Herpes Zoster & Post-herpetic Neuralgia:

A Clinical Update & the Emergent Role of Immunization

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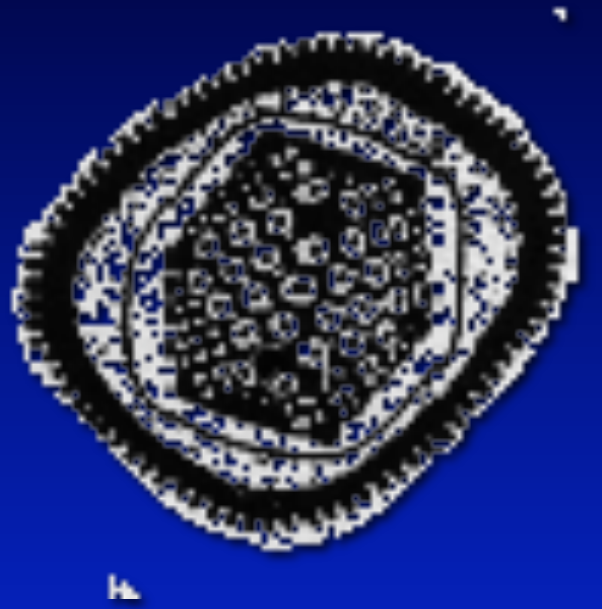
Learning Objectives

- Recognize the natural history and Canadian epidemiology of herpes zoster (HZ) & post-herpetic neuralgia (PHN)
- Discuss the underlying mechanisms of the clinical manifestations of HZ and PHN
- Discuss evidence-based recommendations for managing HZ & PHN
- Assess the benefits of using vaccination for the prevention & attenuation of HZ & PHN

Varicella Zoster Virus (VZV)

- VZV is a member of the herpes virus family like Herpes Simplex, EBV, CMV



- Humans are the only reservoir
- Stays in the body forever after first infection

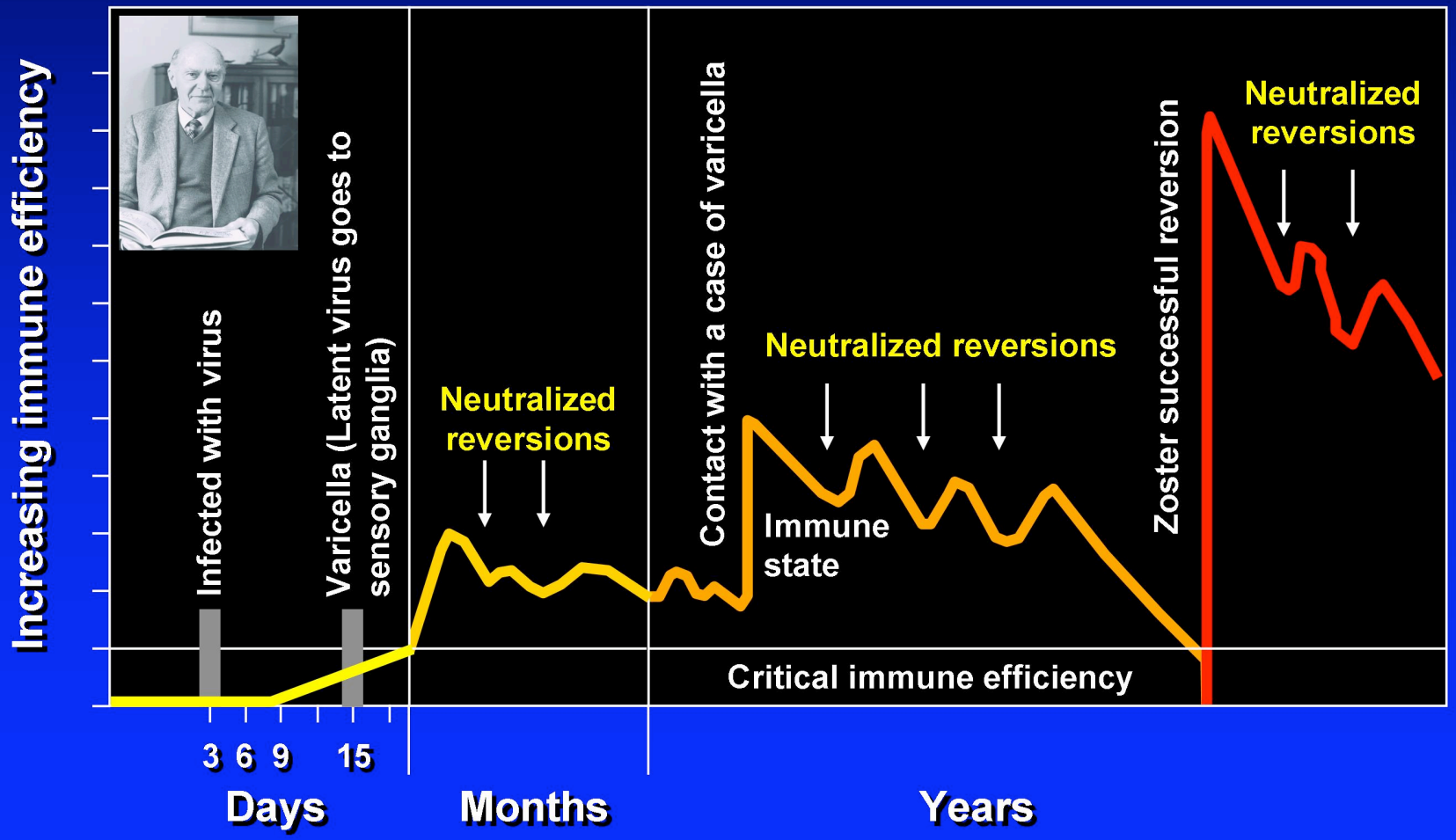
Primary Infection:

- Varicella (Chickenpox)

- Reactivation:
  - Herpes zoster (Shingles)

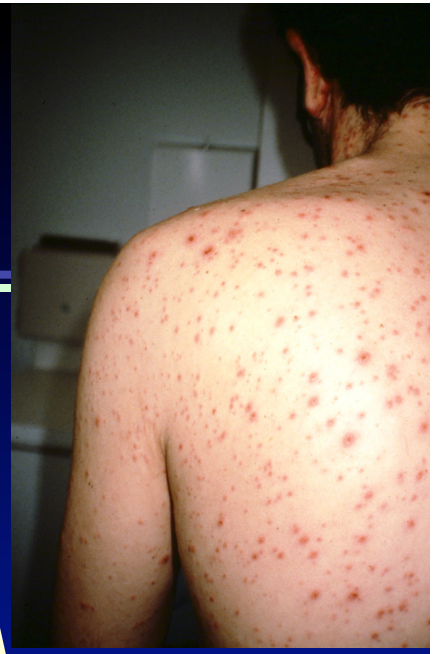
1. Arvin A Virology 344 (2006) 240 – 249. 2005

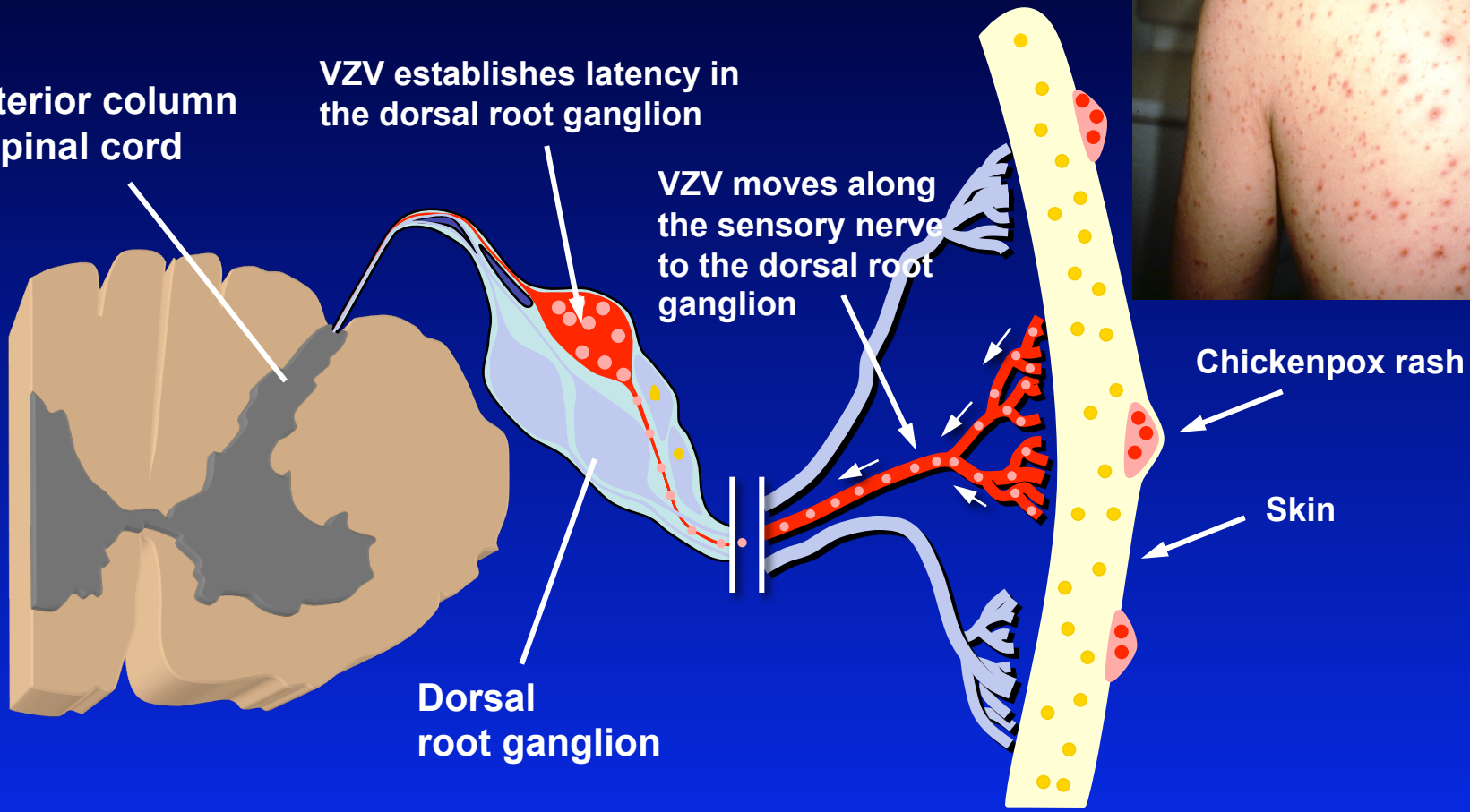
Natural History of Varicella Zoster Virus: Edgar Hope-Simpson



Hope-Simpson RE. *Proc R Soc Med*. 1965

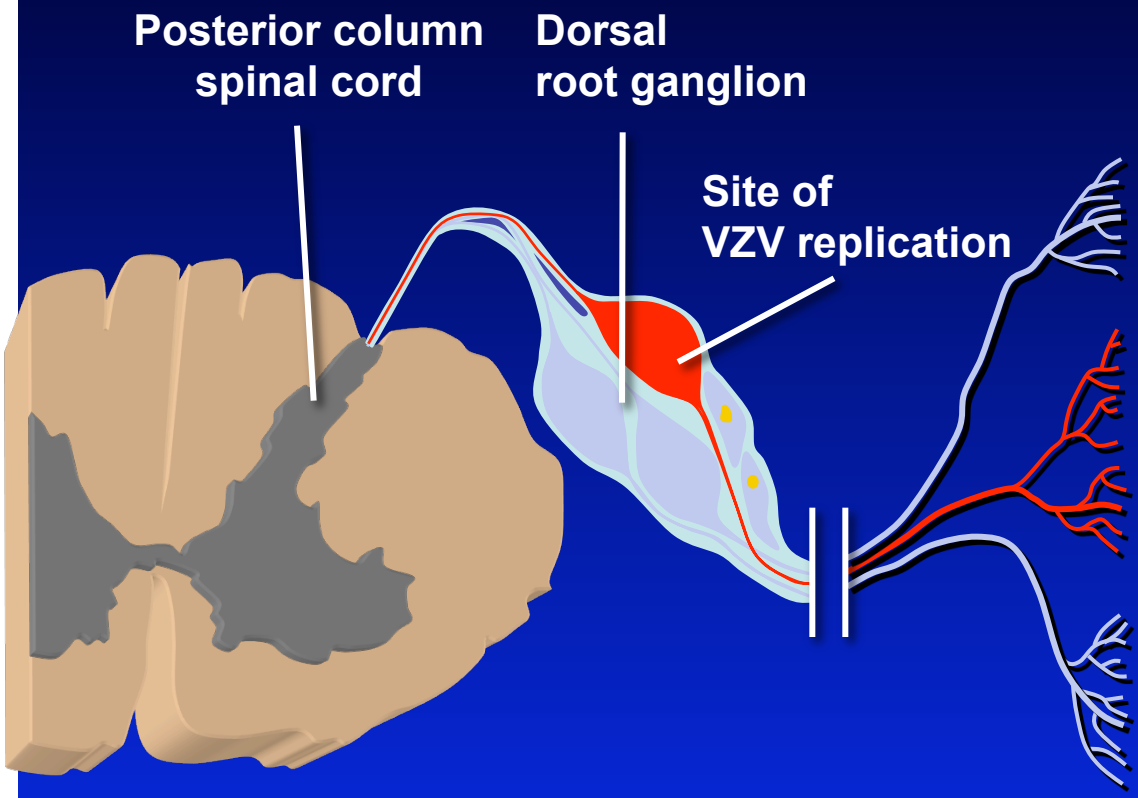
VZV: Latency

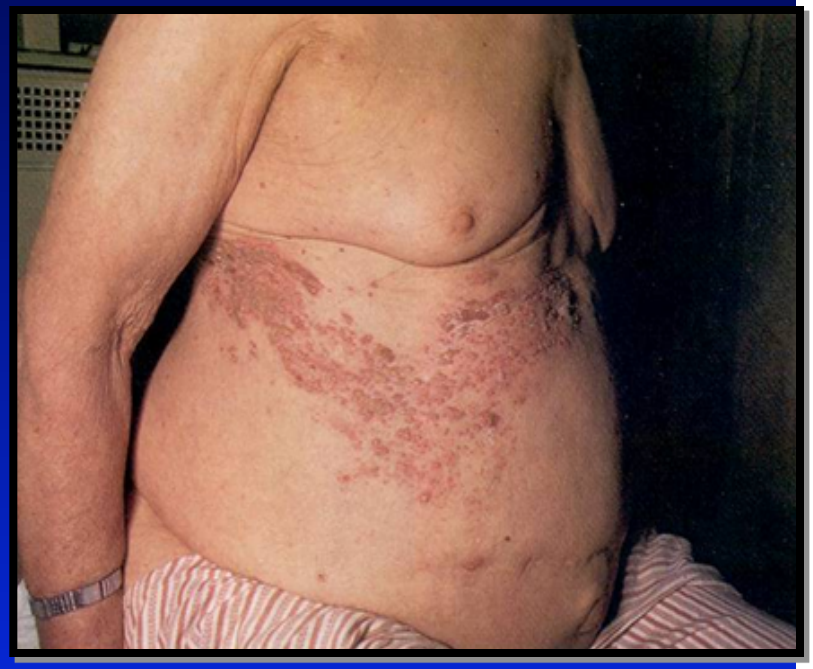




1. Straus SE, Oxman MN. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. *Fitzpatrick's Dermatology in General Medicine*. 5th ed. Vol 2. McGraw-Hill; 1999:2427-50
2. Silverstein S, Straus SE. In: Arvin AM, Gershon AA, eds. *Varicella-Zoster Virus: Virology and Clinical Management*. Cambridge, UK: Cambridge University Press; 2000:123-141

VZV: Reactivation



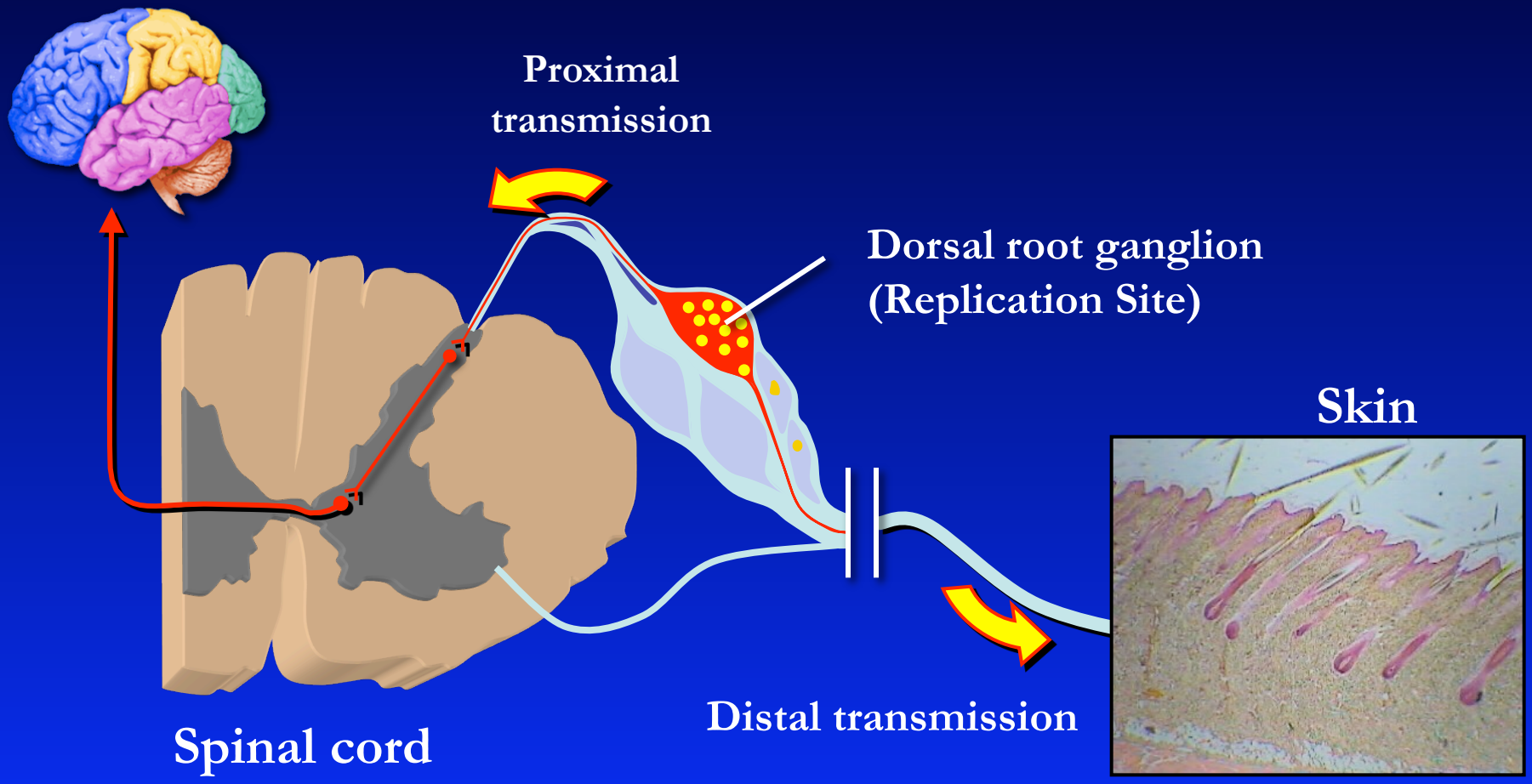


Arvin AM. Varicella-zoster virus. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. Vol 2. New York, NY: Lippincott Williams & Wilkins; 2001:2731-67

Straus SE, Oxman MN. Varicella and herpes zoster. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. *Fitzpatrick's Dermatology in General Medicine*. 5th ed. Vol 2. New York, NY: McGraw-Hill; 1999:2427-50

Pathogenesis of Acute Pain

Pain associated with shingles is neuropathic



Epidemiology of the Varicella Zoster Virus

- In Canada, 90-95% of people are infected with the VZV by age 12 (prior to the varicella vaccine program)[1]
- Approximately 20–30% of Canadians would be expected to develop HZ at some point in their lives. [2]
- Complications of HZ occur in up to 40% of cases[2]
  - Post herpetic Neuralgia (PHN) is the most common.[2]

1. NACI Update on Varicella. 2004 30:1-28.
2. Brisson et al Human Vaccines 2008

Canadian Epidemiology

- 130,000 cases of herpes zoster episodes/ year in Canada
- 13% of herpes zoster episodes will result in post-herpetic neuralgia
  - 17,000 cases of post herpetic neuralgia per year
  - 70% in adults over 60 y.o.

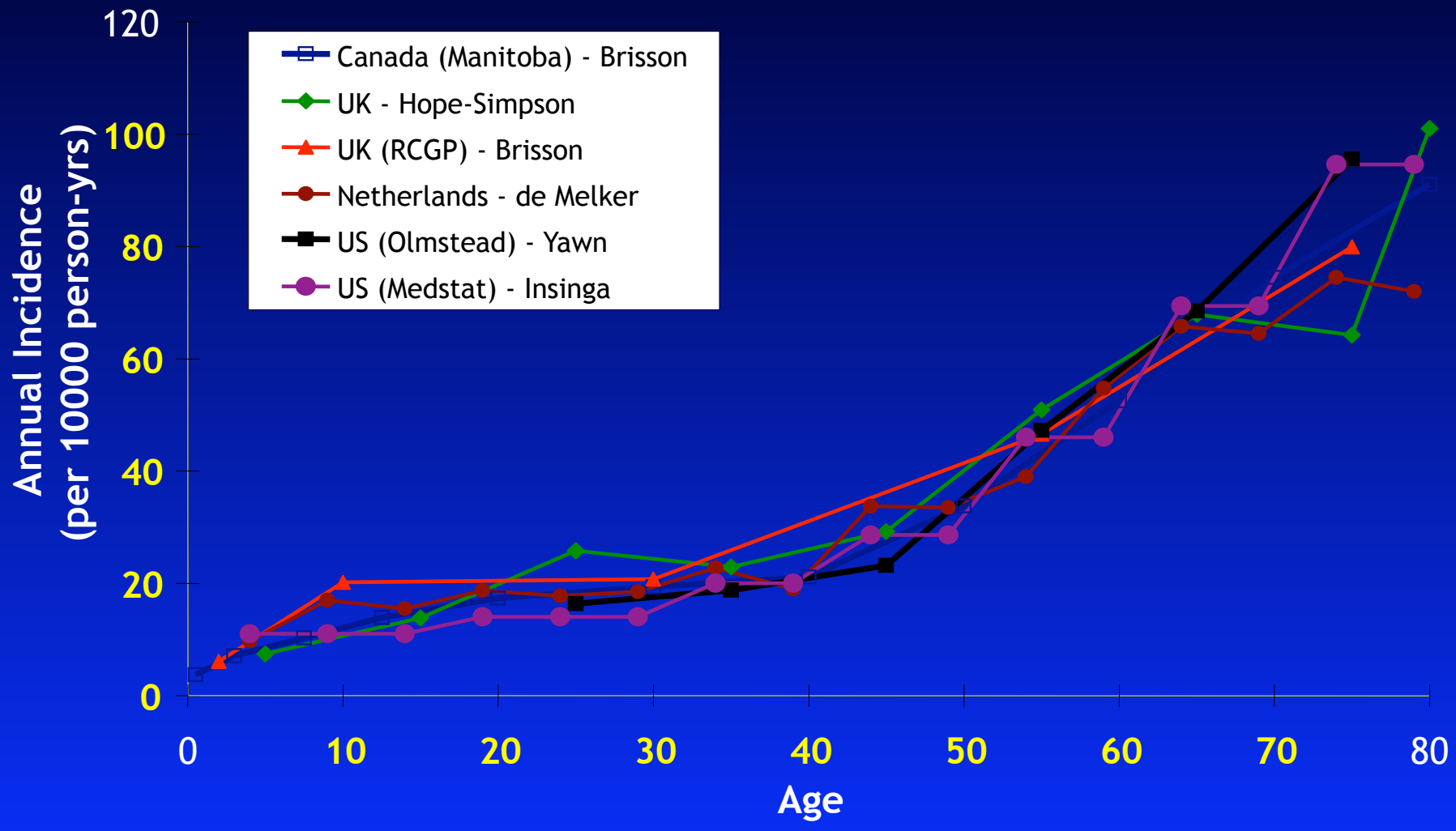
Brisson M et al. human Vaccine 2008

Herpes Zoster Incidence by Age

Age (y)	2005 US popl'n in millions	HZ incidence rates per 1000 person years	HZ cases per year, No in thousands (%)
22-29	41	1.6	65 (8)
30-39	41	1.9	78(9)
40-49	45	2.3	104(12)
68% of cases occur in ≥ 50 y.o & older			
60-69	23	7.1	165(19)
70-79	16	10.0	160(18)
≥80	11	12.0	127(14)
All ages	214		876 (100)

Yawn, B, et al Mayo Clin Proc. 2007;82(11):1341-1349

Incidence of Herpes Zoster



Johnson et al. IJID 2007 11 (suppl 2), S43-S48

How Common is Shingles?

- 1 per 100 year adults over 70 years' old
- 28% lifetime risk
- 1 to 50 per 100 per year in adults with significant cellular immune suppression
  - Eg: HIV infections, systemic lupus erythematosus, lymphoid cancers, organ transplants

Brisson M et al. human Vaccine 2008

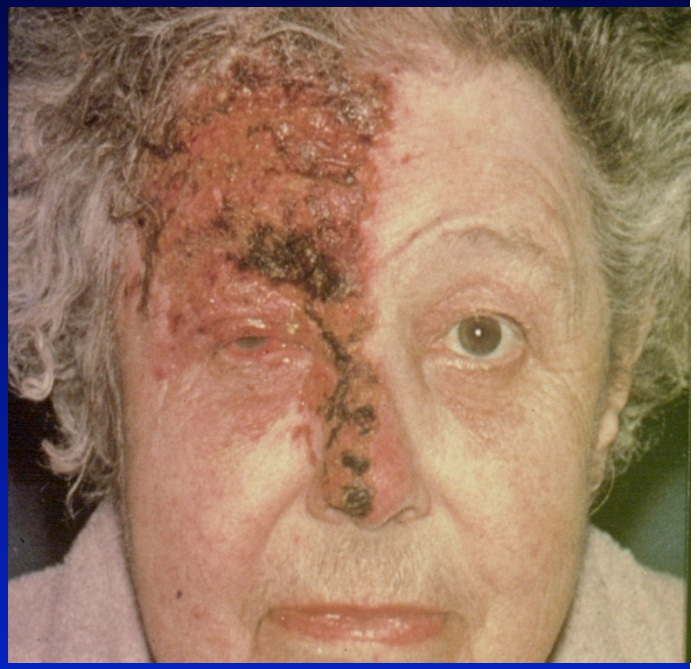
Shingles: Risk Factors

- Advancing age[1,2]
  - Level of VZV-specific, cell-mediated immunity (CMI) naturally wanes with increasing age[2]
  - Severity of shingles increases with age[1]
- Immunosuppression[1]
  - HIV – AIDS[1]
  - Organ Transplants[1]
  - Malignances[1]
  - Immunosuppressive therapies[1]

1. Gnann J et al. NEJM 2002; 347:340-46
2. Arvin A et al. NEJM 2005; 352:226-67

Herpes Zoster: Clinical Features

- **Clinical Features of the HZ Rash**
  - **Localized, unilateral**
  - **Generally limited to area of skin innervated by a single sensory dermatome**
  - **Favours T4,5 (nipple) V1(forehead)**
  - **Vesicles on erythematous base, pustules, crusts**
  - **Pain more in older person (60+)**



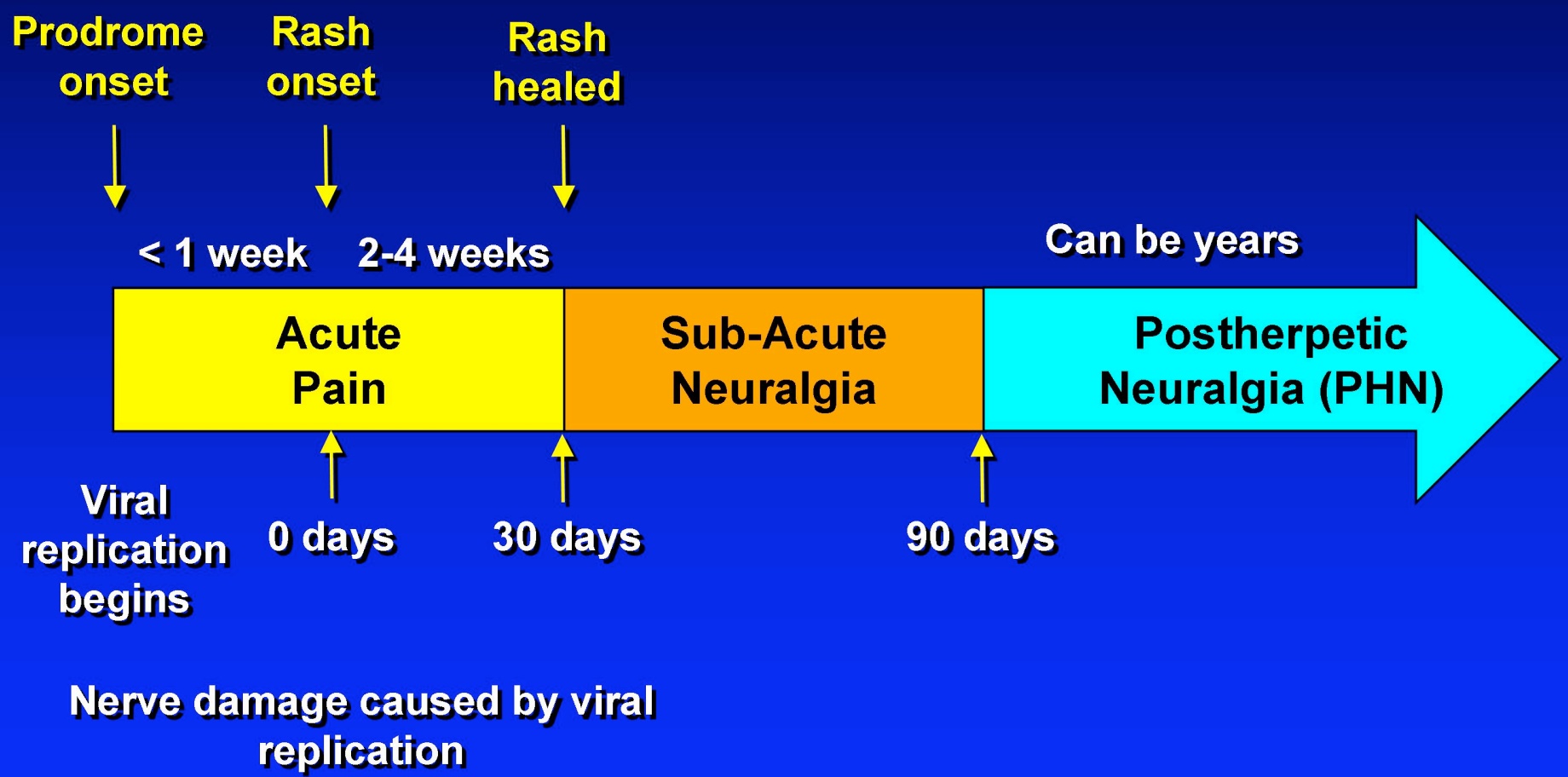
1. Oxman MN. In: Arvin AM, Gershon AA, eds. *Varicella-Zoster Virus, Verology and Clinical Management*. Cambridge Press; 2000:246-75
2. Lycka BAS, Williamson D, Sibbald RG. *Herpes Zoster and Postherpetic Neuralgia, 2nd Revised and Enlarged Edition.* Elsevier Science B.V. 2001; 11:97-106

Pain

Is The Chief Problem Posed by Herpes Zoster in Older Adults --

Acute Herpes Zoster Pain and Post-herpetic Neuralgia

Zoster-Associated Pain (ZAP)



Adapted from Dworkin RH. *Antiviral Research* 1997

Acute HZ Pain - Prodrome

- Pain that precedes the rash[1]
  - sensation ranges from itching to severe pain[1,2]
- Pain may mimic other conditions:
  - Myocardial infarction, biliary or renal colic, appendicitis[1,2]
- 90% of patients ≥ 60 years of age experience prodrome[1]
- 40% experience pain for >4 days prior to rash[2]

1. Oxman, MN In: Arvin AM, Gershon AA, eds. Varicella-zoster virus, Virology and clinical Management. Cambridge Press: 2000: 246-75.
2. Lycka, BAS, et al, Herpes Zoster and postherpetic neuralgia, 2nd Revised and Enlarged Ed. Elsevier science B.V.:2001;11;97-106.

Acute zoster pain

- A violent hemorrhagic inflammation in one dorsal ganglion and nerve, the spinal cord and the skin with cell death and neuronal and glial injury

Acute Zoster Pain

- Described as: sharp, stabbing, shooting, burning, throbbing, tender, boring, itching, or hot
  - Constant or intermittent
  - Mild to severe
- Pain accompanies rash in >90% of persons >60 years
- Acute HZ pain gradually resolves as rash heals
  - Some patients pain persists for months or years beyond rash healing

Oxman, MN In: Arvin AM, Gershon AA, eds. Varicella-zoster virus, Virology and clinical Management. Cambridge Press: 2000: 246-75.

Herpes Zoster: Complications

Common

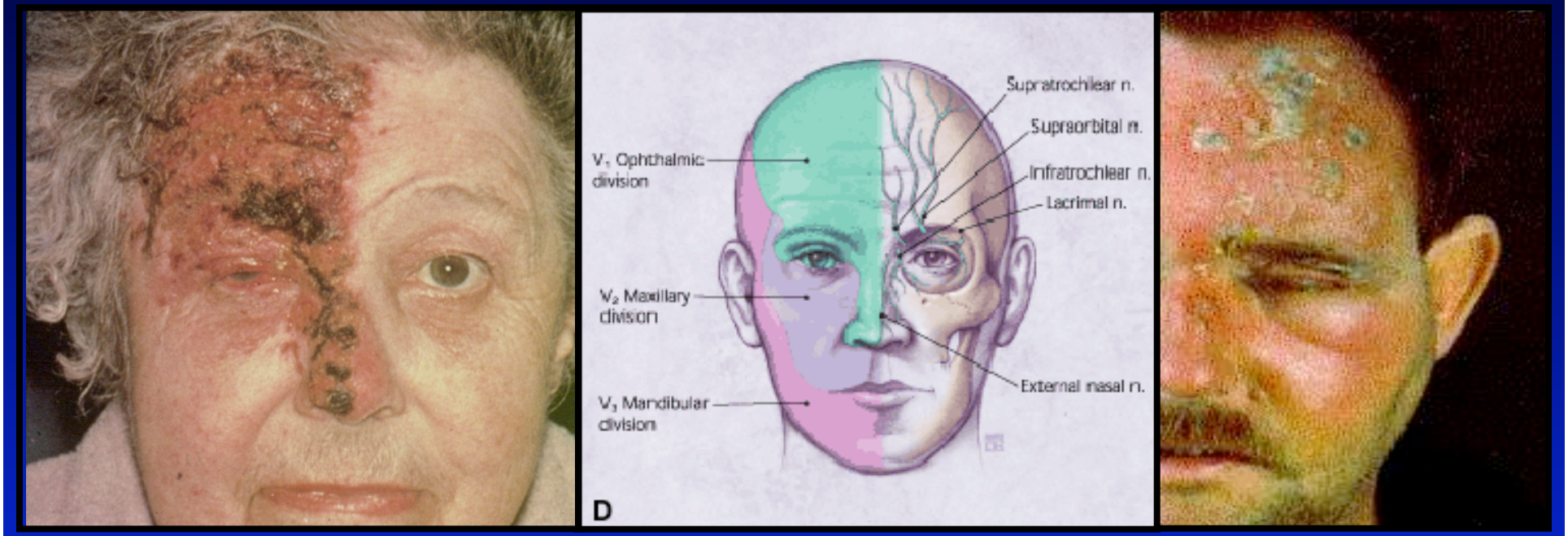
- Post herpetic neuralgia (PHN)
- Ocular complications of Ophthalmic zoster
- Scarring
- Bacterial superinfection

Less common

- Cutaneous dissemination
- Herpes gangrenosum
- Pneumonitis
- Hepatitis
- Encephalitis
- Motor neuropathies
- Myelitis
- Hemiparesis (granulomatous CNS vasculitis)

Gnann J et al. N Engl J Med. 2002;347:340-346.

Ophthalmic Complications



Classic unilateral vesicular rash appears along the corresponding dermatome.
Swelling and inflammation of the eyelid is common
Eye is affected in about 50% of cases (Hutchinson's Sign)

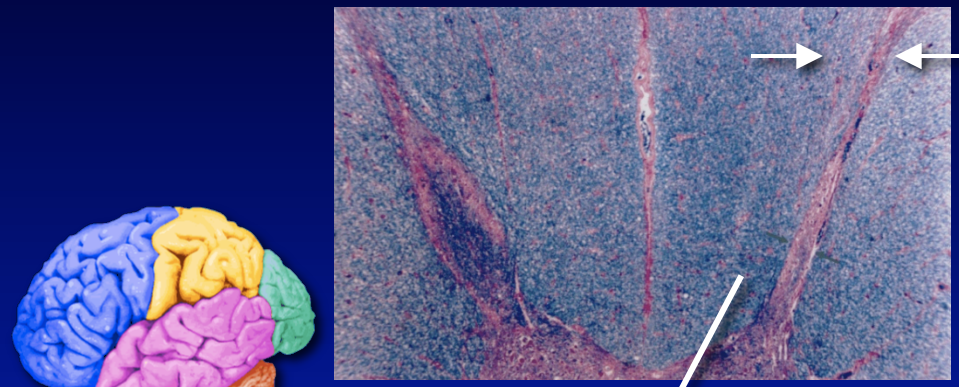
Courtesy of MN Oxman, UCSD/San Diego VAMC.
Shaikh S, Ta CN. Evaluation and management of herpes zoster ophthalmicus. *Am Fam Physician*. 2002;66:1723-32

Post Herpetic Neuralgia

- PHN is a chronic neuropathic pain syndrome that persists or recurs in the dermatome affected by herpes zoster after the rash has healed[1]
  - Most common serious complication of herpes zoster[2]
  - Most debilitating aspect of herpes zoster[3]
  - Single most common neurologic condition in the elderly[4]

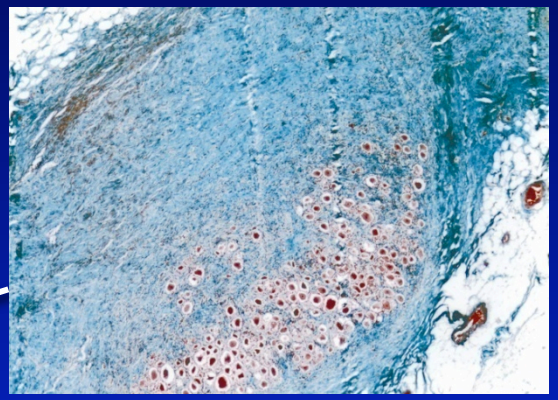
1. Bowsher D 2001;143-47
2. Jonhson RW & Dworkin RH *BMJ* 2003; 326
3. Schmader K. Herpes Zoster in Older Adults. 2001 *CID* 32
4. Lee PJ & Annunziato P. *Infect Med* 1998; 15:709-13

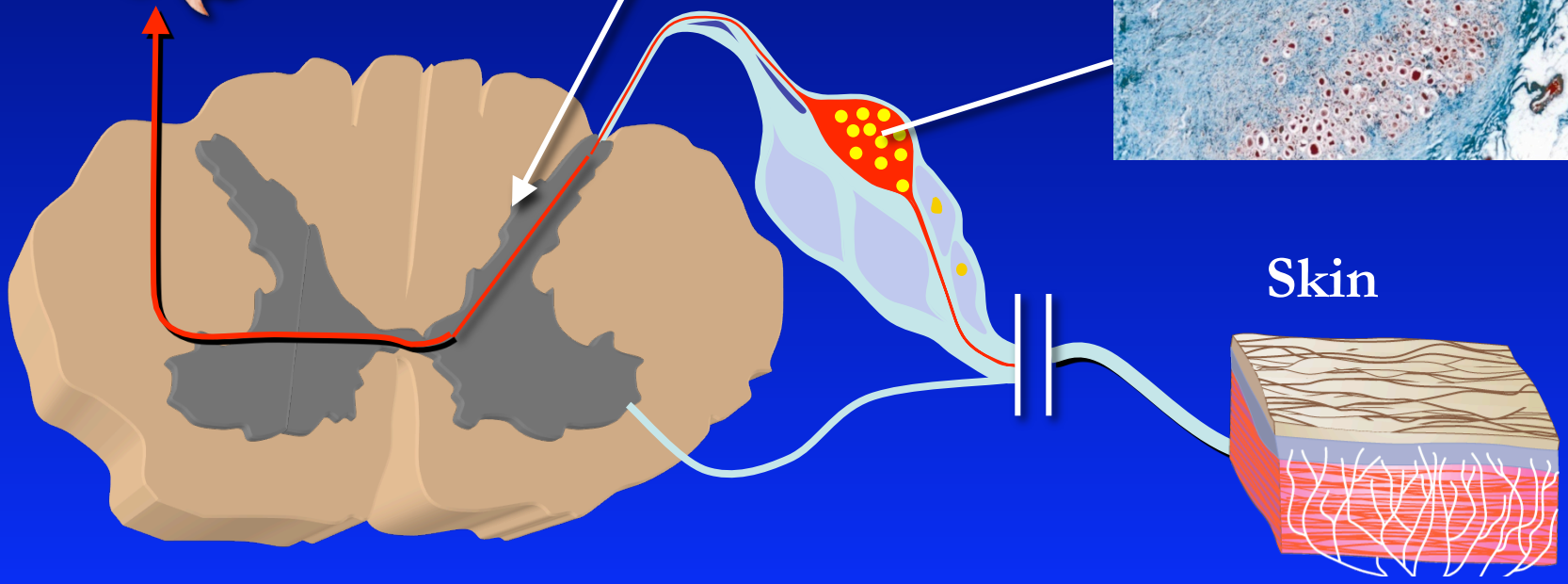
Pathogenesis of Postherpetic Neuralgia



Atrophic Dorsal Horn

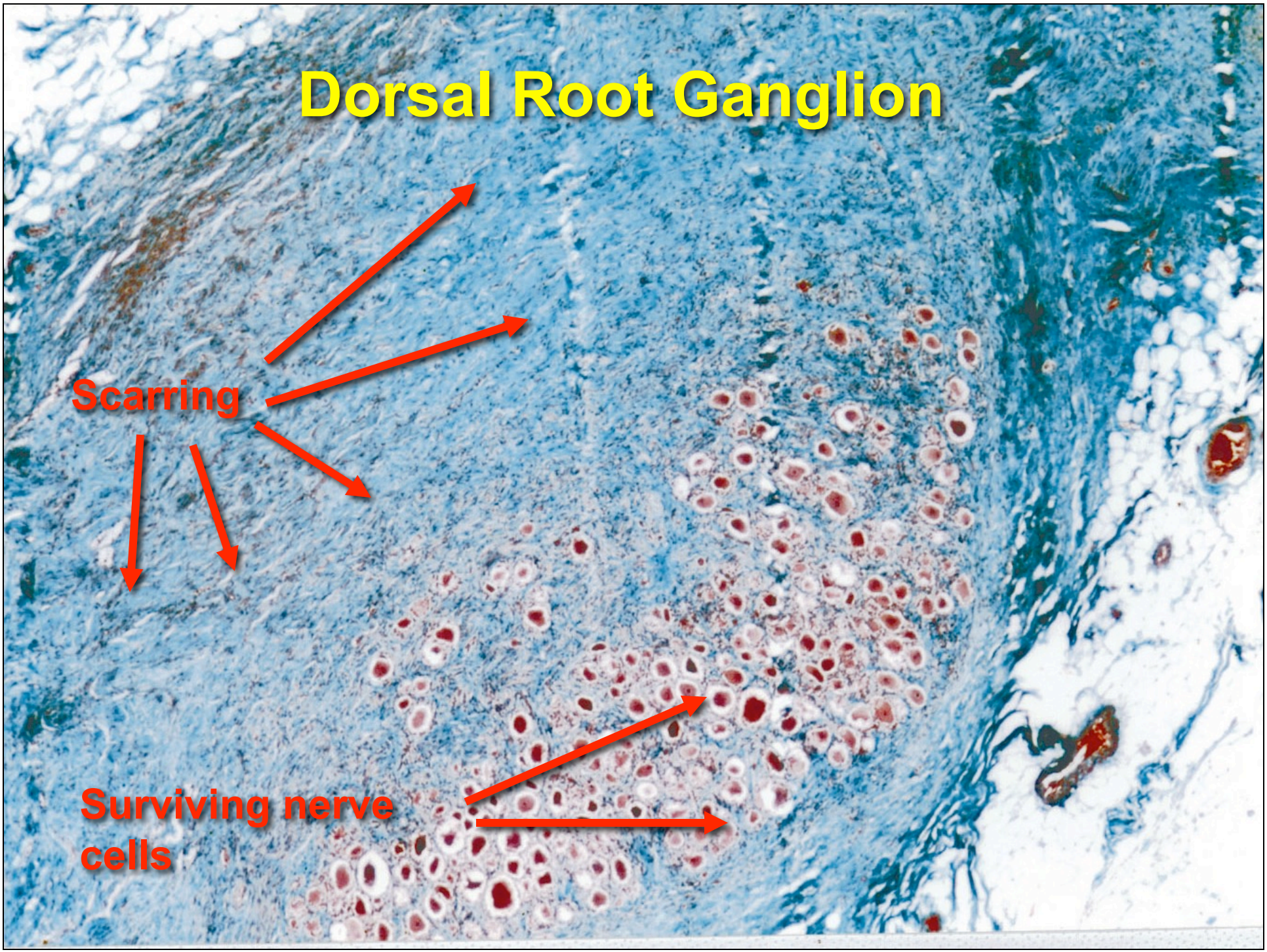
Dorsal Root Ganglion

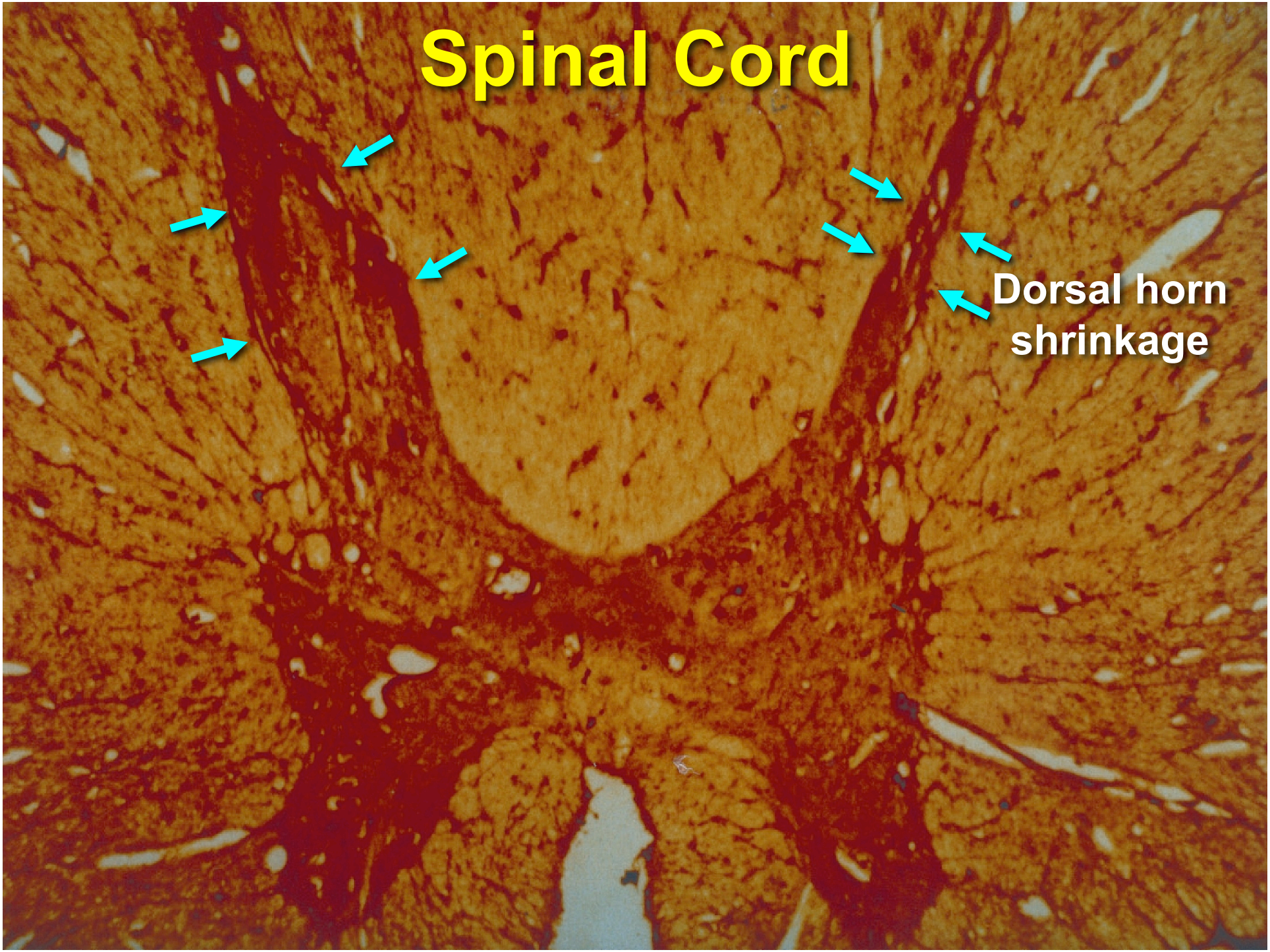




Skin

Spinal cord


Dorsal Root Ganglion
Scarring
Surviving nerve cells

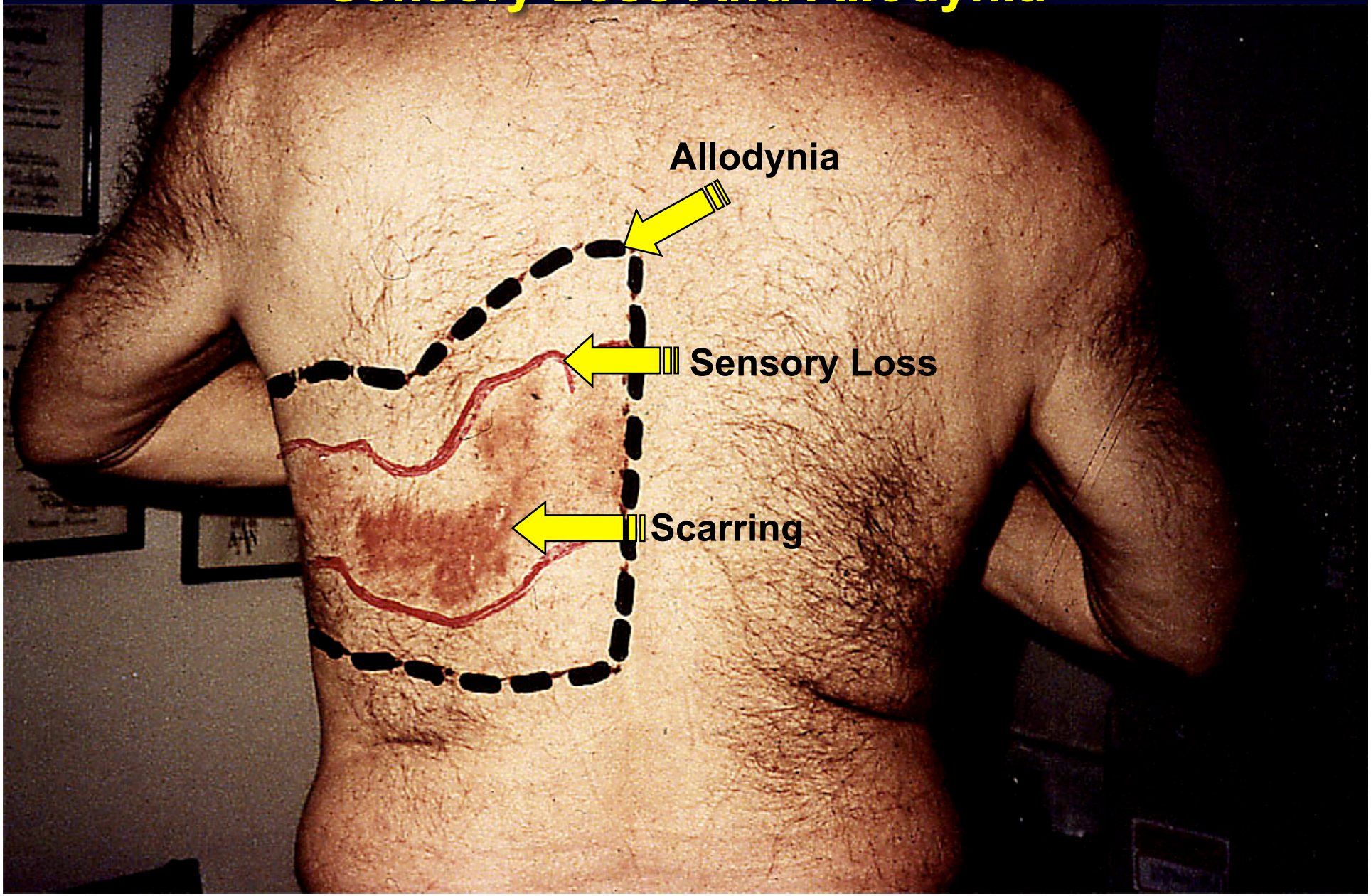

Spinal Cord
Dorsal horn shrinkage

PHN: Clinical Features

- **PHN patients may experience some or all of the following:**
  - **Constant Pain**: aching, burning or throbbing
  - **Intermittent Pain**: stabbing or shooting
  - **Allodynia**: Pain evoked by a mild normally non-noxious stimulus – heat, cold or tactile
  - **Hyperalgesia**: severe pain evoked by application of a normally mildly painful stimulus
  - Intense Itching

Schmader K. Herpes Zoster in Older Adults. 2001 *CID* 32
Johnson & Whitton Expert Opin. Pharmacother. 2004 5(3) 551-559

PHN: Clinical Features
Sensory Loss And Allodynia



HZ/PHN: Significant Impact on Quality of Life

- **Physical functioning[1]**
  - Performing physical tasks
  - Chronic fatigue, loss of appetite
  - Disrupted sleep
- **Role functioning[1]**
  - Performing household or work-related tasks
  - Difficulty concentrating
- **Social functioning1**
  - Social isolation
- **Emotional functioning1**
  - Depression
  - Anxiety

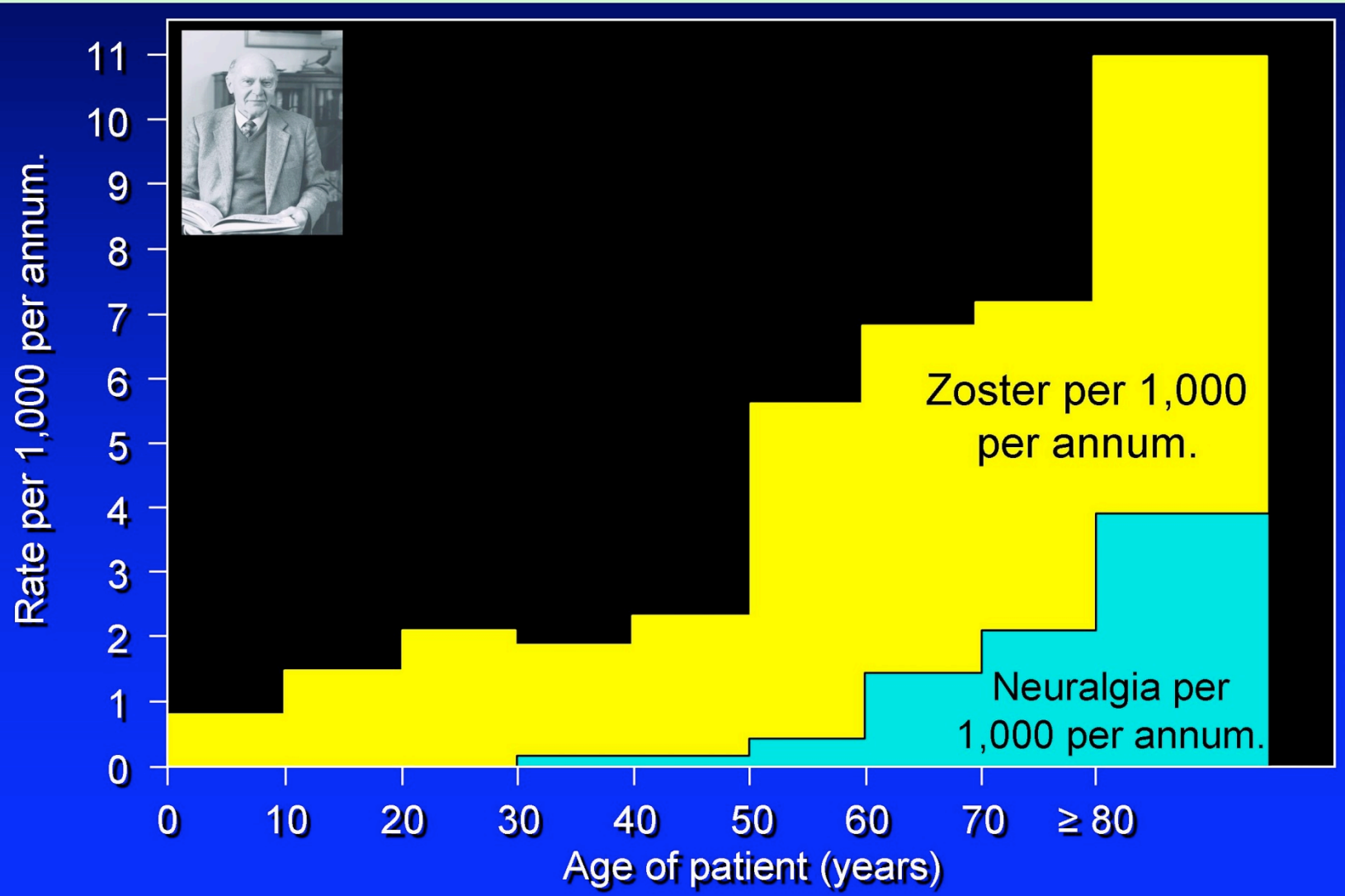
1. Katz J et al. Clin Infect Dis 2004;39:342-8.

PHN: Risk Factors

- **Greater age (> 50 years old)[1,3,6]**
- **Greater severity of acute pain [2,3,6] (VAS>5)[1]**
- **Greater rash severity[2,3]**
- **Prodromal pain[3,6]**
- Greater sensory abnormalities in the affected dermatome[6]
- Other possible risk factors:
  Dermatome affected[5,6], female sex[3,7], psychosocial factors[4,7]

1. Coen P.G. Eur J Pain 2006
2. Whitley R.J. et al. J Infectious Diseases 1999; 179:9-15
3. Jung B.F. Neurology 2004; 62:1545-51
4. Katz J. et al. Journal of Pain 2005 6; 12:782-90
5. Opselten W. et al. Family Practice 2002; 19:471-75
6. Decroix et al. EADV 2000; 14:23-33
7. Bowsher D. Eur J Pain 1999; 3:335-42

PHN: Risk Factor – Greater Age

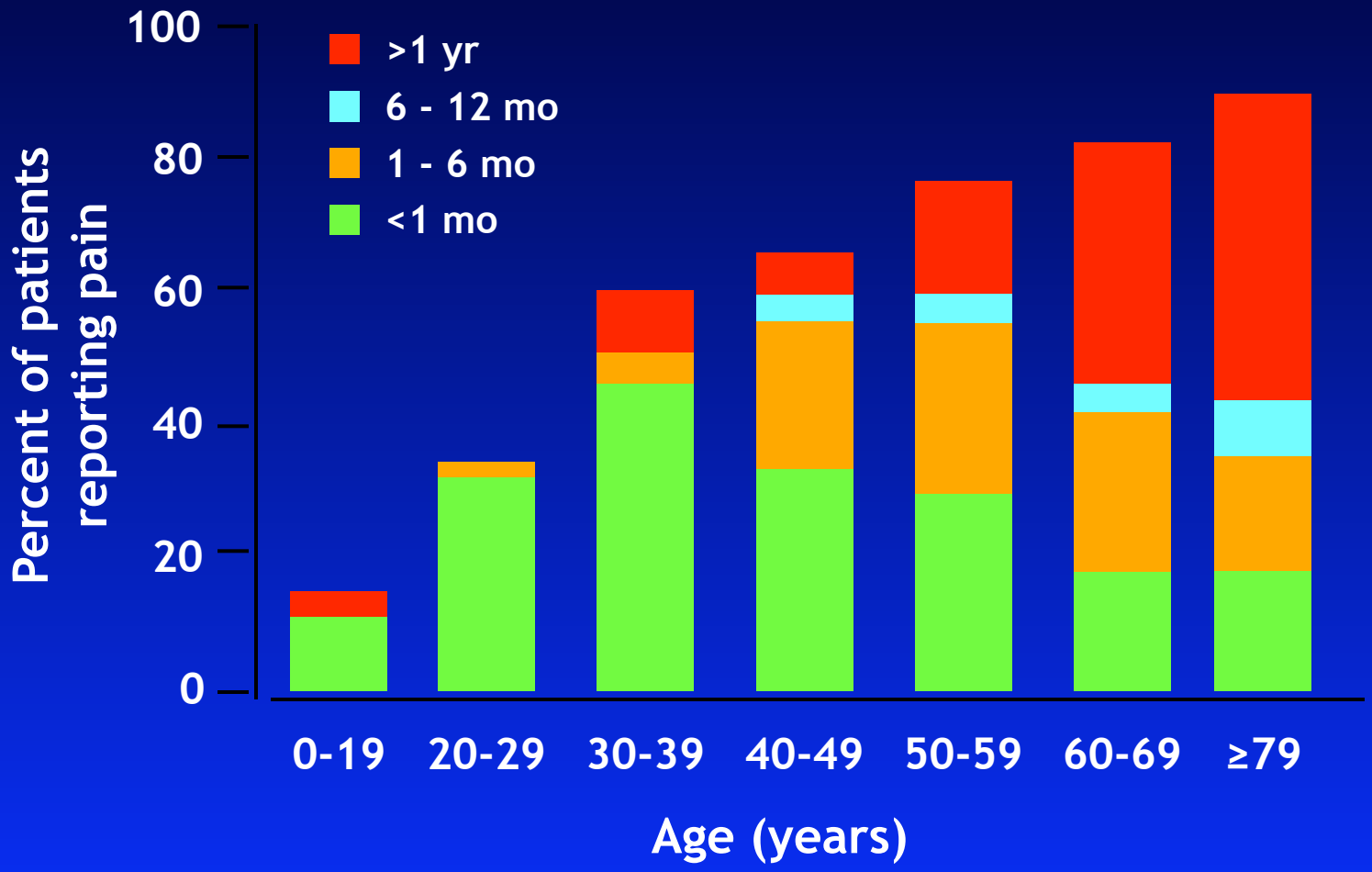


Hope-Simpson RE. *Proc R Soc Med.* 1965

Post-herpetic Neuralgia: Incidence

- About 10% of cases of herpes zoster of all ages will have PHN at one month after the rash
- 50% of zoster cases if over age 60
- 70% if over age 80
- With PHN for 1 year, more than 50% of patients will continue to suffer at 1+ year follow-up

Prevalence of PHN and Duration of Pain Associated With PHN Increase With Age



Kost R et al. N Engl J Med. 1996;355:32-42.

Shingles: Strategies of Therapy

The objective of acute shingles treatment is to:

- Reduce acute symptoms of pain and malaise[1]
- Prevent rash progression and hasten rash healing[1]
- Reduce the risk of PHN[2]
- Reduce the risk of other complications[2]

1.Johnson, R.W. et al. Expert Opinion. 2004; 5(3):551-559.
2. Volpi A et al. Am J Clin Dermatal. 2005; 6: 317-25

Aggressive Rx of Herpes Zoster
(RCT's for approaches above dotted line)

1. Antivirals: valacyclovir, famciclovir, acyclovir
2. Antidepressants (amitriptyline)
3. Gabapentin

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4. Analgesics: opioids if necessary
5. Nerve blocks

Shingles: Antiviral Therapy

- The antiviral drugs: Acyclovir, Valacyclovir, Famciclovir
  - Reduce prolonged pain, acute pain, hasten rash healing and shorten duration of viral shedding[1]
- Limitations
  - Antiviral therapy should be started within 72 hours[2]
  - There is often a delay between onset of symptoms and visit to MD / initiation of antiviral therapy[2]
  - Viral activity and neural damage can go on for several days before diagnosis[2]

1. Johnson, R.W. et al. Expert Opinion. 2004; 5(3):551-559
2. Volpi A et al. Am J Clin Dermatal. 2005; 6: 317-25

Antivirals 7 Day Course

- Acyclovir 800 mg 1 tab po 5x/day
- Famciclovir 500 mg (1 tablet) po 3x/day
- Valacyclovir 1 g (2tabs) po 3x/day

Brisson M et al. human Vaccine 2008

Antiviral Therapy for Herpes Zoster

Randomized, Controlled Clinical Trial of Valacyclovir and Famciclovir Therapy in Immunocompetent Patients 50 Years or Older

% Patients with Pain	Valacyclovir (n=297)	Famciclovir (n=300)
Upon or after rash healing	86%	87%
At 1 month post rash	64%	62%
At 3 months post rash	32%	34%
At 6 months post rash	19%	19%

Tyring SK et al. *Arch Fam Med.* 2000

Shingles: Treatment of Acute Pain

Analgesic Therapy

The principal goal of acute pain management for shingles is reduction or elimination of pain and disability.

Choice of non-opiate or opiate analgesic drugs depends on the patient's pain severity, underlying conditions, and response to the drug.

Schmader, K. Clinical Infectious Dis. 2001;32:1481-6.

Aggressive Rx of Herpes Zoster (RCTs for approaches above dotted line)

1. Antivirals: valacyclovir, famciclovir, acyclovir
2. Antidepressants (amitriptyline)
3. Gabapentin

---

4. Analgesics: opioids if necessary
5. Nerve blocks

Post-herpetic neuralgia: Definition (definitions of post-herpetic neuralgia vary)

Pain persisting 3 months after rash onset

(for clinical trials of PHN)

Schmader KE. Clin J Pain 2002;18:350-54

PHN: Strategies of therapy

- Complex, often ineffective, and requiring a multi-faceted approach[1]
- Patients often need referral to pain specialists and pain clinics
- Polypharmacy poses added challenge in elderly patients

Kost RG et al. N Engl J Med 1996;335:32-42.
Action West. Pain wait lists survey. CPS June 2006.
Gnann JW Jr et al. N Engl J Med 2002;347:340-6.
Swift CG. BMJ 2001;322:855-7.

Post-herpetic neuralgia: Treatment (randomized controlled trials)

1. antidepressants
   - (amitriptyline, nortriptyline)
2. anticonvulsants
   - (gabapentin, pregabalin)
3. opioids
   - (oxycodone, morphine)

Poor/non-responsivity in clinical trials in post-herpetic neuralgia

- Watson 1982 amitriptyline 33%
- Max 1988 amitriptyline 53%
- Kishore-Kumar 1990 desipramine 54%
- Watson 1992 amitriptyline/maprotiline 53%
- Watson 1998 amitriptyline/nortriptyline 32%
- Watson and Babul 1998 oxycodone 42%
- Pregabalin trials (N=7) 70%

Post-herpetic neuralgia: pharmacotherapy

All drugs for postherpetic neuralgia have:

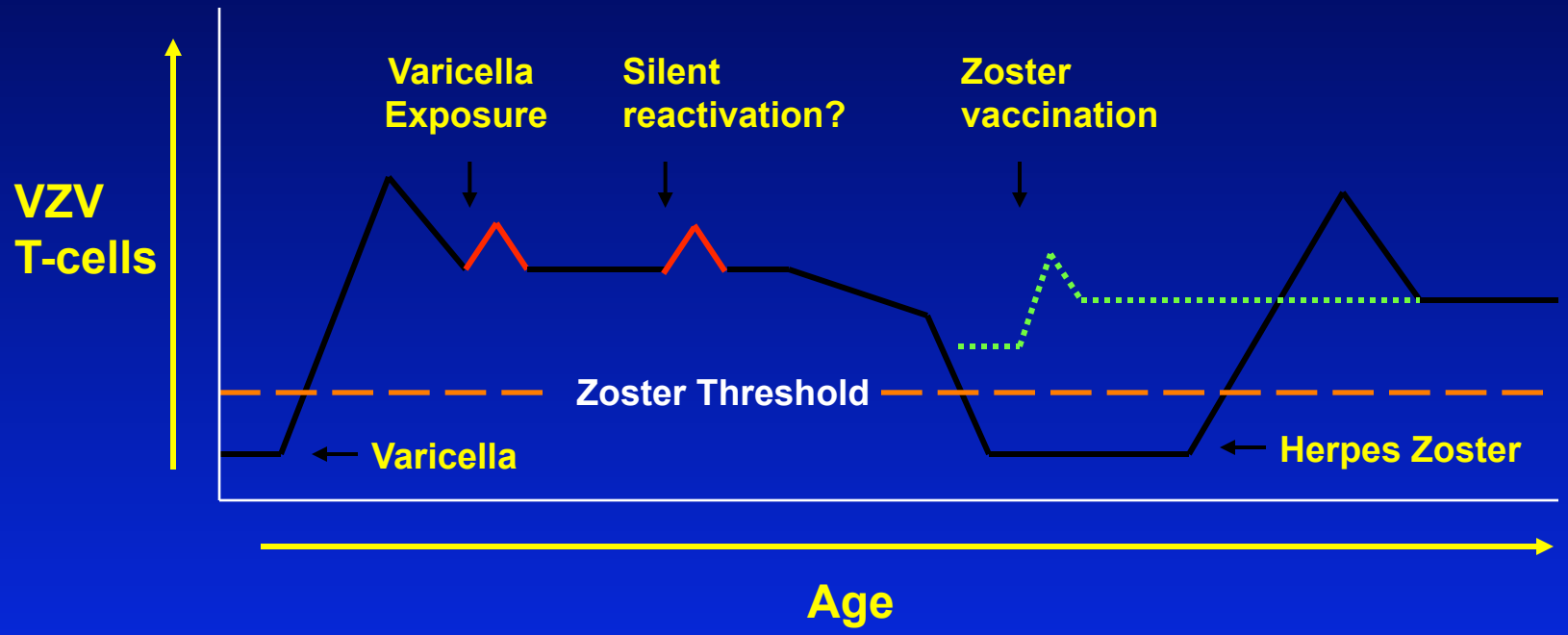
- a modest effect
- take pain from severe to mild in 50% in RCT's
- side effects

Theoretical Basis for the Shingles Prevention Study

Hope-Simpson - 1965

Hope-Simpson RE.
Proc R Soc Med
1965;58:9-20

Aging & Zoster Risk



Arvin A, NEJM 352:2266, 2005

A Vaccine to Prevent Herpes Zoster & PHN in Older Adults

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2005 VOL. 352 NO. 22

A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

M.N. Oxman, M.D., M.J. Levin, M.D., G.R. Johnson, M.S., K.E. Schmader, M.D., S.E. Straus, M.D., L.D. Gelb, M.D., R.D. Arbeit, M.D., M.S. Simberkoff, M.D., A.A. Gershon, M.D., L.E. Davis, M.D., A. Weinberg, M.D., K.D. Boardman, R.Ph., H.M. Williams, R.N., M.S.N., J. Hongyuan Zhang, Ph.D., P.N. Peduzzi, Ph.D., C.E. Beisel, Ph.D., V.A. Morrison, M.D., J.C. Guatelli, M.D., P.A. Brooks, M.D., C.A. Kauffman, M.D., C.T. Pachucki, M.D., K.M. Neuzil, M.D., M.P.H., R.F. Betts, M.D., P.F. Wright, M.D., M.R. Griffin, M.D., M.P.H., P. Brunell, M.D., N.E. Soto, M.D., A.R. Marques, M.D., S.K. Keay, M.D., Ph.D., R.P. Goodman, M.D., D.J. Cotton, M.D., M.P.H., J.W. Gnann, Jr., M.D., J. Loutit, M.D., M. Holodniy, M.D., W.A. Keitel, M.D., G.E. Crawford, M.D., S.-S. Yeh, M.D., Ph.D., Z. Lobo, M.D., J.F. Toney, M.D., R.N. Greenberg, M.D., P.M. Keller, Ph.D., R. Harbecke, Ph.D., A.R. Hayward, M.D., Ph.D., M.R. Irwin, M.D., T.C. Kyriakides, Ph.D., C.Y. Chan, M.D., I.S.F. Chan, Ph.D., W.W.B. Wang, Ph.D., P.W. Annunziato, M.D., and J.L. Silber, M.D., for the Shingles Prevention Study Group*

The Shingles Prevention Study
Research Question

- To determine whether vaccination with a live attenuated VZV vaccine would decrease the incidence, severity, or both of HZ and PHN, in adults 60 years of age or older.

Oxman M et al. *N Engl J Med.* **2005;352:2271-2284.**

The Shingles Prevention Study
Study Design

- **Randomized**
  - **1:1 Zoster Vaccine or placebo**
- **Double-blind, placebo-controlled, multicenter trial**
  (22 sites in the U.S)
- **Enrolled 38,546 subjects ≥ 60 years of age**
- **Median of 3.12 years of surveillance for Herpes Zoster**

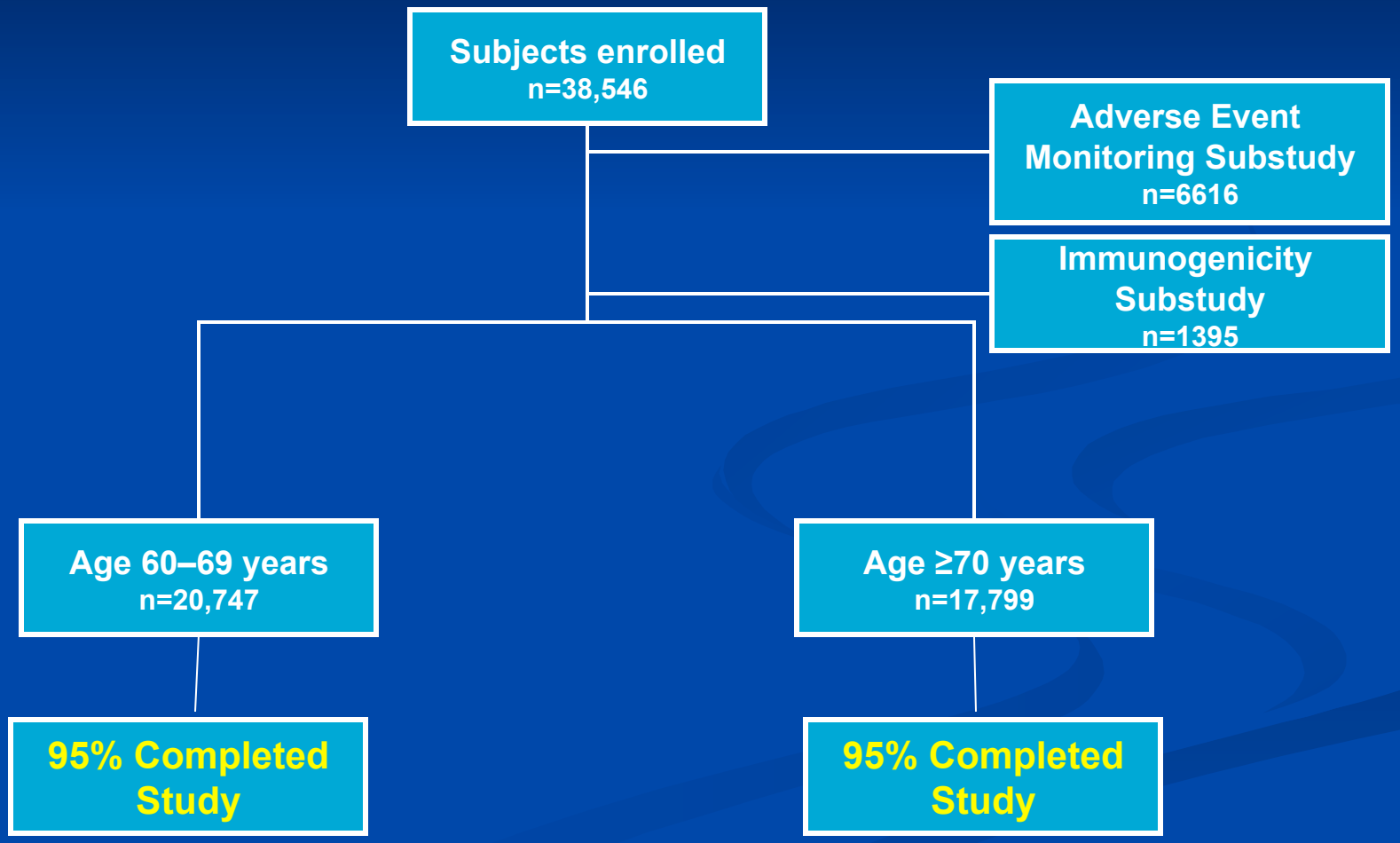
Oxman M et al. *N Engl J Med.* **2005;352:2271-2284.**

The Shingles Prevention Study
Zoster Vaccine

- **Vaccine type:**
  - Live attenuated Oka/Merck VZV vaccine (Zoster Vaccine)
- **Administration:**
  - Subcutaneous injection of 0.5 ml

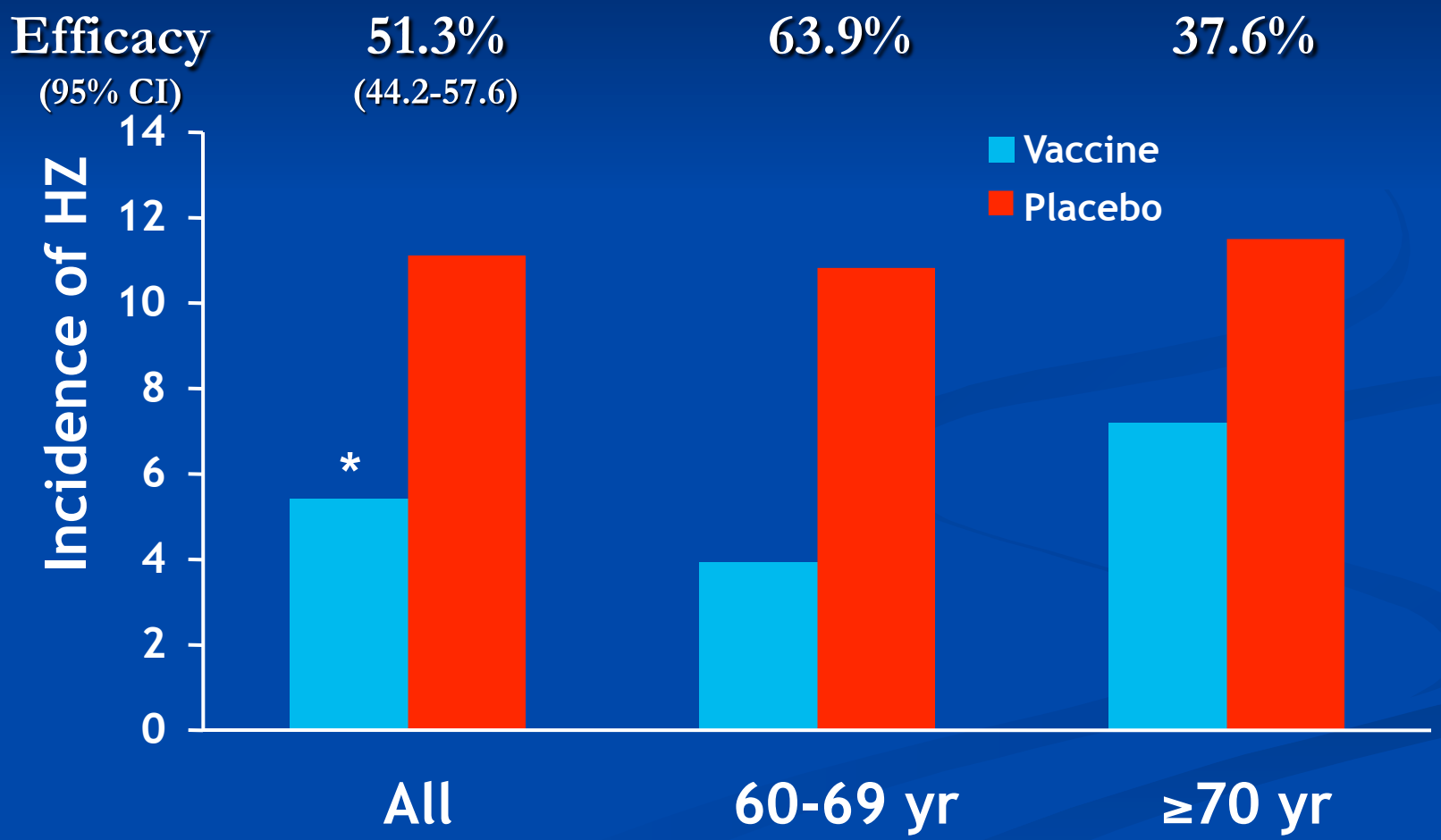
Oxman M et al. ***N Engl J Med.*** **2005;352:2271-2284.**

The Shingles Prevention Study
Study Design



Oxman M et al. *N Engl J Med.* 2005;352:2271-2284.

The Shingles Prevention Study
Results
Vaccine Efficacy: HZ Incidence by age



*P <0.001

Adapted from Oxman M et al. *N Engl J Med.* 2005;352:2271-2284.

Evaluation of Clinical Efficacy

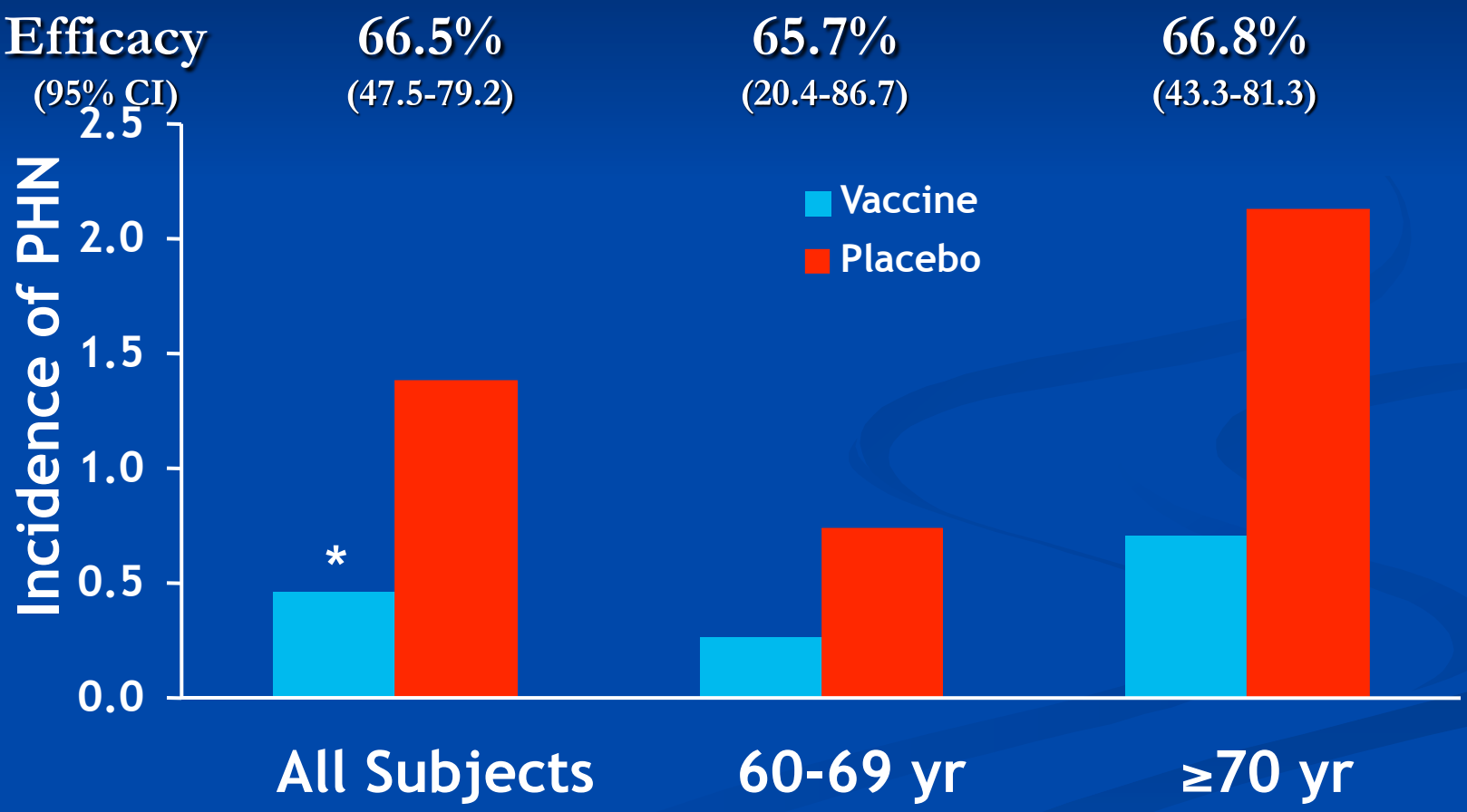
Shingles Prevention Study (SPS)

Efficacy of ZOSTAVAX™ on the incidence of severe and long-lasting zoster-associated pain compared with placebo

	ZOSTAVAX™	Placebo	Vaccine Efficacy
Number of subjects with severity-by-duration score >6oo	11	40	73% (95% CI 46-87.6%)

The Shingles Prevention Study Results

Vaccine Efficacy: PHN Incidence by age



*P <0.001

Adapted from Oxman M et al. *N Engl J Med.* 2005;352:2271-2284.

Evaluation of Clinical Efficacy

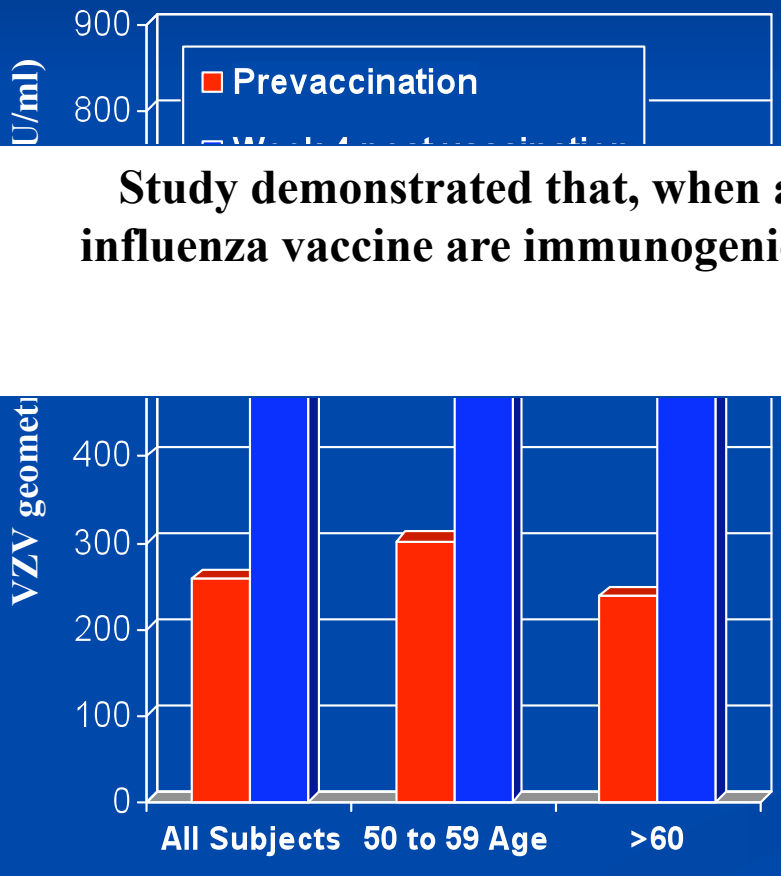
Shingles Prevention Study (SPS)

- Among vaccinated individuals who developed PHN, ZOSTAVAX™ significantly reduced PHN-associated pain compared with placebo.

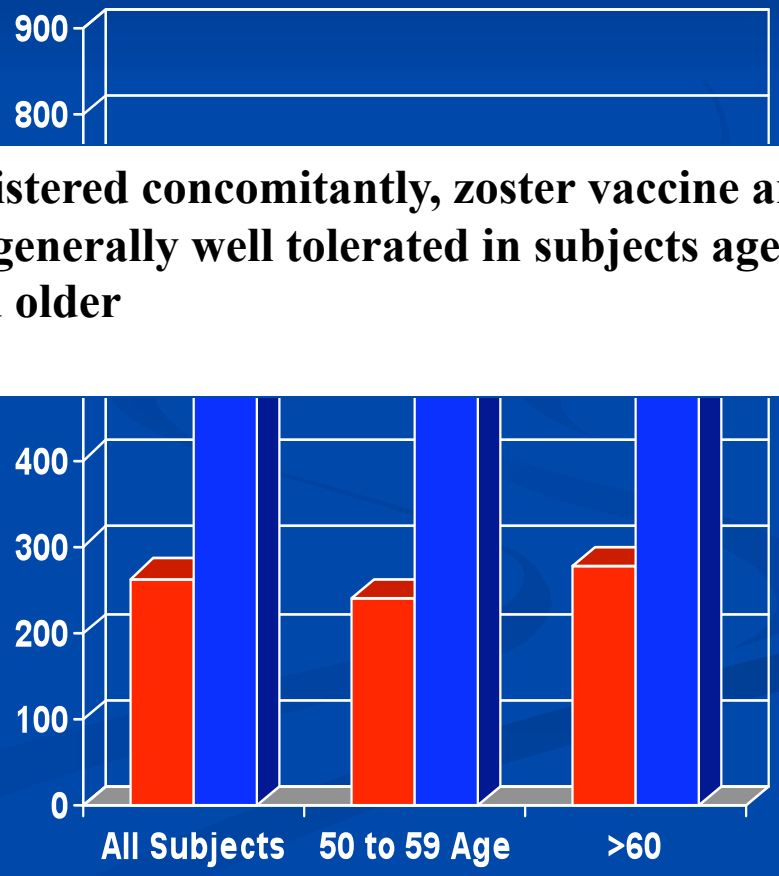
	ZOSTAVAX™	Placebo	Vaccine Efficacy
Average scores	347	805	57% (p=0.016)

Varicella-zoster virus and Influenza Antibody Response

Zoster vaccine 4 weeks after influenza vaccine



Concomitant Zoster vaccine and influenza vaccine



Study demonstrated that, when administered concomitantly, zoster vaccine and influenza vaccine are immunogenic and generally well tolerated in subjects aged 50 and older

Kerzner, B, et al. JAGS 55(10) 1498 - 1507

Adverse Reactions

In clinical trials, ZOSTAVAX™ has been evaluated for safety in more that 20,000 adults 50 years of age or older.

– ZOSTAVAX™ was generally well tolerated

The Shingles Prevention Study
Serious Adverse Events Among
All Subjects

Event	Vaccine Group	Placebo Group
No. Subjects	19,270	19,276
Day of Vaccination. To End of Study		
Death	218 (2.1%)	246 (2.4%)
Vaccine-related SAE	2 (<0.1%)	3 (<0.1%)
Day of Vaccination. To Day 42		
Death	14 (0.1%)	16 (0.1%)
≥1 SAEs	255 (1.4%)	254 (1.4%)

Adapted from Oxman M et al. *N Engl J Med.* 2005;352:2271-2284.

Shingles Prevention Study
Adverse Events Among Sub-study

	Zoster Vaccine	Placebo
Number of subjects in Sub-Study	3345	3271
Temperature 38.3° C or higher	27	27
One or more events at injection site	1604	539
Erythema	1188 (35.8%)	227
Pain or Tenderness	1147 (34.4%)	278
Swelling	871 (26.2%)	147
Pruritus	237 (7.1%)	33
Warmth	57	11
Hematoma	53	46
Rash	10	5

Oxman, M, et al, Shingles Prevention Study. NEJM 2005

NNV – Comparison to Other Vaccines Recommended in Older Adults

Age at vaccination	Annual incidence of disease*	Vaccine efficacy	Duration of protection	NNV to prevent 1 case
HZ vaccine for HZ ≥65 years of age	8.9	51%	5 years	~41
HZ vaccine for PHN ≥60 years of age	1.5 to 2.3	67%	5 years	~130-200
Influenza vaccine ≥50 years of age	40†	~60%	1 year	~42
Pneumococcal vaccine ≥50 years of age	0.5 to 1†	~60%	5 years	~335-670

* Incidence rate per 1,000
† Annual incidence rate in persons ≥65 years of age

NNV = number needed to vaccinate
Kelly H *et al*. *Vaccine* 2004; 22(17-18):2192-8.

Number Needed to Vaccinate to Prevent a Single Case

	Age 60	Age 70
Shingles	9	16
PHN	41	44

Canadian Status Zoster Vaccine

August 25, 2008

Health Canada Approval

Zoster Vaccine for the prevention of shingles (herpes zoster) in individuals 60 years of age or older

2009 – Vaccine Available

Vaccine is available September 2009 through Canadian physicians and pharmacists

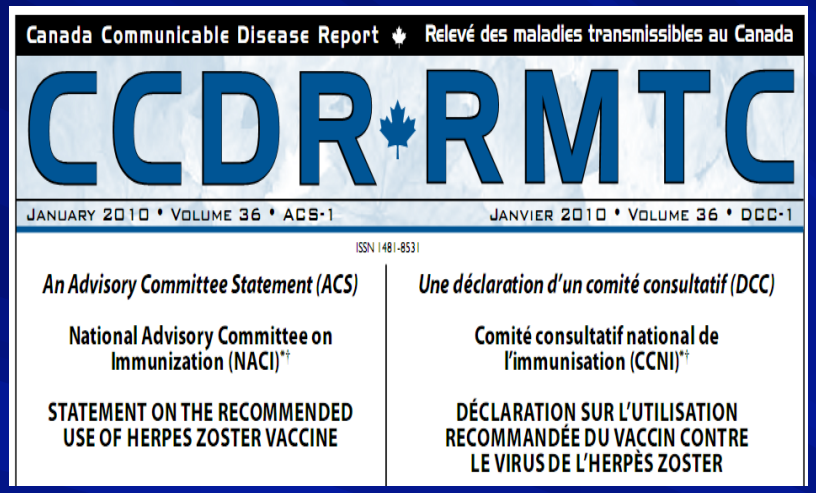
Zoster Vaccine (Oka/Merck)

- Live, attenuated, Oka/Merck strain of Varicella-zoster Virus
- Single-dose of entire vial (approx. 0.65ml)
- S.Q. administration only
- Contain at least 14-fold more PFU of VZV Oka/Merck/ dose than the Varicella Vaccine

STORE FROZEN - Average temperature of –15°C or colder until it is reconstituted for injection

DISCARD RECONSTITUTED VACCINE IF NOT USED WITHIN 30 MINS

CCDR - A Publication from the Public Health Agency of Canada



The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to immunization. The Public Health Agency of Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge.
This statement was prepared by Dr. Kevin Laupland and approved by NACI and the Public Health Agency of Canada.

Members: Dr. J. Langley (Chairperson), Dr. B. Warshawsky (Vice-Chairperson), Dr. S. Ismail (Executive Secretary), Ms. A. Hanrahan, Dr. K. Laupland, Dr. A. McGeer, Dr. S. McNeil, Dr. B. Seifert, Dr. D. Skowronski, Dr. B. Tan. **Liaison Representatives**: Dr. B. Bell (CDC), Dr. P. Orr (AMMI Canada), Ms. S. Pelletier (CHICA), Ms. K. Pielak (CNCI), Dr. P. Plourde (CATMAT), Dr. S. Rechner (CFPC), Dr. M. Salvadori (CPS), Dr. D. Scheifele (CAIRE), Dr. N. Sicard (CPHA), Dr. V. Senikas (SOGC).

Zostavax™ - Composition, Dosage and Schedule

- Based on the Oka/Merck strain
- Same components as the varicella vaccine Varivax™ (Merck) but ~ ≥14-fold higher virus concentration
- Each 0.65-mL single dose vial contains ≥ 19,400 plaque-forming units, and:
  - sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, residual DNA and protein from MRC-5 cell culture, trace amounts of neomycin and bovine calf serum
- Single dose given by subcutaneous injection in the deltoid region of the upper arm

Indications and clinical use

- ZOSTAVAX™ is indicated for the prevention of herpes zoster (shingles)

- For immunization of individuals 60 years of age or older. In a clinical trial of subjects 60 years of age or older, the overall efficacy of ZOSTAVAX™ against herpes zoster was 51%

Simultaneous administration with other adult vaccines

- Trivalent inactivated influenza vaccine: immunogenicity of zoster vaccine not compromised
- Td, Tdap and pneumococcal polysaccharide vaccines: separate syringe at a different site

  → If simultaneous administration is not possible, Zoster Vaccine can be administered:
  - at any time before or after an inactivated vaccine
  - at least 4 weeks before or after another live, attenuated vaccine

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Special groups and circumstances

- Persons with a reported history of zoster:
  can be vaccinated (recurrence, similar risk as first episode, no lab test, erroneous diagnosis/history and no safety concerns).

- Persons anticipating immunosuppression:
  (immunocompetent patients ≥60 years before immunosuppressive treatment or disease leading to immunodeficiency): should receive 1 dose administered 14 days before immunosuppressive therapy. Alternatively, wait 1 month after zoster vaccination to begin immunosuppressive therapy.

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Special Groups and Circumstances

- Persons receiving antiviral medications:
  persons taking chronic acyclovir, famciclovir, or valacyclovir should stop these meds at least 24 hours before administration of the Zoster Vaccine and for at least 14 days after vaccination.

- Persons receiving blood products:
  Zoster Vaccine can be administered at any time before, concurrent with, or after receiving blood or other Ab-containing blood product.

- Nursing mothers: not a contraindication (not secreted in breast milk), extremely rare situation.

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Contraindications

- **Allergy** to vaccine components: contraindicated when history of anaphylactic reaction to any component (including gelatin and neomycin) of Zoster Vaccine

  → contact dermatitis to neomycin is not a contraindication

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Contraindications (cont'd)

- **IMMUNOCOMPROMISED PERSONS**: should not be administered to persons with either primary or acquired immunodeficiency including:

- *Leukemia, lymphomas, or other malignant neoplasms* affecting the bone marrow or lymphatic system

- *AIDS/HIV including persons with CD4+T lymphocyte values ≤200/mm³ or ≤15% of total lymphocyte*

→ Patients whose leukemia is in remission and who have not received chemotherapy or radiation for at least 3 months can receive the ZV.

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Contraindications (cont'd)

- **IMMUNOCOMPROMISED PERSONS**:

  should not be administered to persons with either primary or acquired immunodeficiency including:

  - ***Persons on immunosuppressive therapy*** including:

    - high-dose corticosteroids (≥20 mg/day of prednisone or equivalent) lasting 2 or more weeks. Zoster Vaccine should be differed for at least 1 month after discontinuation of therapy

    - Short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive Zoster Vaccine

    - Therapy with low-doses of methotrexate (≤0.4 mg/Kg/week), azathioprine (≤3.0 mg/Kg/day), or 6-mercaptopurine (≤1.5 mg/Kg/day) for treatment of RA, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of Zoster Vaccine

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Contraindications (cont'd)

- **IMMUNOCOMPROMISED PERSONS**:

  should not be administered to persons either primary or acquired immunodeficiency including:

  - *Evidence of unspecified cellular immunodeficiency* however patients with impaired humoral immunity can receive the Zoster Vaccine
  - *HSCT:* physicians should assess the immune status of the recipient to determine the relevant risks. If decision is made to vaccinate, Zoster Vaccine should be administered at least 24 months after transplantation
  - *Persons receiving recombinant human immune mediators and modulators (adalimumab, infliximab, and etanercept):* safety unknown. If not possible to vaccinate before initiation of therapy, physicians should assess the immune status of the patient to determine the relevant risks and benefits. Otherwise, vaccination should be deferred for at least 1 month after discontinuation of such therapy
  - *Pregnancy:* not recommended. Women should avoid becoming pregnant for 4 weeks following Zoster Vaccine

    → Pregnancy registry (Merck & Co., Inc. and CDC) to monitor the maternal-fetal outcomes.

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Contraindications (cont'd)

- **IMMUNOCOMPROMISED PERSONS**:

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CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Precautions

Moderate to Severe Illness

- Zoster vaccination of persons who have severe acute illness should be postponed until recovery
- Delay of vaccination depends on the severity of symptoms and the etiology of the disease
- ZV can be administered to persons who have mild acute illnesses with or without fever

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Transmission of Vaccine Virus

- Risk for transmission of Oka/Merck strain after receiving Zoster Vaccine
  - Persons having close contact with persons at risk for severe varicella need NOT to take any precautions after receiving Zoster Vaccine except in rare instances in which a varicella-like rash develops
  - Rates of varicella-like rash appear to be less common following Zoster vaccination than following Varicella vaccination, and transmission of the Oka/Merck strain VZV from recipients of Zoster Vaccine has not been detected
  - The risk for transmitting the attenuated vaccine virus to susceptible persons should be weighed against the risk for developing wild-type zoster that could be transmitted to a susceptible person
  - If a susceptible, immunocompromised person is inadvertently exposed to a person who has a vaccine-related rash, VARIZIG™ need to be administered because disease associated with this type of transmission is expected to be mild
  - Acyclovir, valacyclovir and famciclovir can be used in patients in the unlikely situations in which severe illness develops in the susceptible contact

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

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CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

Shingles Prevention Study* – Safety and Adverse Events

- All adverse events within 42 days and all serious events thereafter reported for all subjects
  - Adverse events closely monitored in sub-study of 6,616 patients
- ≥ 1 adverse event
  - More common with vaccine than with placebo: 58.1% vs. 34.4%, *P*<.05
  - Mainly injection site reactions: e.g., erythema (35.8% vs. 7.0%), pain or tenderness (34.5 vs. 8.5%)
- During the first 42 days:
  - Varicella-like rash at injection site: vaccine (20 cases, 0.1%) vs placebo (7 cases, 0.04%) *P*<.05
  - But herpes zoster less common in vaccine recipients (7, <0.1% vs. 24, 0.1%)

* Oxman MN, Levin MJ, Johnson GR et al. N Engl J Med 2005, 352(22):2271-2284.

Shingles Prevention Study* – Serious Adverse Events

- ≥ 1 Serious adverse events:
  - Vaccine (1.9%) vs placebo (1.3%), *P*<.05
  - However, a case-by-case review suggested no clinically significant differences in serious adverse events between groups
  - Serious adverse events deemed potentially vaccine-related: 2 in vaccine, 3 in placebo recipients
- Hospitalization:
  - Overall: vaccine (34.0%) vs placebo (34.1%)
  - Herpes zoster–related: 0.2% in each
- Mortality:
  - Vaccine: 14 (4.1%) deaths vs placebo: 16 (4.1%) deaths

* Oxman MN, Levin MJ, Johnson GR et al. N Engl J Med 2005, 352(22):2271-2284.

Routine vaccination of persons aged ≥60 years

- All persons aged **≥60 years**: routine vaccination with 1 dose.
- Persons with a previous episode of **zoster**: can be vaccinated.
- Persons with **chronic medical conditions** (chronic renal failure, DM, RA & COPD): can be vaccinated unless those conditions are contraindicated or precautions.

→ Not to treat acute HZ, not to prevent PHN in HZ patients, or not to treat PHN.

→ Not necessary to ask for history of varicella or to conduct serologic testing before vaccinating.

CDC. Prevention of Herpes Zoster.MMWR 2008; 57:1-29

The importance of vaccination of older age groups

- Severe damage to nervous system after zoster
- Post-herpetic neuralgia: difficult to treat
- Post-herpetic neuralgia: difficult to prevent by treating herpes zoster
- Herpes zoster and post-herpetic neuralgia are likely to increase

Additional information about zoster and zoster vaccine

www.zostavax.ca

www.cdc.gov/vaccines/vpd-vac/shingles/default.htm

Clinical Pearls

- **Herpes zoster:** the most common neurological disease and a common cause of neuropathic pain
- **Postherpetic neuralgia:** most feared and common complication
- **Postherpetic neuralgia**: will increase and may increase with childhood vaccination

Clinical Pearls

- **Our best treatments of post-herpetic neuralgia have at best a modest effect at the cost of side effects and up to 50% are untreatable or unsatisfactorily relieved**
- **Prevention by early aggressive treatment of zoster has limitations and vaccination appears critical**

NACI Recommendations for Immunization - Grades

Grade	NACI concludes that …
A	there is **good** evidence **to recommend** immunization
B	there is **fair** evidence **to recommend** immunization
C	the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however, other factors may influence decision-making
D	there is **fair** evidence to recommend **against** immunization
E	there is **good** evidence to recommend **against** immunization
I	there is **insufficient** evidence (in either quantity or quality) to make a recommendation; however, other factors may influence decision-making

January 2010 - Statement on the recommended use of the herpes zoster vaccine. Canada Communicable Disease Report. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2010;36(ACS-1):1-19.

Recommended Use – Target Age

Group	Recommendation	Comments
Persons age ≥ 60 years without contraindications	▪ Recommended ▪ Grade A, good	• Administer irrespective of prior chickenpox history or documented varicella infection (Grade A, good) • Routine testing for varicella antibody not recommended
Persons age ≥ 50 years without contraindications	▪ May be used ▪ Grade B, fair	• Safe and immunogenic in patients ≥ 50 years; however, effectiveness has been studied only in patients ≥ 60 years • While patients ≥50 years may benefit, benefit will be greatest in those aged ≥ 60 years • Duration of protection is unknown beyond 4 years; uncertain whether vaccination at age 50 - 60 will provide ongoing protection

January 2010 - Statement on the recommended use of the herpes zoster vaccine. Canada Communicable Disease Report. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2010;36(ACS-1):1-19.

Recommended Use – VZV History

Group	Recommendation	Comments
Persons with past episode of zoster	▪ No recommendation can be made ▪ Grade I, insufficient	• Patients with a history of zoster are at risk for further episodes • Patients with a history of zoster were excluded from the pivotal efficacy trial • In a small study (n=101) of subjects aged ≥ 50 previously immunized with Zostavax™ no safety concerns were identified
Patients known to be serologically susceptible to varicella	▪ Vaccination with 2 doses of varicella vaccine	• There is no known safety risk associated with Zostavax™ vaccination of healthy individuals who are susceptible to varicella

January 2010 - Statement on the recommended use of the herpes zoster vaccine. Canada Communicable Disease Report. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2010;36(ACS-1):1-19.

Recommended Use – Second Dose

Group	Recommendation	Comments
Healthy persons previously vaccinated with Zostavax™	▪ Booster (repeat) doses are not recommended ▪ Grade I, insufficient	• Protection not assessed beyond 4 years; not known whether booster doses of vaccine are beneficial
Patients who inadvertently receive systemic anti-viral therapy against VZV within 2 days before and 14 days after Zostavax™	▪ May benefit from a 2nd dose of Zostavax™ ≥ 42 days after discontinuing antiviral therapy ▪ Grade B, fair	• Systemic anti-viral therapy against VZV should ideally be avoided in the peri-immunization period because it may affect vaccine efficacy

January 2010 - Statement on the recommended use of the herpes zoster vaccine. Canada Communicable Disease Report. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2010;36(ACS-1):1-19.

Recommended Use – Administration with Other Vaccines

Recommendation	Comments
▪ Trivalent infuenza vaccine may be administered concomitantly with Zostavax™ at a different body injection site ▪ Grade A, good	• Concomitant administration of Zostavax™ and trivalent infuenza demonstrated to have comparable safety, tolerability, and immunogenicity to sequential administration
▪ Pneumovax™23 and Zostavax™ should be administered ≥ 4 weeks apart ▪ Grade B, fair	• One clinical trial of co-administration of Zostavax™ with Pneumovax™23 has demonstrated safety of co-administration but inferior VZV GMT at 4 weeks post-vaccination

January 2010 - Statement on the recommended use of the herpes zoster vaccine. Canada Communicable Disease Report. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2010;36(ACS-1):1-19.