia: persists up to four months
- PHN: pain persisting beyond four months

Epidemiology

- Approximately one in three lifetime risk
- Annually in Canada:
- 130 000 cases HZ
- 17 000 cases PHN
- 20 deaths
- Age is major risk factor for development of HZ
- Incidence increases sharply with increasing age

Epidemiology

- PHN Risk increases 1.2-3.X 1 every 10 years
- 50-59: 4-15%
- 60-69: 7-26%
- 70+: 14-29%



* Per 1000 person-years.

Incidence of Zoster with Age

Things we already know

- Primary *varicella zoster virus* infection causes varicella (chickenpox) and reactivated infection results in herpes zoster (shingles).
- Herpes zoster (HZ) occurs most frequently among older adults and immunocompromised persons.
- Person A with Herpes Zoster CANNOT give Person B Herpes Zoster
- Person A with Herpes Zoster CAN give Person B primary varicella provided Person B is susceptible…

Shingles Transmission

- Far less infectious than chickenpox
- **DIRECT** contact with lesions or fluid
- Infectious until lesions have crusted over
- Articles (fomites) freshly soiled by vesicular fluid may be infectious
- Covering lesions decreases transmission potential
- Immunocompromised individuals may be infectious longer
- Disseminated Zoster may spread through airborne route

IP AND C Measures

- Susceptible, exposed individuals are potentially infectious day 10-21
- Routine Practices – Always!
- Localized (covered)-Routine Practices
- Localized (not covered)- Contact and Airborne
  - This could be large areas of lesions or a lot of weeping where there could be significant viral load

IP AND C Measures

- Localized disease in immunocompromised individual: Airborne and Contact
- Risk of dissemination
- Disseminated disease: Airborne and Contact
- Cohort HCWs/Caregivers/Roommates immune to Chickenpox
- Visitors with lesions should not enter facility
- Patients should notify outpatient and day surgery if Zoster develops

Exposure Assessment

- Was there PPE breach(including no PPE!)? N=not exposed Y=assess further
- Touched rash, exposed lesions, or vesicular fluid=exposed
- Any contact with patient with disseminated shingles=exposed
- Touched articles freshly soiled by vesicular fluid=exposed
- Touched articles freshly soiled by vesicular fluid or secretions in a disseminated case=exposed
- Exposure to immunocompromised person with localized shingles=???- would need to be disseminated

Post-Exposure

- Is exposed susceptible? Yes - report
- Consider infectious from day 10-21
- Give varicella vaccine (unless pregnant or contraindicated) within 3-5 days
- If vaccine contraindicated give VZIG within 96 hours
- If exposed is pregnant: check immunity ASAP, if results not available in less than 96 hours give VZIG
- There are maternal and fetal sequelae of Chickenpox infection in pregnancy

Prevention: Live Zoster Vaccine

- Based on Oka/Merck live attenuated varicella virus strain
- Serial passage through tissue culture
- Single dose 0.5ml
- Subcutaneous
- Contraindications: history of hypersensitivity to gelatin, neomycin, or any component of the vaccine, pregnancy, immunosuppression

Live Zoster Vaccine:VE Zoster

- 14 studies considered
- 50-59 years of age, 22 000 participants, VE: 69.8 (54.1-80.6) at 1.5 years
- VE dropped to 50.34 (36.01-51.55) at one year
- 60-69 years of age VE: 63.9 (55.5-79.9)
- 70+ years of age VE: 37.6 (25-48.1)
- Overall – 51.3%
- VE decreases with age, VE decreases to 0 by 6 years

Live Zoster Vaccine: VE PHN

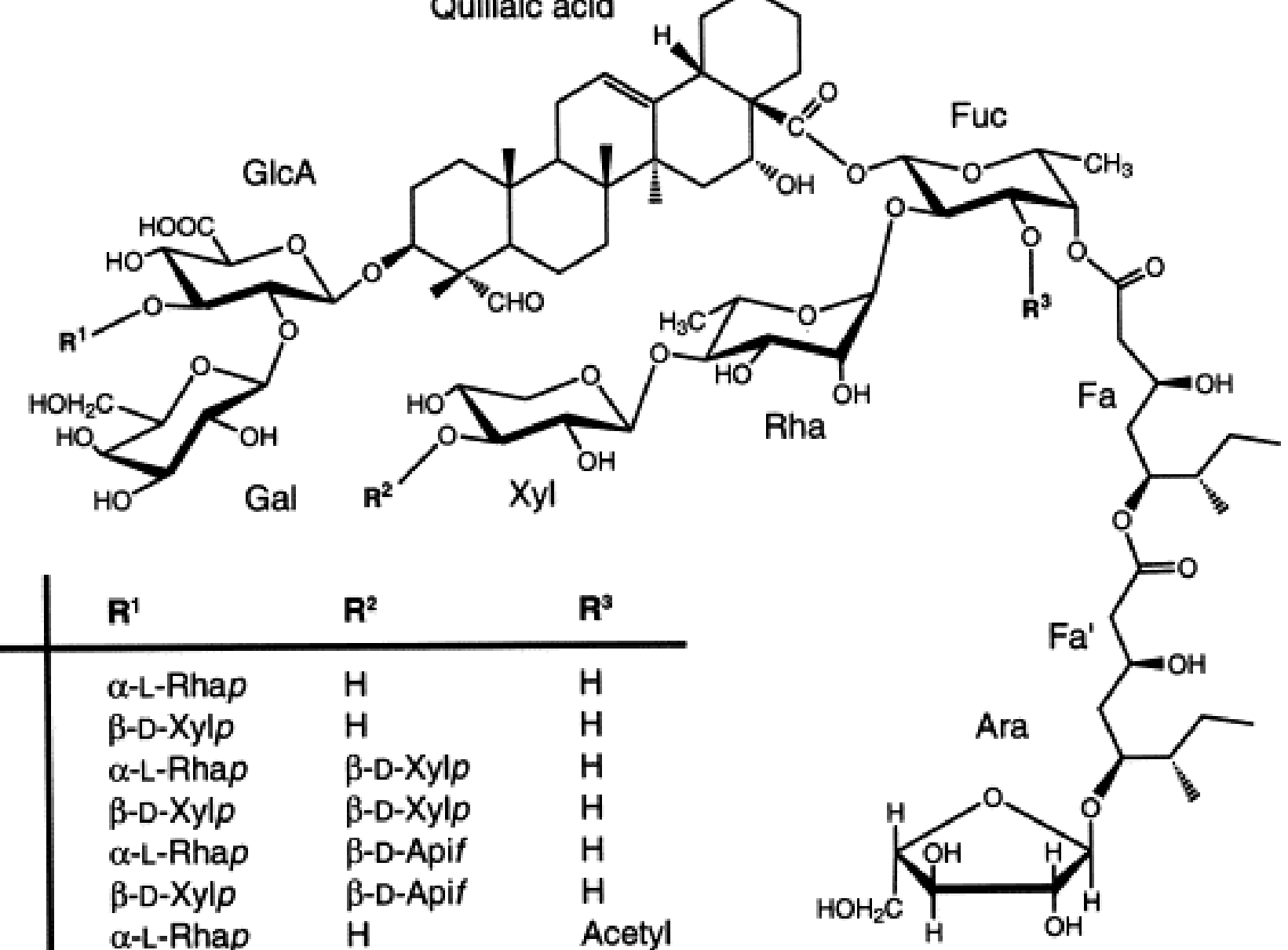
- 65.7% at 3 years in 60-69
- 66.8% at 3 years 70+

Recombinant Zoster Vaccine

- Recombinant subunit vaccine
- VZV glycoprotein E: selected as its essential for viral replication and cell to cell spread
- Primary target of VZV specific immune responses
- AS01b adjuvant system: promotes strong CD4+ T-cell and humoral responses
- 50ug recombinant VZV glycoprotein E
- 50 ug MPL (monophosphoryl lipid)
- 50 ug of Quillaja sapnaria Molina, fraction 21
- .5ml deltoid (0, 2-6 months)

Recombinant Zoster Vaccine

- 2 doses 0.5ml
- 2-6 months apart
- Intramuscular
- Contraindications: known hypersensitivity to any vaccine component



	R^1	R^2	R^3
S1	α-L-Rha*p*	H	H
S2	β-D-Xyl*p*	H	H
S3	α-L-Rha*p*	β-D-Xyl*p*	H
S4	β-D-Xyl*p*	β-D-Xyl*p*	H
S5	α-L-Rha*p*	β-D-Api*f*	H
S6	β-D-Xyl*p*	β-D-Api*f*	H
S7	α-L-Rha*p*	H	Acetyl
S8	β-D-Xyl*p*	H	Acetyl
S9	α-L-Rha*p*	β-D-Xyl*p*	Acetyl
S10	β-D-Xyl*p*	β-D-Xyl*p*	Acetyl
S11	α-L-Rha*p*	β-D-Api*f*	Acetyl

AS01 is a liposome-based vaccine adjuvant system containing two immunostimulants: 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) and the saponin QS-21.

Quillaja saponaria, the soap bark tree or soapbark, is an evergreen tree in the family Quillajaceae, native to warm temperate central Chile. In Chile it occurs from 32 to 40° South Latitude approximately. Populations are found even 2000 m (6500 ft) above sea level. It can grow to 15–20 m (50–65 ft) in height.

Where the Saponin hits the Road:ZOE 50

- 14759 participants
- 408 reported suspected herpes zoster
- 220 were confirmed by pcr, 24 by committee
- 216 of these included in analysis
- 6 in the vaccinated group
- 210 in the placebo group
- VE at 3.2 years 97.2% (93.7-99.00, p <0.001) 50+
- NO DIFFERENCE in VE among the age groups

ZOE-50/70

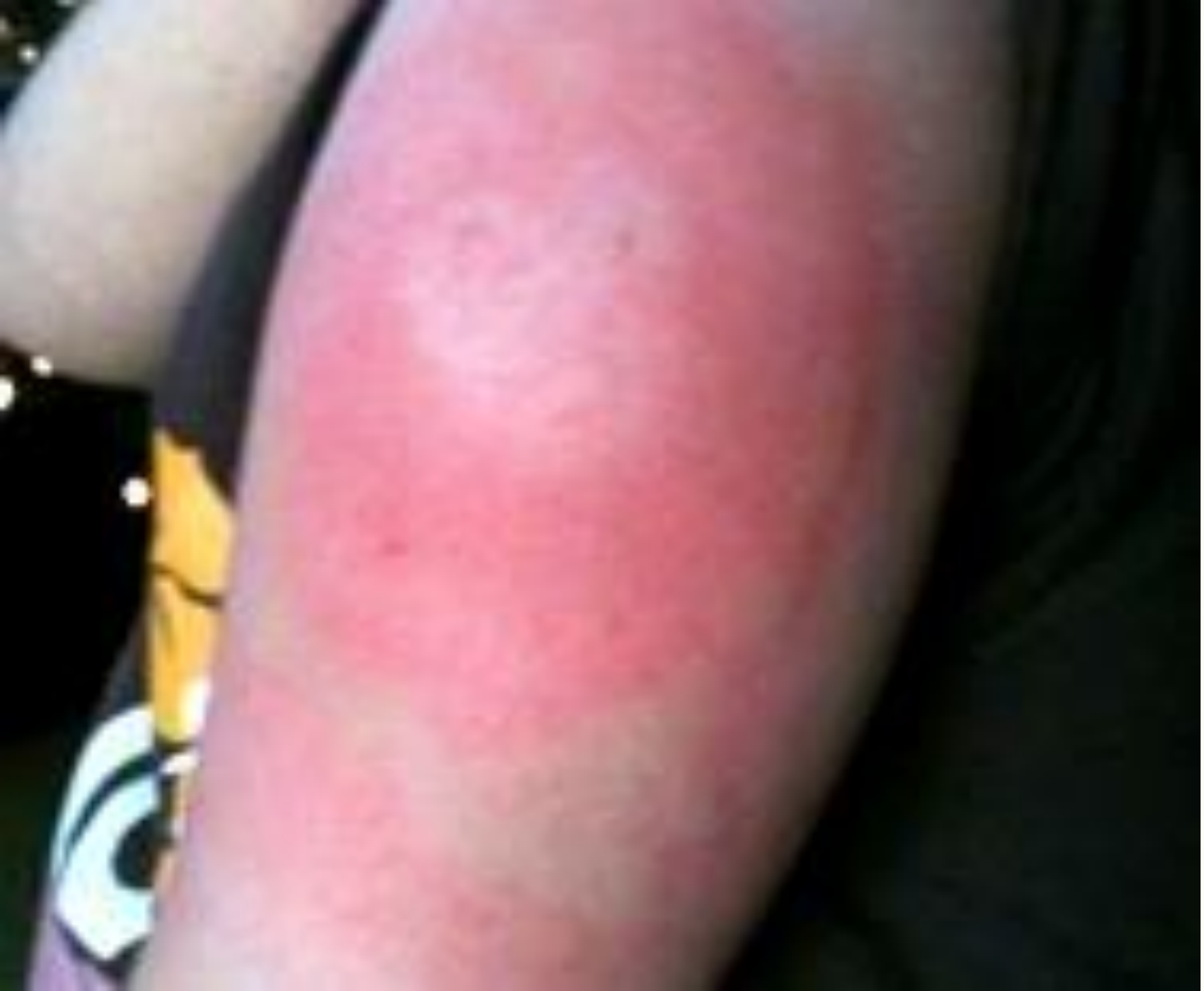
- 28 000 participants 50+
- 50-59 years of age 96.6% (89.6-99.3) at three years against HZ
- 100% (40.8-100) against PHN
- 60-69 years of age 97.4 (90.1-99.7) against HZ
- 70+ years of age 91.3 (86.8-94.5) against HZ
- Declined over 4 years from 97.6-84.7 not statistically significant

VE?

- Estimates of RZV vaccine efficacy (two doses) were available from two pivotal clinical trials that recruited over 28,000 adults over 50 years of age
- Among adults 50 to 59 years of age, three year efficacy was estimated to be 96.6% (95% CI: 89.6%-99.3%) for incident HZ and 100% (95% CI: 40.8%-100%) against PHN.
- In adults 60-69 years of age, efficacy was reported to be 97.4% (95% CI: 90.1%-99.7%). For adults 70 years of age and older, using pooled data from both studies, vaccine efficacy against incident HZ was estimated to be 91.3% (95% CI: 86.8%-94.5%).

Reaction to Action

- 8926 assigned to reactogenicity subgroup
- 84.4% of vaccinated patients had local/systemic reactions!!! OUCH
- 37.8% placebo
- 17% vs 3.2% reported symptoms that prevented normal activity=- Yikes!
- Most local injection site reactions
- Myalgia most common systemic reaction
- Serious A/E same in both groups 1.1 vs 1.3%



Reactogenicity is generally due to an innate immune response and occurs soon after vaccination. Some reactogenicity is needed in order to induce a good adaptive antibody and cellular immune response

What we mean by immunogenicity is the induction of a humoral / cell mediated response (ie. in vaccination the generation of antibodies and a secondary memory b cell response against the specific disease).

NACI

- Current NACI recommendations indicate that:
  - HZ vaccine is recommended for the prevention of herpes zoster and its complications in persons 60 years of age and older without contraindications. (2)
  - Herpes Zoster vaccine may be used in patients aged 50 to 59 Years (2)
- **Note: NACI has not completed a statement that includes Shingrix vaccine. It is planned to be released early 2018.**

ACIP

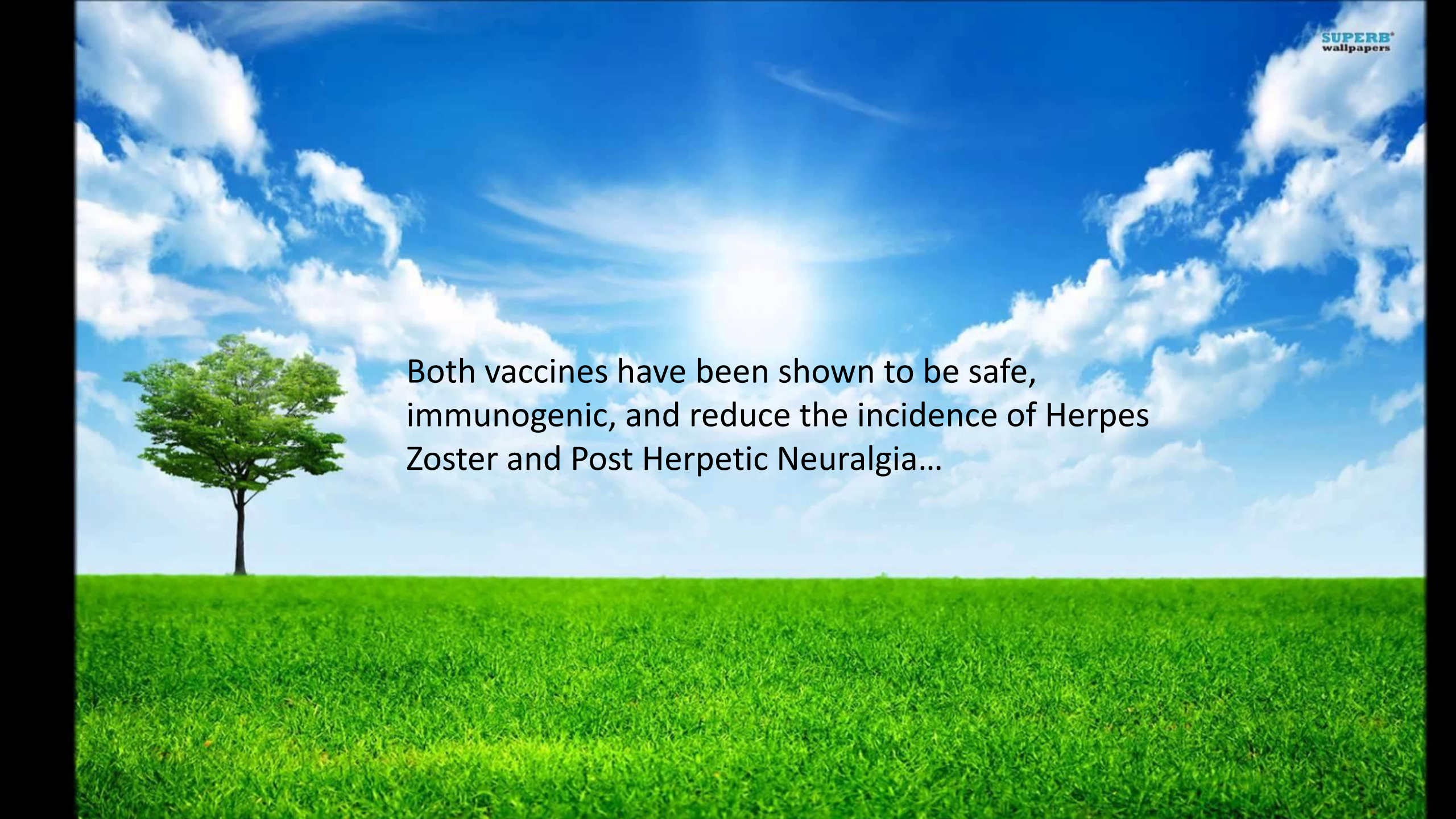
- The Advisory Committee on Immunization Practices (ACIP) in the USA approved the following recommendations on October 25, 2017: (4)
  - Shingrix is recommended for immunocompetent adults aged 50 years and older to prevent shingles and related complications.
    - *Rationale: With high efficacy among adults ≥50 years, and modest waning of protection over 4 years following vaccination, Shingrix has the potential to prevent substantial HZ disease burden and will likely continue to provide substantial protection beyond 4 years as recipients age.*

ACIP

- Shingrix is recommended for immunocompetent adults who previously received Zostavax to prevent shingles and related complications
  - *Rationale: studies have shown that Zostavax effectiveness wanes substantially over time, leaving recipients with reduced protection against HZ. Shingrix elicited similar safety, reactogenicity, and immunogenicity profiles regardless of prior Zostavax receipt; therefore, Zostavax recipients will likely benefit from vaccination with Shingrix.*

ACIP

- Shingrix is the preferred vaccine for preventing shingles and related complications over Zostavax.
  - *Rationale: Shingrix estimates of efficacy against HZ were higher than those of Zostavax. Estimates of efficacy against PHN are also higher for Shingrix than Zostavax. However confidence intervals overlap. Zostavax efficacy wanes substantially during the 4 years following receipt. As a result of higher and more long-lasting efficacy, Shingrix is estimated to prevent more HZ and PHN compared to Zostavax.*



Both vaccines have been shown to be safe, immunogenic, and reduce the incidence of Herpes Zoster and Post Herpetic Neuralgia…

References

- *MMWR*, January 26, 2018, Vol 67, #3
- **Update on the Use of Herpes Zoster Vaccine: An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)**[Footnote]
- **N Engl J Med 2016 Sep 15: Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. Cunningham et al.**
- N Engl J Med. 2015 May 28;372(22):2087-96. doi: 10.1056/NEJMoa1501184. Epub 2015 Apr 28 **Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. Lai, et al.**