BC Centre for Disease Control

IMMUNIZATION FORUM 2009

Zoster Vaccine for Older Adults

Michael N. Oxman, M.D.

Professor of Medicine and Pathology

University of California, San Diego

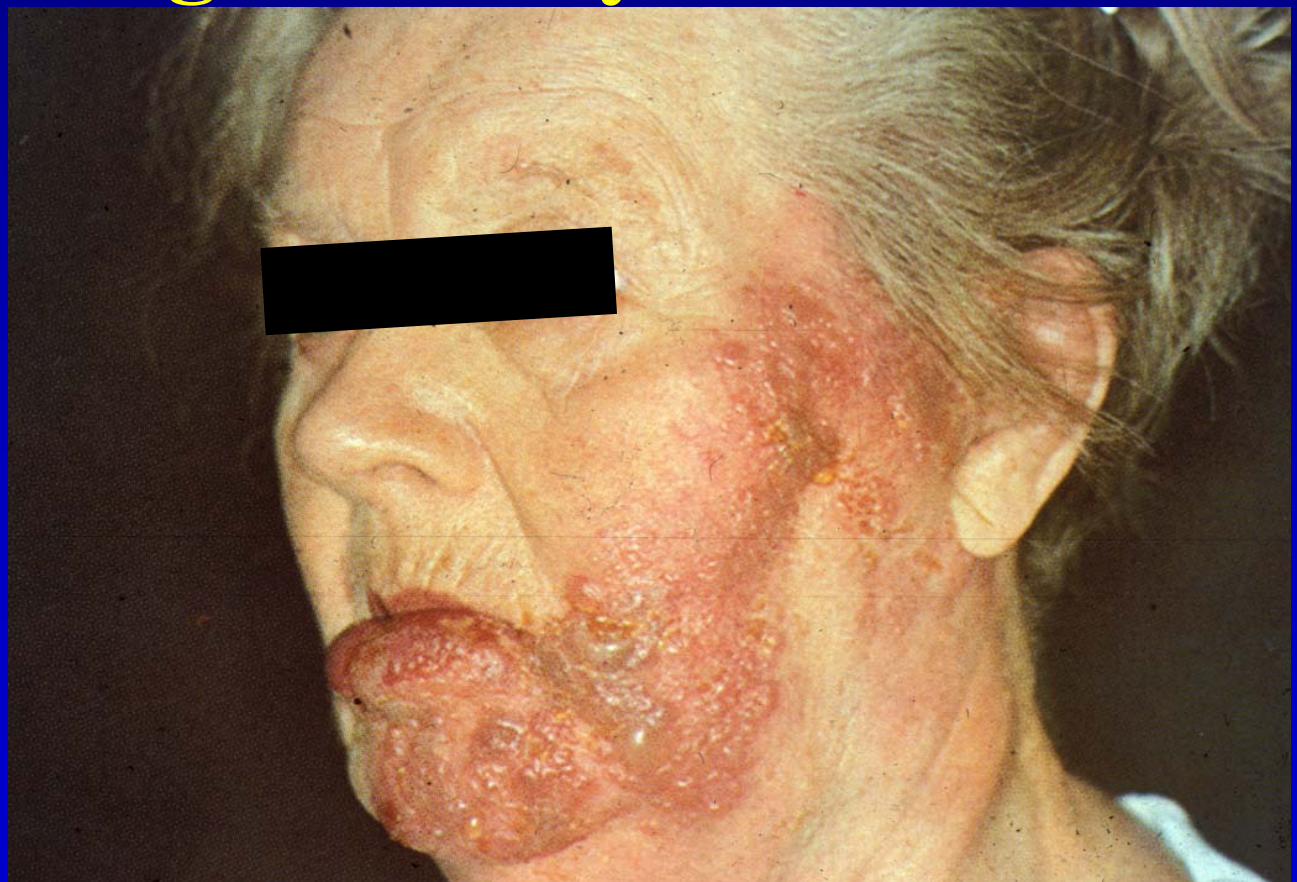
VASDHS Staff Physician (Infectious Diseases)

Study Chairman, VA Cooperative Study #403:

"The Shingles Prevention Study"

Why Do We Need a Shingles Vaccine?

There are more a million new cases of shingles each year in the USA



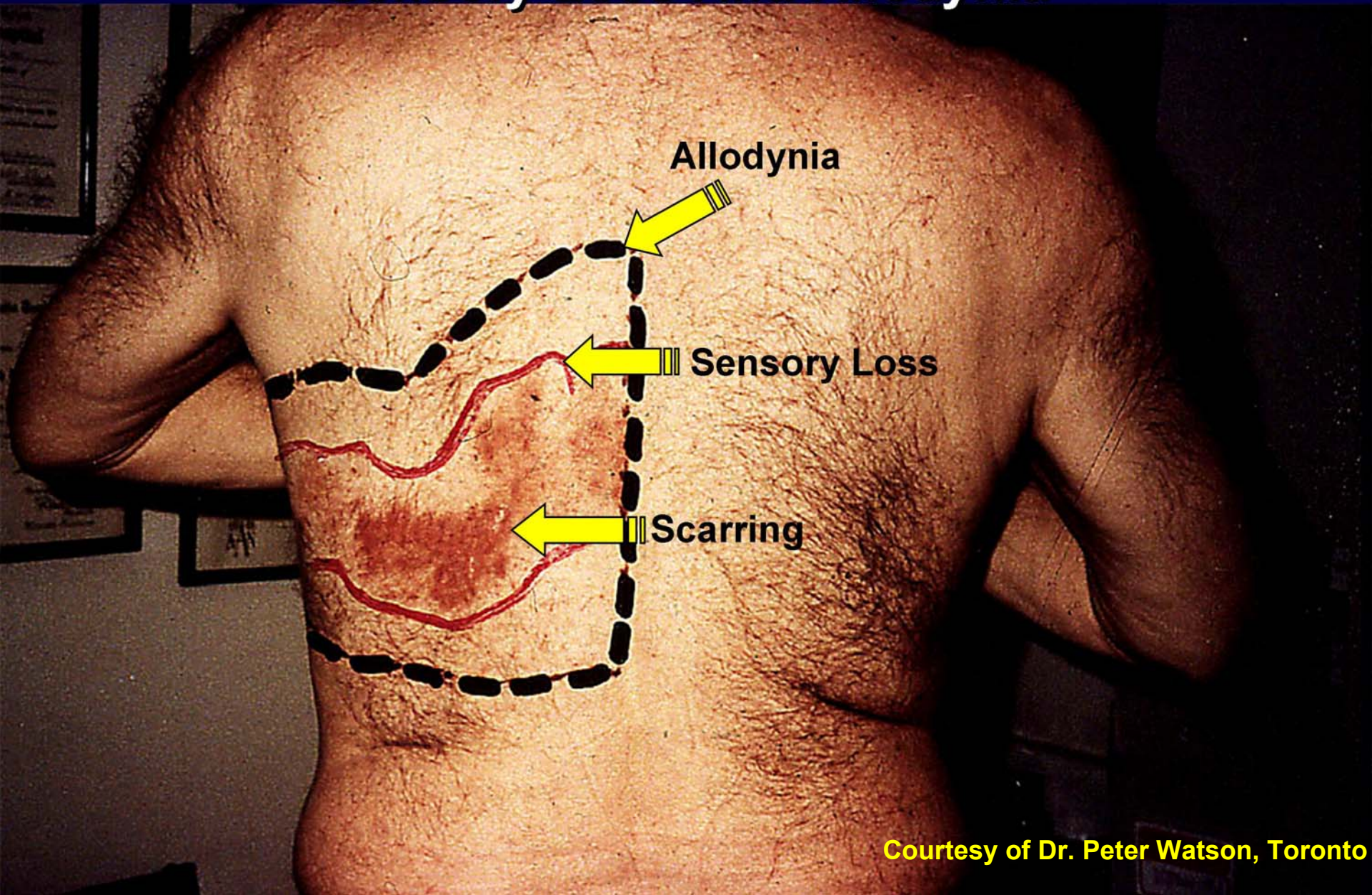
PAIN is a Major Manifestation of Herpes Zoster

- ***Prodromal Pain***
- ***Pain during the Acute Phase***
- ***Persisting Pain***

  Postherpetic Neuralgia **(PHN) - the most common debilitating complication of herpes zoster**

PHN: Clinical Features

Sensory Loss And Allodynia



Courtesy of Dr. Peter Watson, Toronto

Why Do We Need A Shingles Vaccine?

- **Once shingles develops, the available treatments do not prevent PHN**

Antiviral therapy

- Modestly shortens duration of rash if initiated early
- Even early treatment does not prevent PHN
- We still need to choose the right antiviral drug

Corticosteroids

- Decrease severity of acute pain
- Do not reduce the incidence or severity of PHN
- Side effects and toxicity argue against use

Pain medications

- Even narcotics have limited effectiveness against chronic neuropathic pain (i.e., PHN)
- Side effects are especially problematic in older persons

Vaccination against Shingles Presents a Unique Challenge

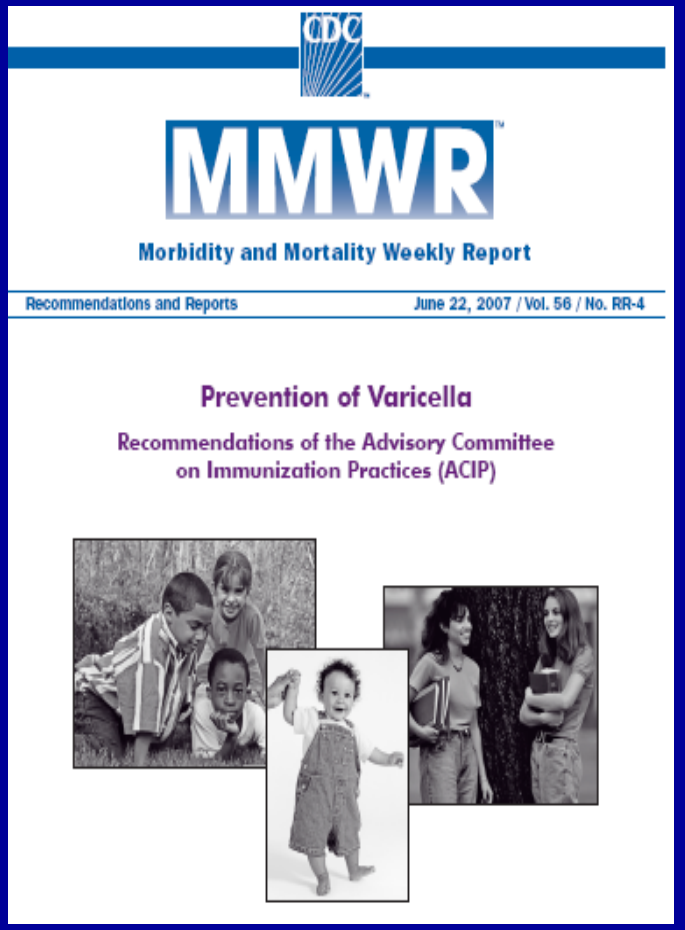
Vaccination against Chickenpox

- **Varicella Vaccine is typical of vaccines against other common childhood viral diseases, such as measles, mumps and poliomyelitis. It is administered to susceptible persons prior to exogenous exposure, and it induces immunity that prevents primary infection and disease (ie, the vaccine prevents VZV infection and Chickenpox)**

- **Expectations:**
  - **Vaccine Efficacy ≥95%**
  - **Herd Immunity**

Chickenpox Vaccine Policy in the US

- 1996 – Universal one-dose childhood Chickenpox vaccination initiated in the US
  - One dose recommended at age 12-18 months, with catch-up vaccination for children up to 12 years of age
- 2006 – Policy changed to a routine two-dose program
  - 1st dose at age 12-15 months
  - 2nd dose at age 4-6 years
  - Catch-up vaccination of persons who had received one dose
- Vaccine coverage Reached 90% in July 2006 – June 2007 among children age 19-35 months



MMWR 2007;56(RR-4):1-39

Reduction in Age-Specific Chickenpox Incidence Rate Active Surveillance Project, 1995-2006

Age group	Antelope Valley, CA (%)	West Philadelphia, PA (%)
< 1	-80	-94
1-4	-96	-90
5-9	-89	-94
10-14	-66	-85
15-19	-79	-90
20+	-86	-77
Total	-89	-91

Guris D, Jumaan AO, Mascola L, et al. J Infect Dis 2008;197(Suppl 2):S71-5 and CDC, unpublished data

In Contrast

When we attempt to vaccinate against herpes zoster, we are dealing with persons seen after primary infection in whom disease prevention requires changing the host-virus relationship rather than preventing primary infection. (we face a similar challenge with recurrent HSV, HIV-AIDS, and Hepatitis C)

Vaccination against Shingles

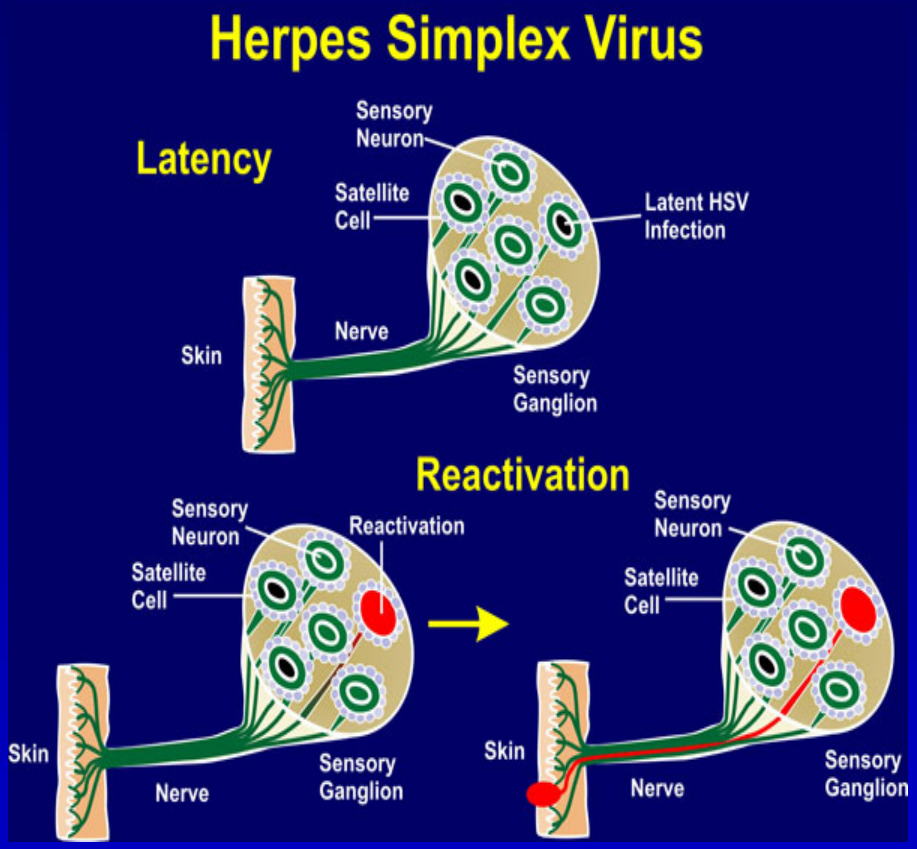
- **Zoster Vaccine is administered to persons who are already infected with VZV. It acts by boosting the declining level of pre-existing cell mediated immunity to VZV in older adults, thereby reducing the frequency and severity of a disease (Shingles) that is caused by reactivation and multiplication of endogenous latent VZV**

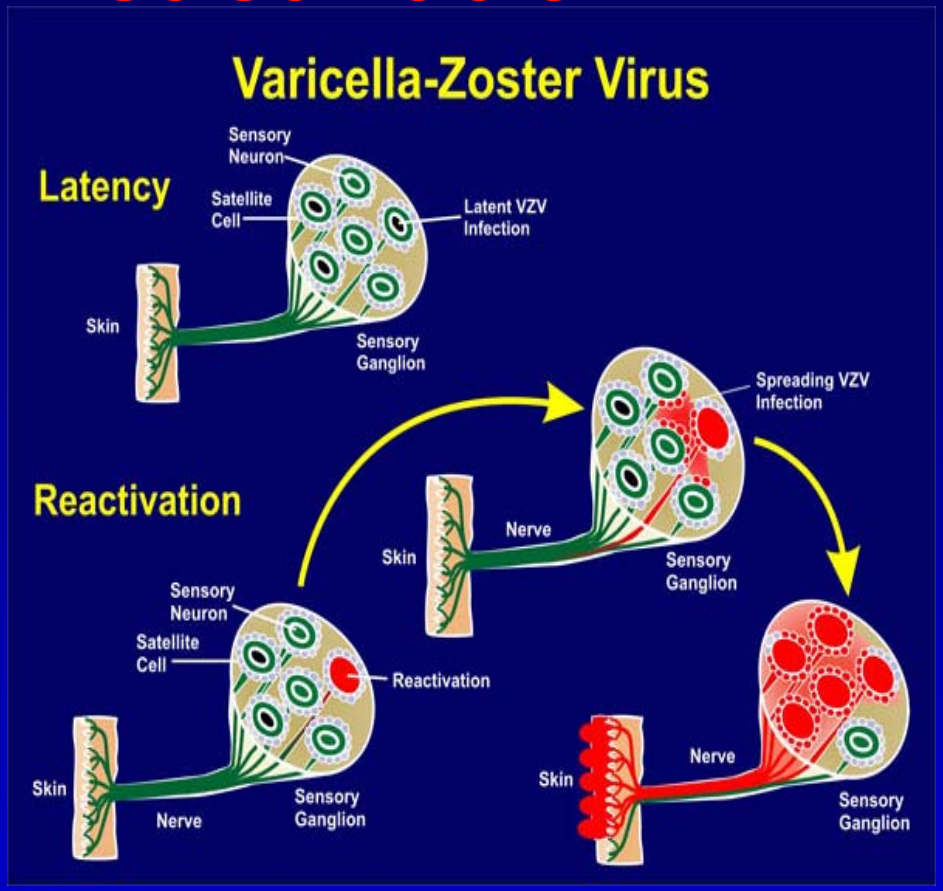
- **Expectations:**
  - **Vaccine Efficacy much less than 95%**
  - **No Herd Immunity**

Why Did We Think That A Shingles Vaccine Might Work?

1. Pathogenesis
2. Epidemiology
3. Live Attenuated Oka/Merck VZV vaccine

HSV vs. VZV
Latency and Reactivation

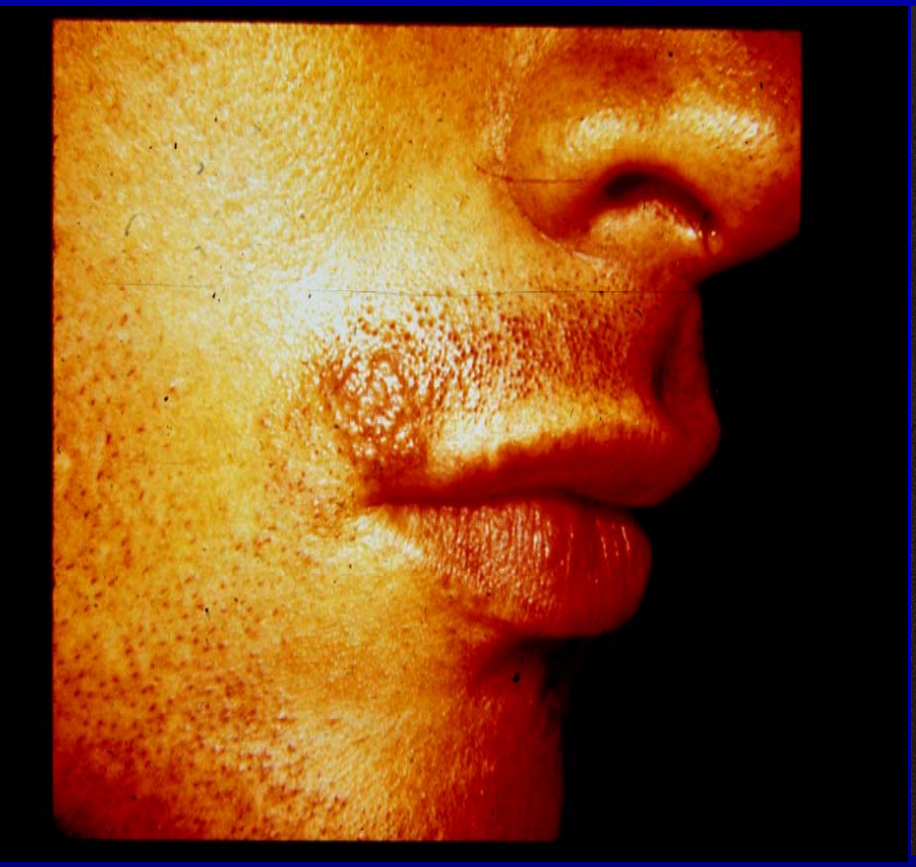


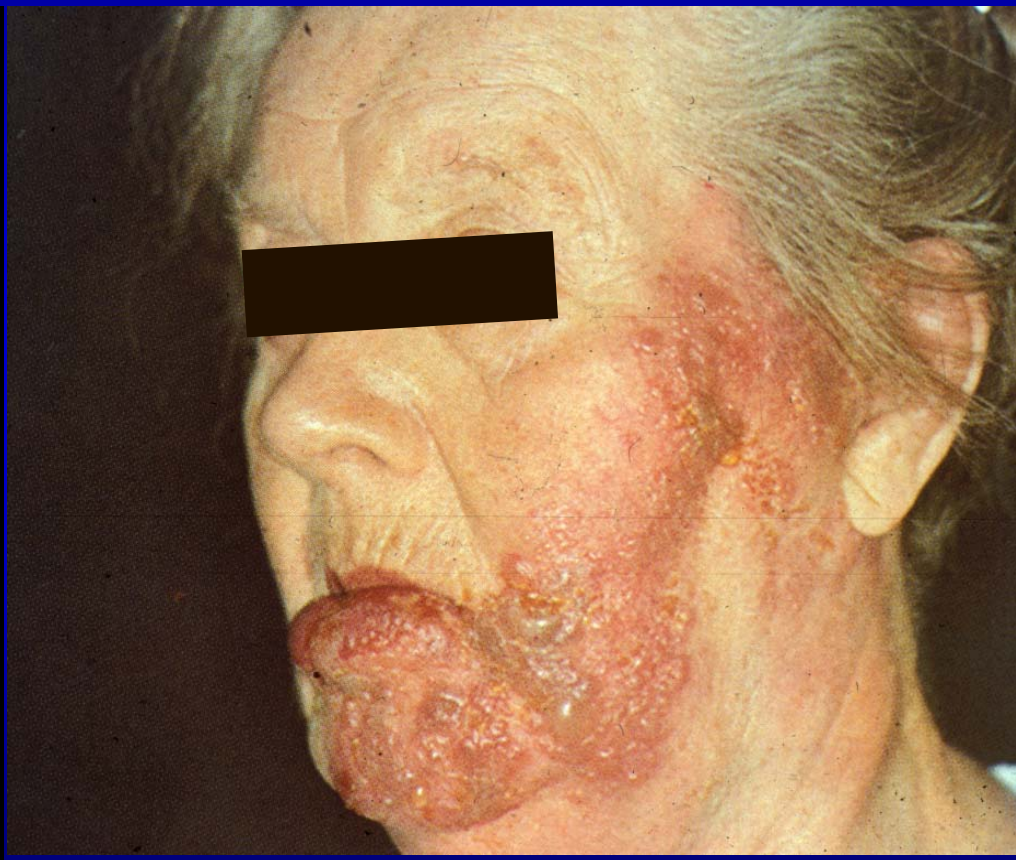


- No HSV Spread within Ganglion
- No Neuronal Damage or Death
- Little or No Prodromal Pain
- No Postherpetic Neuralgia (PHN)

- Extensive Spread within Ganglion
- Severe Neuronal Damage & Death
- Severe Prodromal Pain
- Postherpetic Neuralgia (PHN)

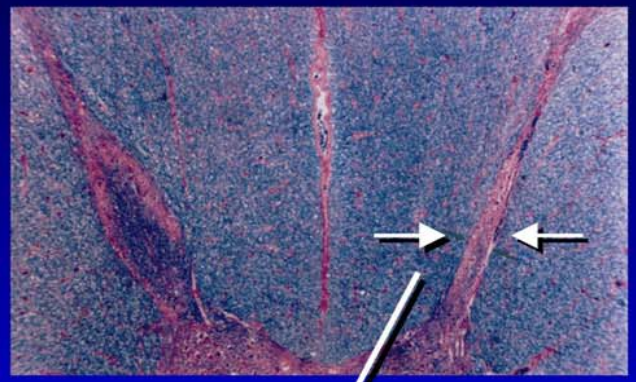
Herpes Simplex vs. Herpes Zoster





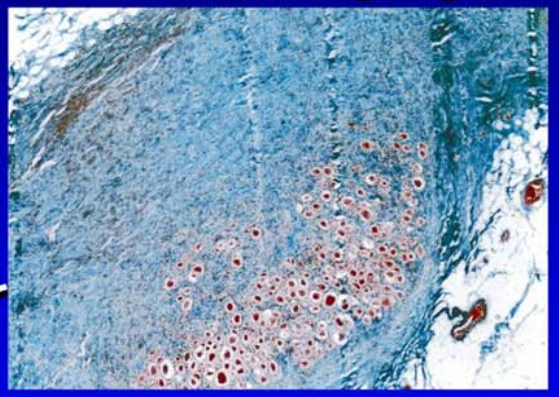
PHN: Pathophysiology

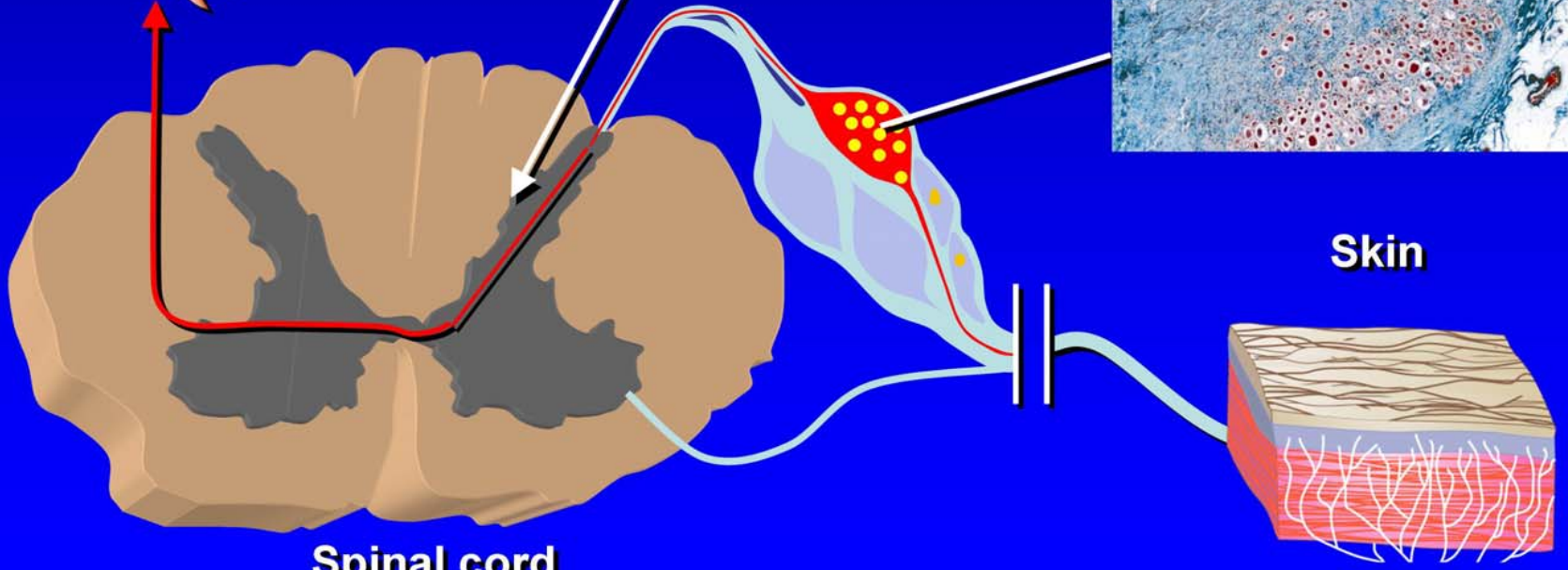
(Courtesy of Dr. Peter Watson, Toronto)



1. Atrophic Doral Horn

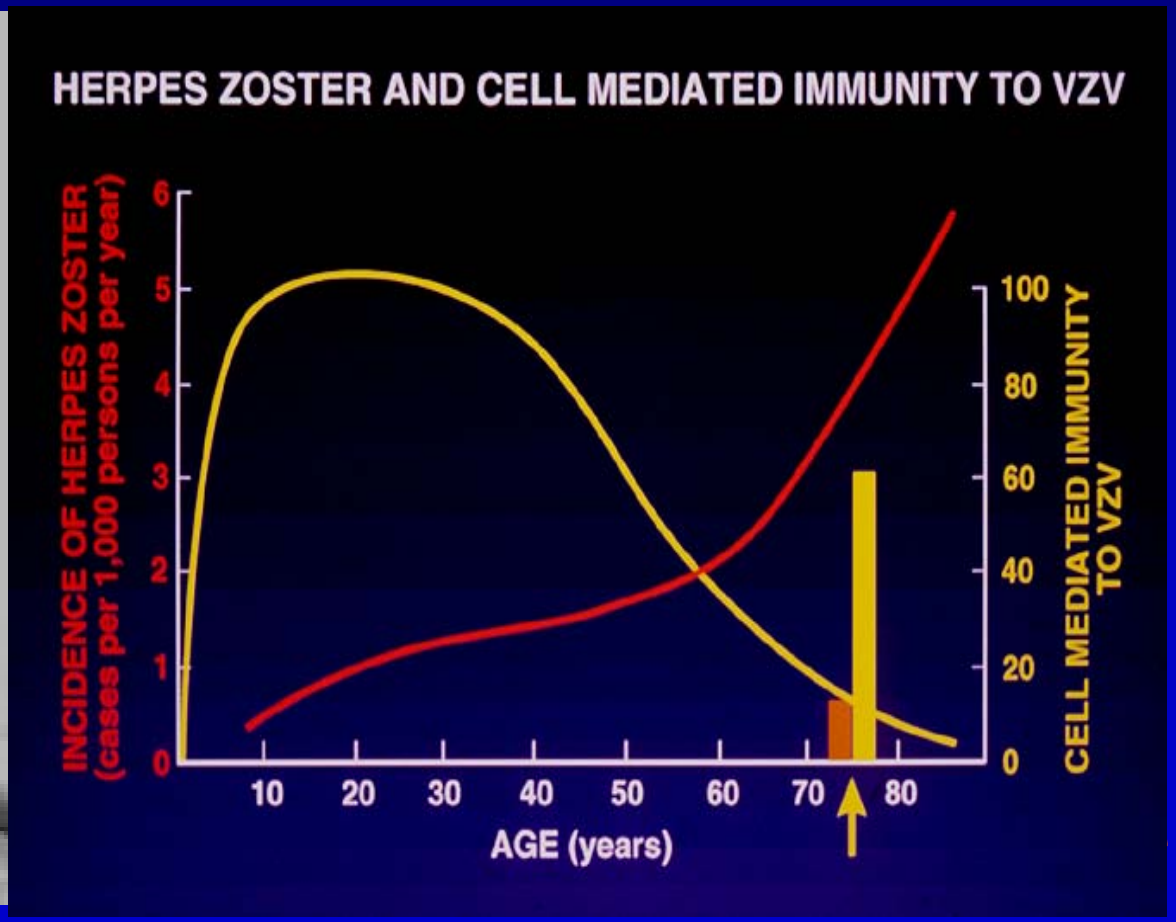
2. Dorsal root ganglion





Theoretical Basis for the Shingles Prevention Study

R Edgar Hope-Simpson - 1965



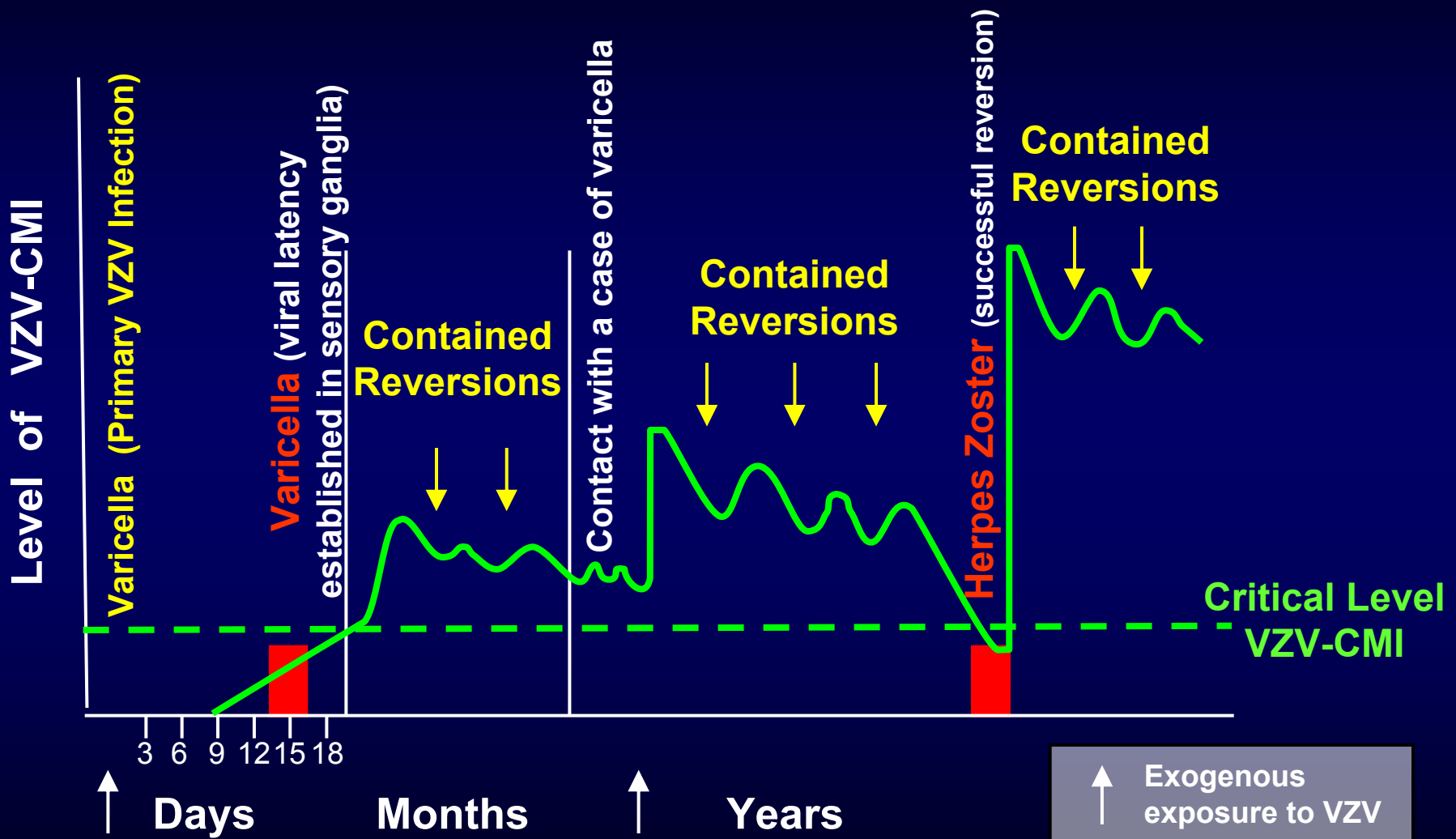
The nature of herpes zoster: a long-term study and a new hypothesis. *Proc Royal Soc Med* 1965; 58:9-20

In Contrast to neurons latently infected with HSV, which express no HSV proteins, neurons latently infected with VZV express *Immediate Early* and *Early* VZV proteins

Thus they may be "recognized" by host immune defenses

This may explain the critical role of Cell-Mediated Immunity in VZV latency and reactivation

Pathogenesis of Herpes Zoster

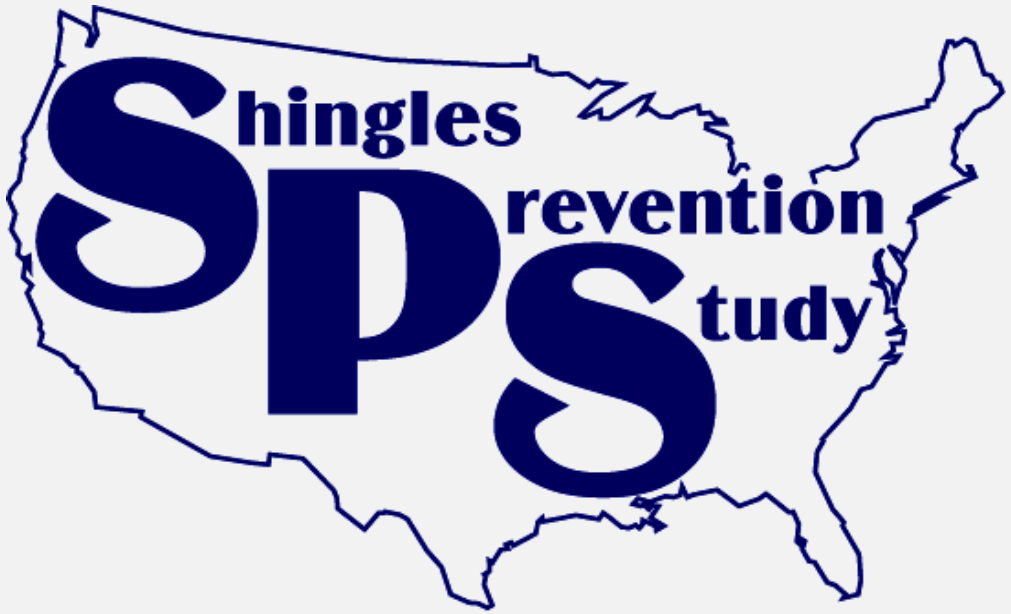


VZV = varicella-zoster virus

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

HYPOTHESIS

If we can mimic the host's immune response to herpes zoster by administering a VZV vaccine, we should be able to protect older adults from herpes zoster and PHN



A VA COOPERATIVE STUDY CARRIED OUT WITH THE COLLABORATION OF THE NIAID AND MERCK & COMPANY

THE ZOSTER VACCINE

Dr. Michiaki Takahashi

- The Same Live Attenuated Oka/Merck Strain of VZV Used in the Varicella Vaccine Currently Licensed in the US to Prevent Chickenpox
- The Minimum Potency of the Zoster Vaccine was at least 14 Times Greater than that of Varicella Vaccine
  [Median = 24,600 PFU (19K-60k)]

The Shingles Prevention Study

Study Design and End Points

The Shingles Prevention Study

A randomized double-blind placebo-controlled clinical trial in which 38,546 subjects ≥ 60 years of age were randomized into two age strata (60-69 and ≥70) at 22 study sites across the United States and received a single dose of live attenuated Oka/Merck VZV vaccine or placebo

Subjects were actively followed for herpes zoster and postherpetic neuralgia (PHN) for an average of 3.13 years

Major Challenges

- **ENROLLMENT** of a large number of subjects age 60 or older (in whom the risk of Shingles and PHN are substantial)
- **ACTIVE FOLLOW-UP** of >38,000 subjects to identify all cases of Shingles as soon as possible after rash onset; and follow each case for severity
- Develop a **QUANTITATIVE MEASURE** of **SHINGLES SEVERITY**
- Define a **PRIMARY ENDPOINT** that measured the impact of the vaccine on the incidence and/or severity of Shingles
- Determine **EVALUABLE CASES** of **SHINGLES** for Analysis of Vaccine Efficacy

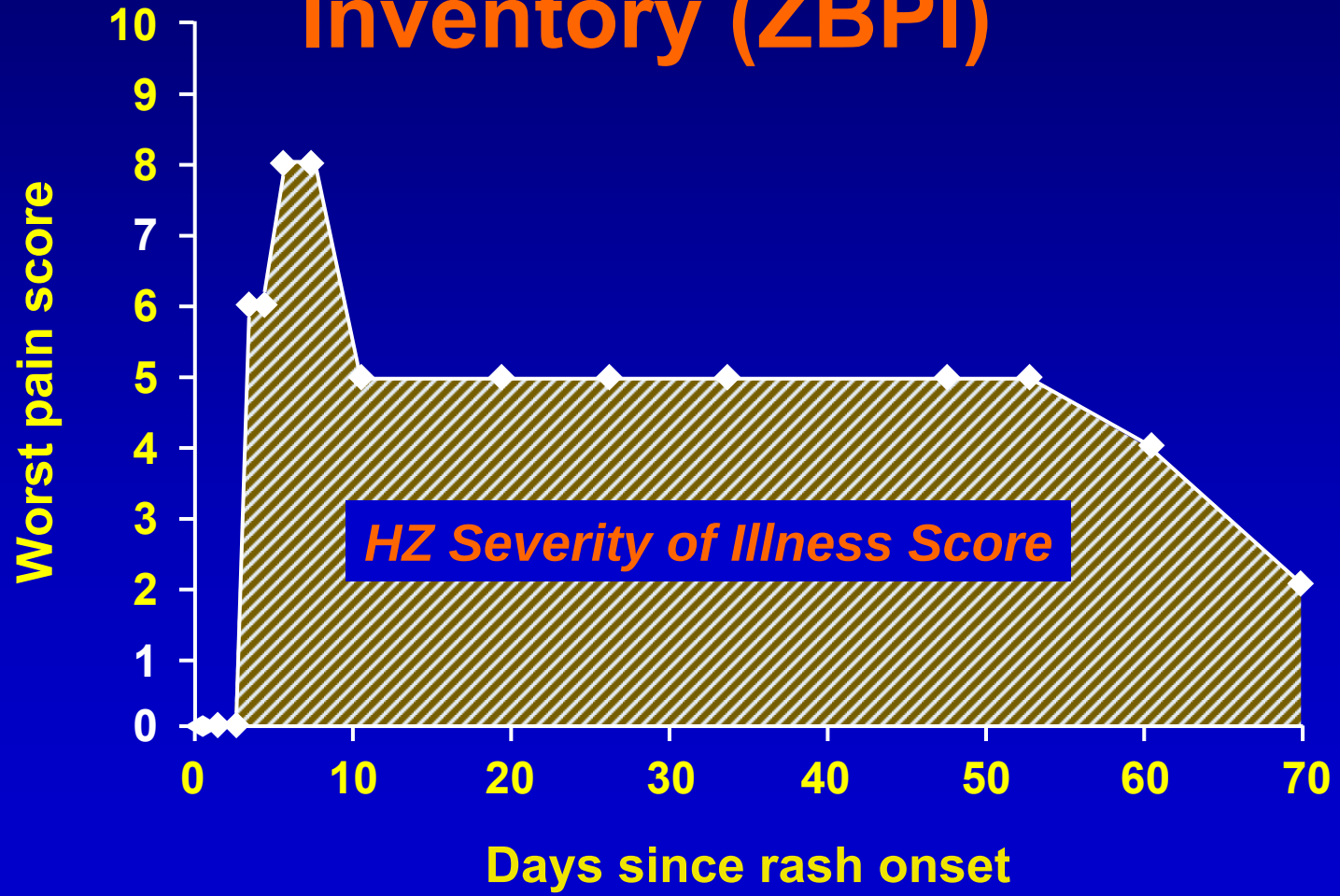
How Do You Measure the Adverse Impact of Herpes Zoster on Older Persons, Since Pain is the Major Cause of their Morbidity

AND

PAIN IS SUBJECTIVE

HZ Severity of Illness Score

= AUC of Worst Pain Scores Over Time assessed with the Zoster Brief Pain Inventory (ZBPI)



Coplan PM et al. *Pain.* 2004;5:344-356

The Primary End Point

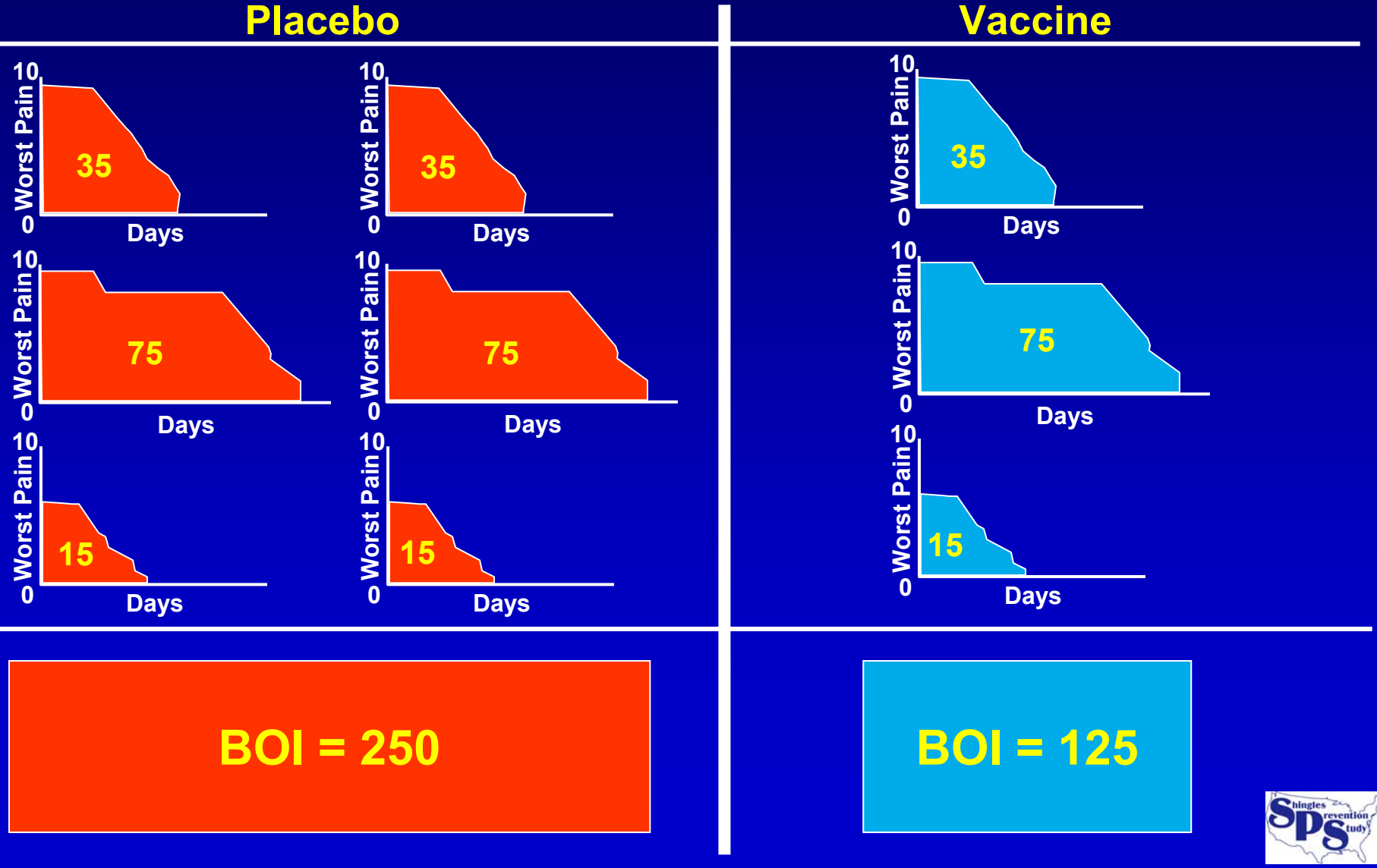
(Chosen to be sensitive to an effect of Zoster Vaccine on the incidence of HZ, on the severity of HZ, or on both)

THE BURDEN OF ILLNESS (BOI) DUE TO HZ

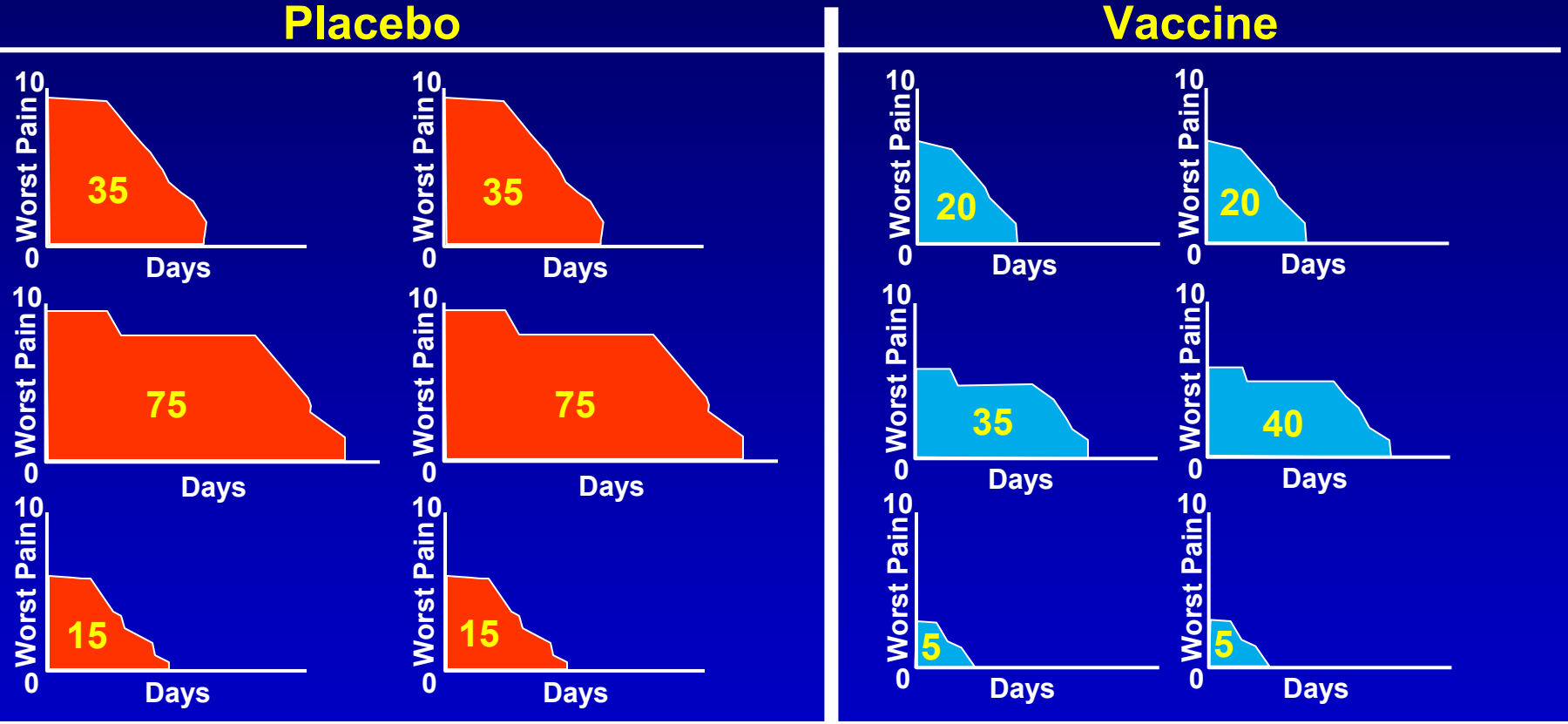
Defined as the Sum of the *HZ Severity of Illness Scores* (ie, the areas under the *worst pain* vs. *time* curves) in all subjects in the Vaccine or the Placebo group

Subjects who did not develop Shingles were assigned an *HZ Severity of Illness Score* = 0

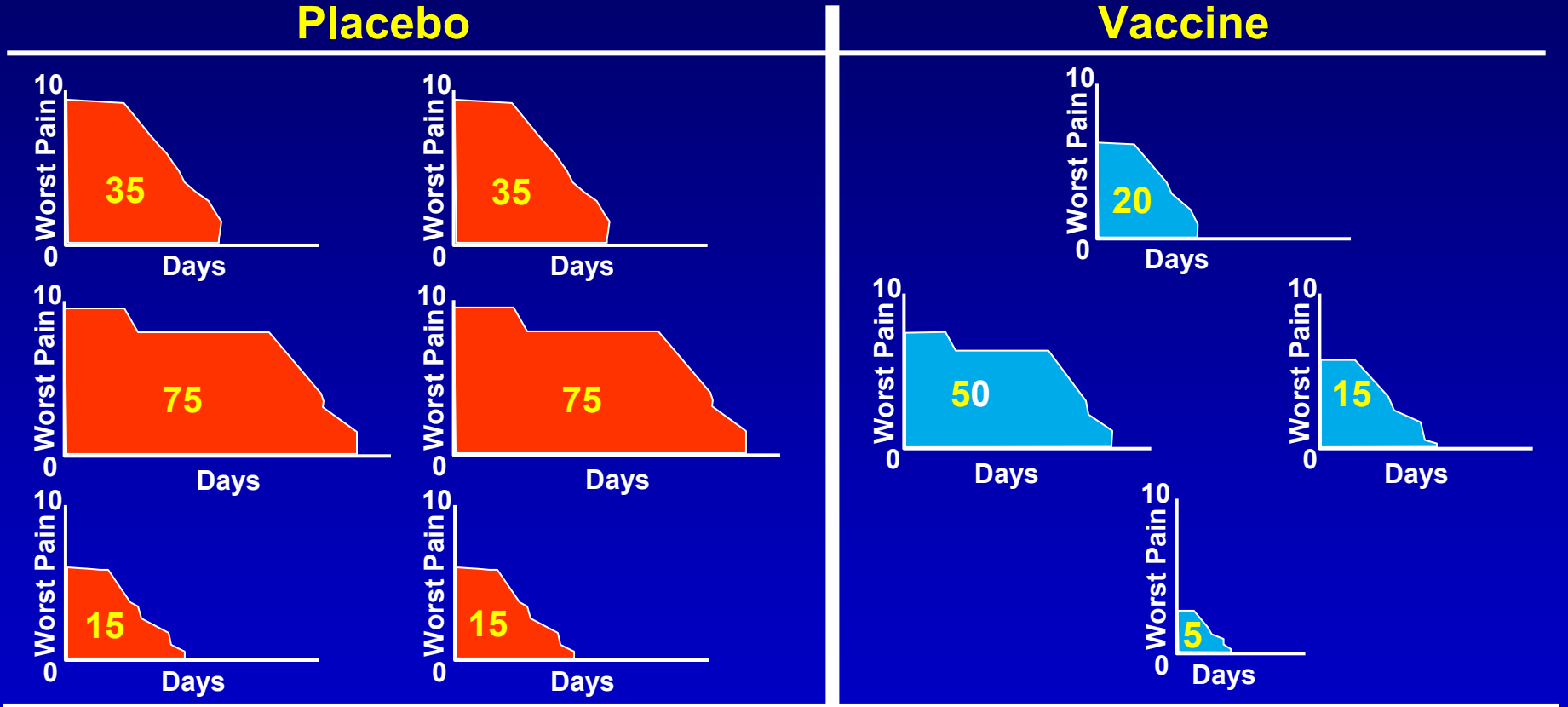
Reduction in the Incidence But Not in the Severity of HZ



Reduction in the Severity But Not in the Incidence of HZ



Reduction in Both the Incidence and the Severity of HZ



SECONDARY END POINT

THE INCIDENCE OF "CLINICALLY SIGNIFICANT" POSTHERPETIC NEURALGIA (PHN)

Where PHN is defined as HZ Pain or Discomfort with a ZBPI Worst Pain Score ≥3 for more than 90 days after HZ Rash onset

Definition of Evaluable Cases of HZ for the Analysis of Zoster Vaccine Efficacy

A *Clinical Assessment* by a Clinical Evaluation Committee (CEC)

and a

***Laboratory Assessment*, primarily with a sensitive and specific PCR assay**

These were separate processes, with the laboratory results having priority

Lawrence D. Gelb Michael N. Oxman Stephen E. Straus

Myron J. Levin Kenneth E. Schmader

THE CLINICAL EVALUATION COMMITTEE

The Clinical Evaluation Committee (CEC) consisted of five physicians with HZ expertise who evaluated all Suspected Cases of HZ. For each Suspected Case of HZ, each CEC member provided an independent clinical diagnosis. All cases lacking unanimity were discussed and voted upon. CEC members were blinded to treatment assignment and laboratory results.

Published Results

The NEW ENGLAND JOURNAL of MEDICINE

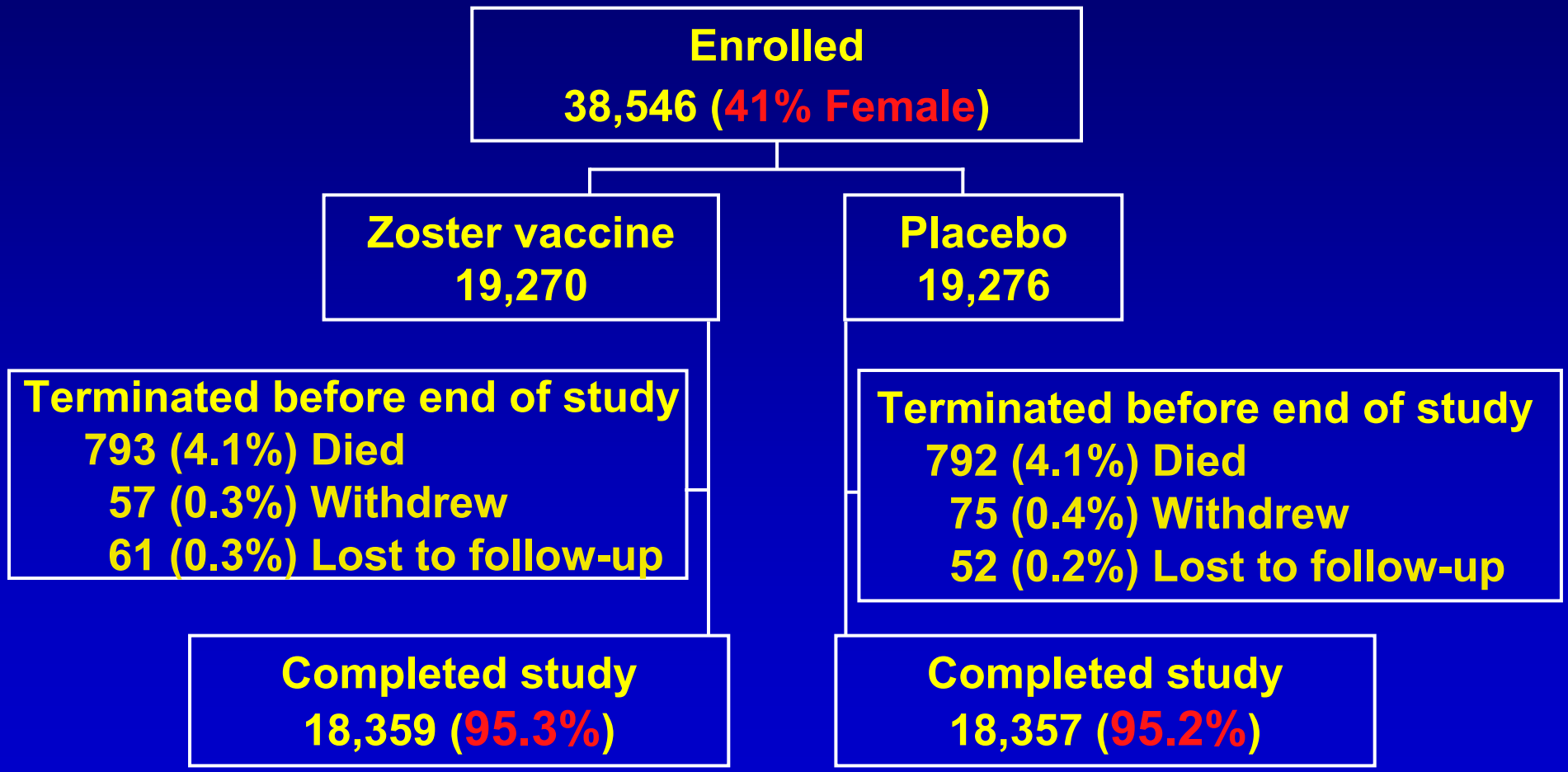
ORIGINAL ARTICLE

◄ Previous Volume 352:2271-2284 June 2, 2005 Number 22 Next ►

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., J.L. Silber, M.D., for the Shingles Prevention Study Group

The Shingles Prevention Study



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

Herpes Zoster Case Determination

Suspected Cases of HZ
1308*

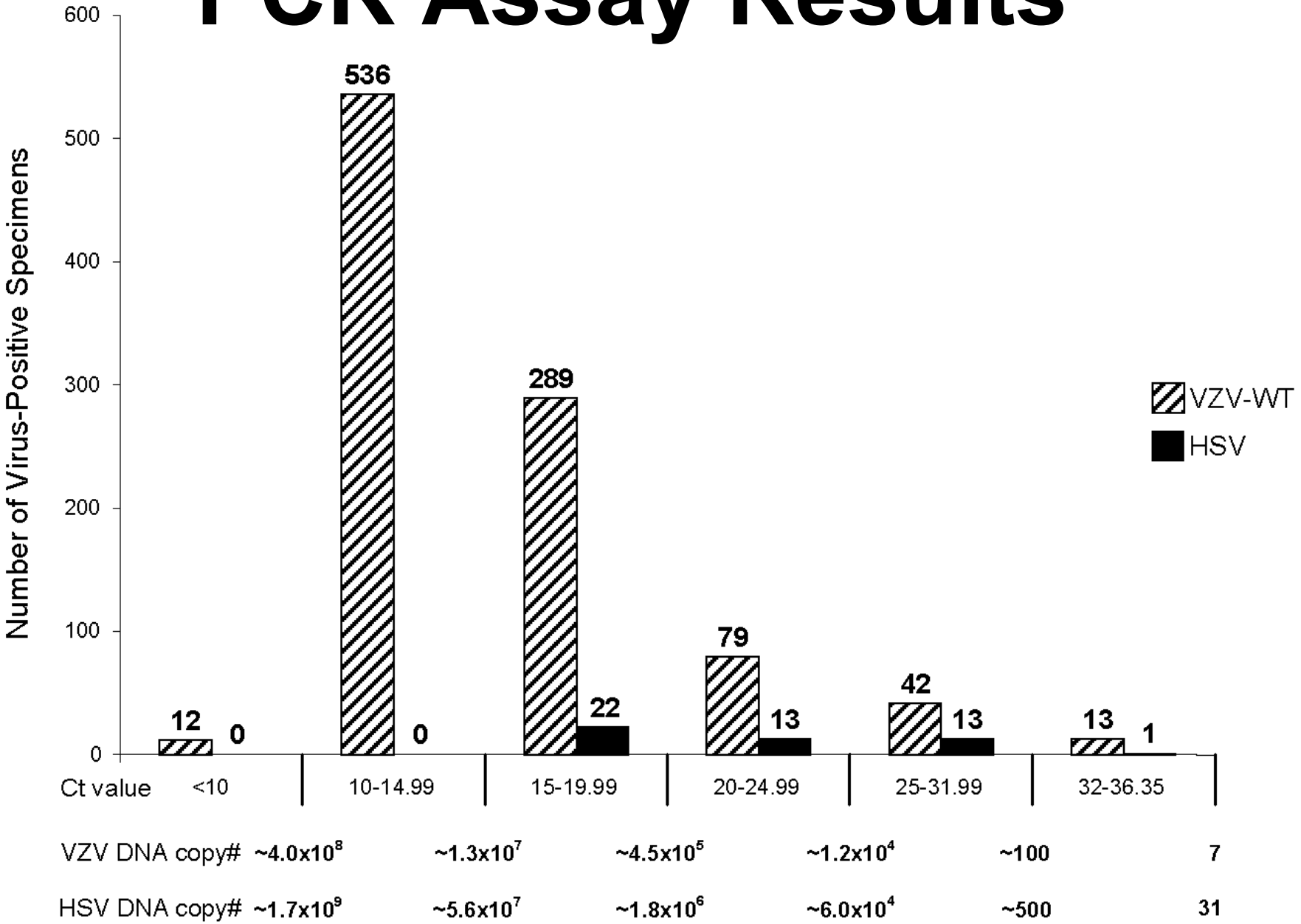
315 Confirmed Cases of HZ
294 (93.3%) VZV+ by PCR
2 (0.6%) VZV+ by local virus culture
19 (6.0%) HZ by CEC only

642 Confirmed Cases of HZ
600 (93.5%) VZV+ by PCR
8 (1.2%) VZV+ by local virus culture
34 (5.3%) HZ by CEC only

*Includes two PCR-positive, unrecognized cases
CEC = Clinical Evaluation Committee

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

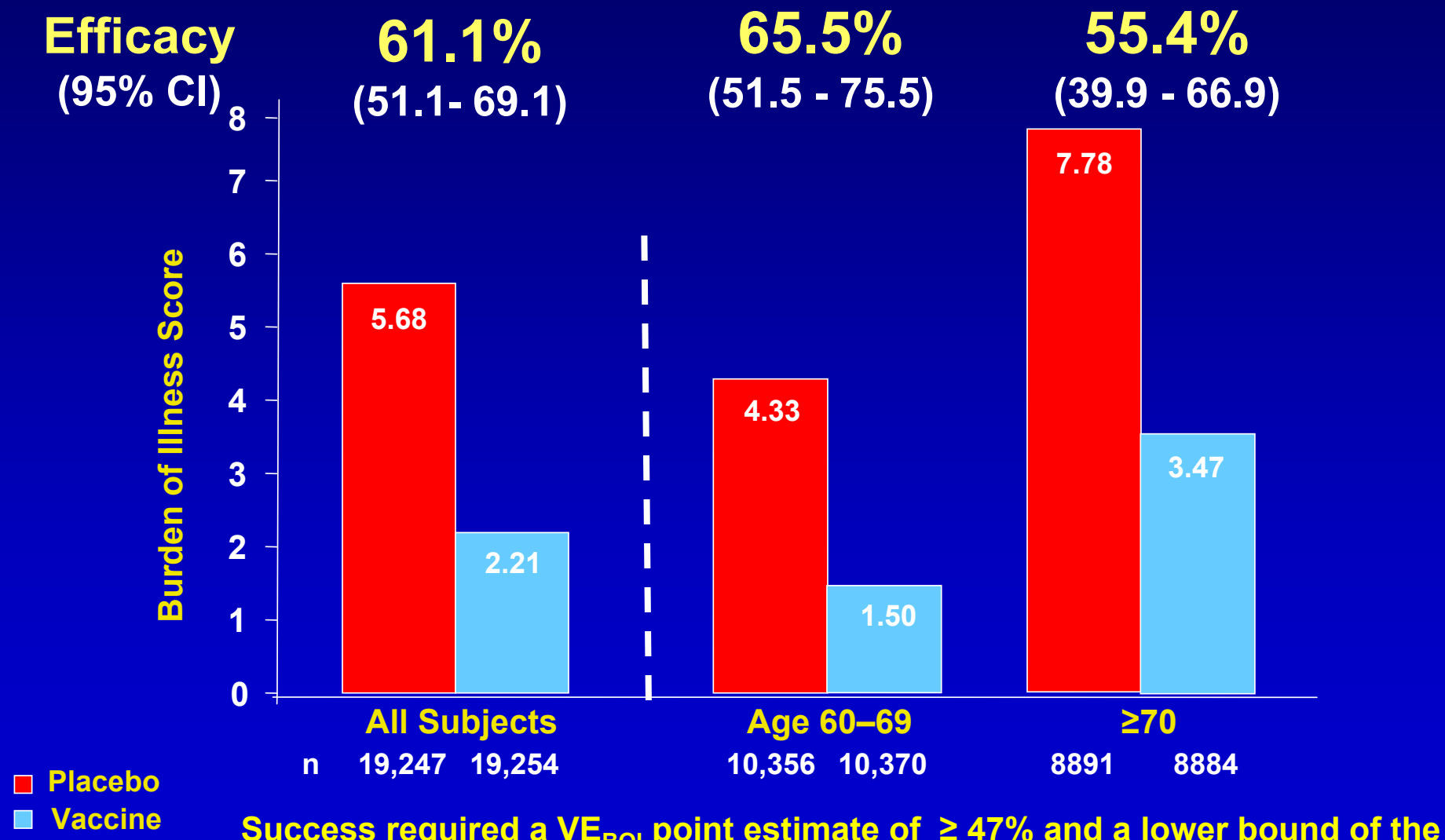
PCR Assay Results



CEC Diagnosis (# of Cases)	PCR Result (%*)		
Unanimous Yes (735) 707 with Adequate PCR specimen	VZV	683	(97%)
	HSV	2	(0.3%)
	Negative	22	(3%)
Non-Unanimous Yes (249) 204 with Adequate PCR specimen	VZV	161	(79%)
	HSV	12	(6%)
	Negative	31	(15%)
Indeterminate (127) 91 with Adequate PCR specimen	VZV	46	(51%)
	HSV	11	(12%)
	Negative	34	(37%)
Non-Unanimous No (162) 124 with Adequate PCR specimen	VZV	26	(21%)
	HSV	20	(16%)
	Negative	78	(63%)
Unanimous No (33) 28 with Adequate PCR specimen	VZV	0	(0%)
	HSV	1	(4%)
	Negative	27	(96%)

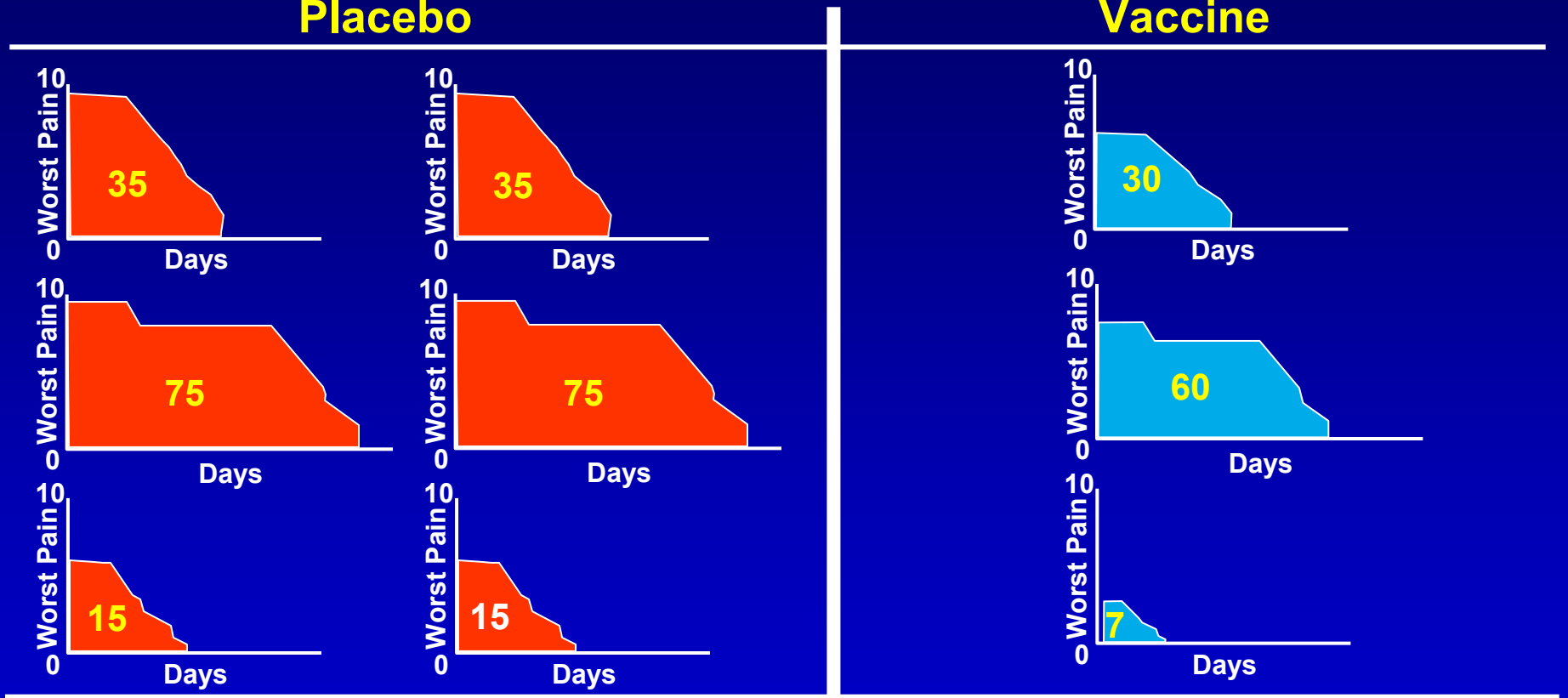
* % of cases with Adequate PCR Specimens

Vaccine Efficacy for the Herpes Zoster BOI

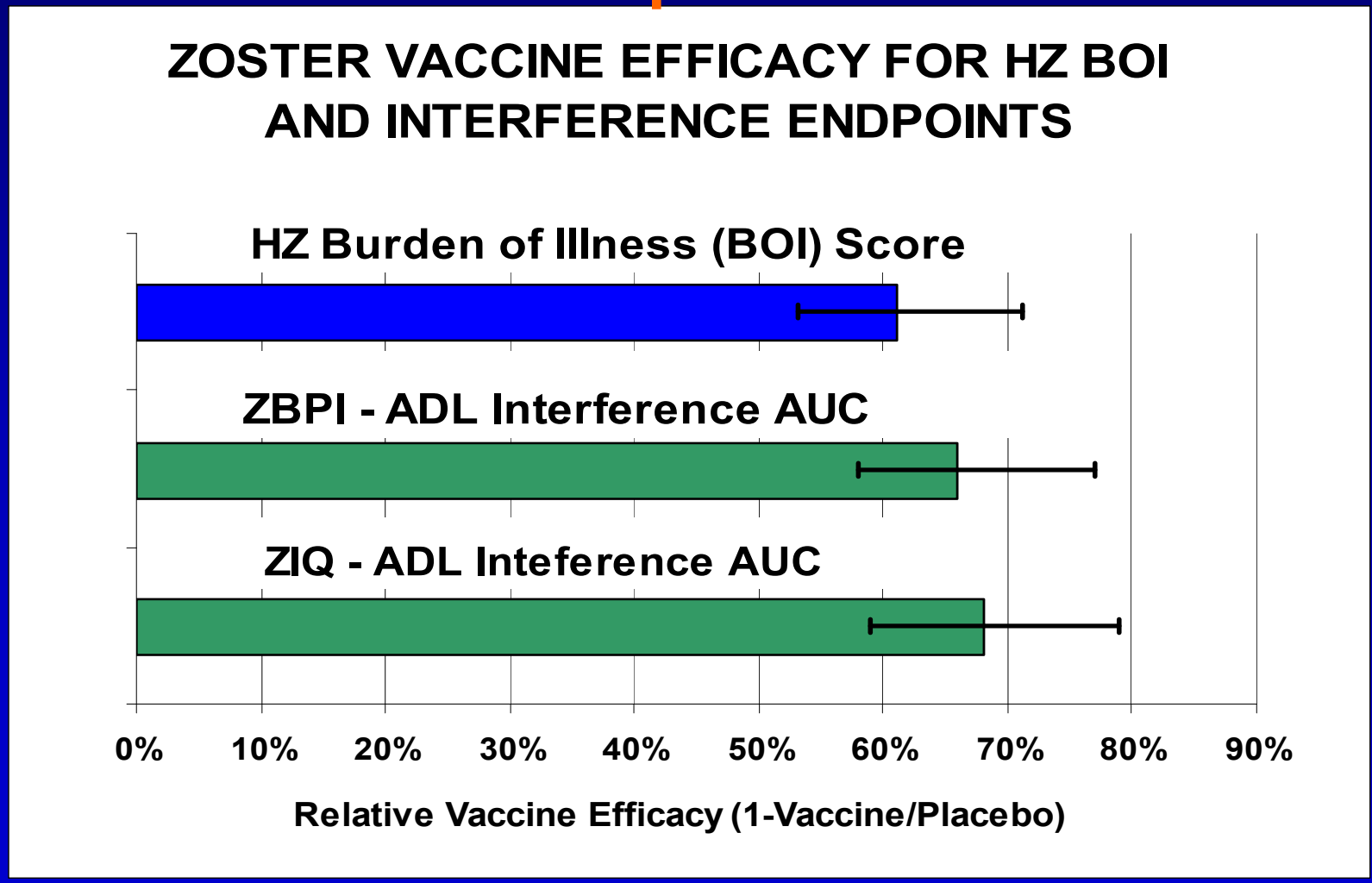


Success required a VE_{BOI} point estimate of ≥ 47% and a lower bound of the 95 percent confidence interval >25%

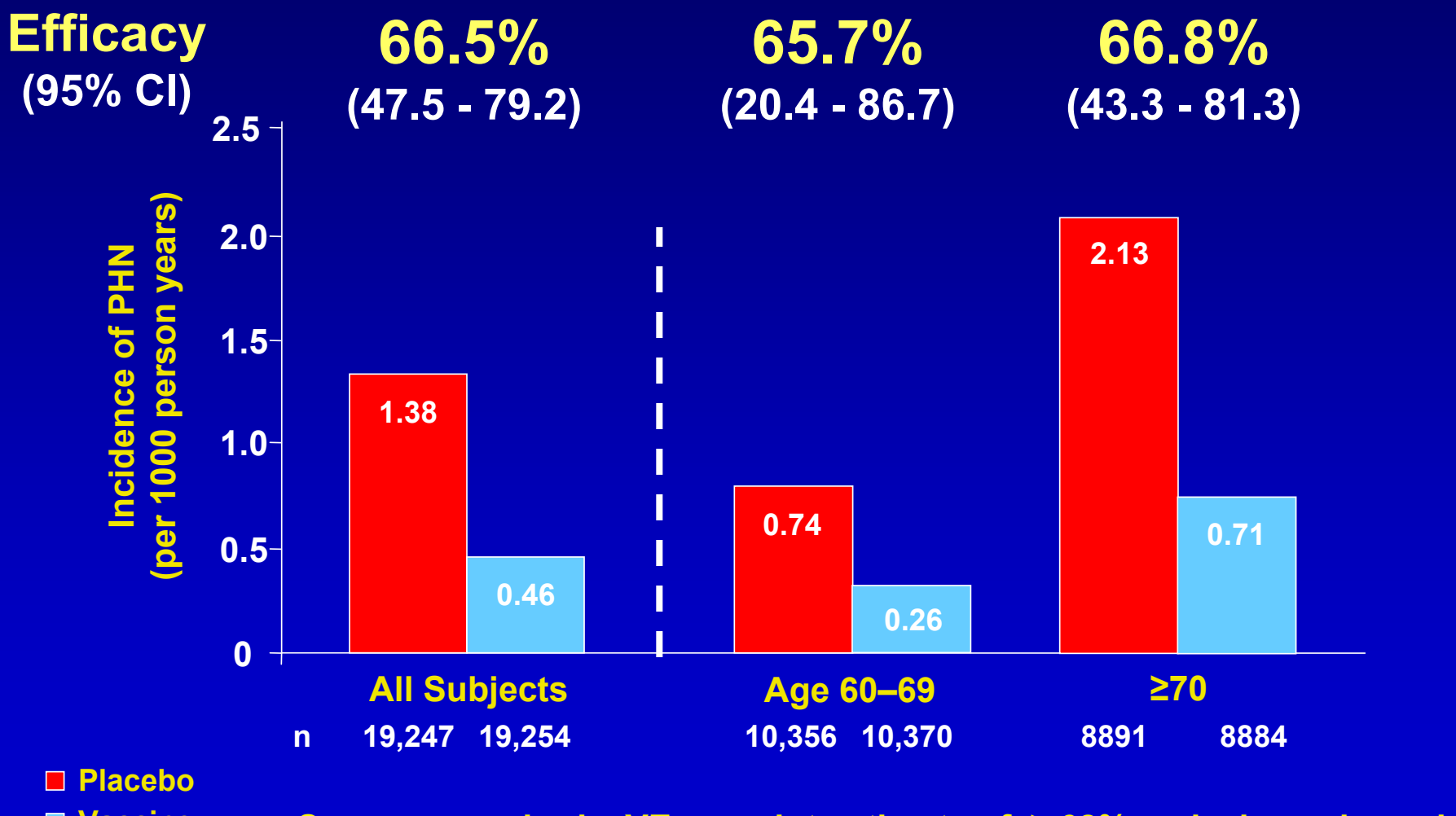
Reduction in HZ Incidence (51%) and HZ BOI (61%)



Zoster vaccine reduced HZ Pain Interference with ADL by ~66% (Schmader et al.), providing further evidence that the HZ BOI is a valid measure of the total adverse impact of HZ on a population of older persons



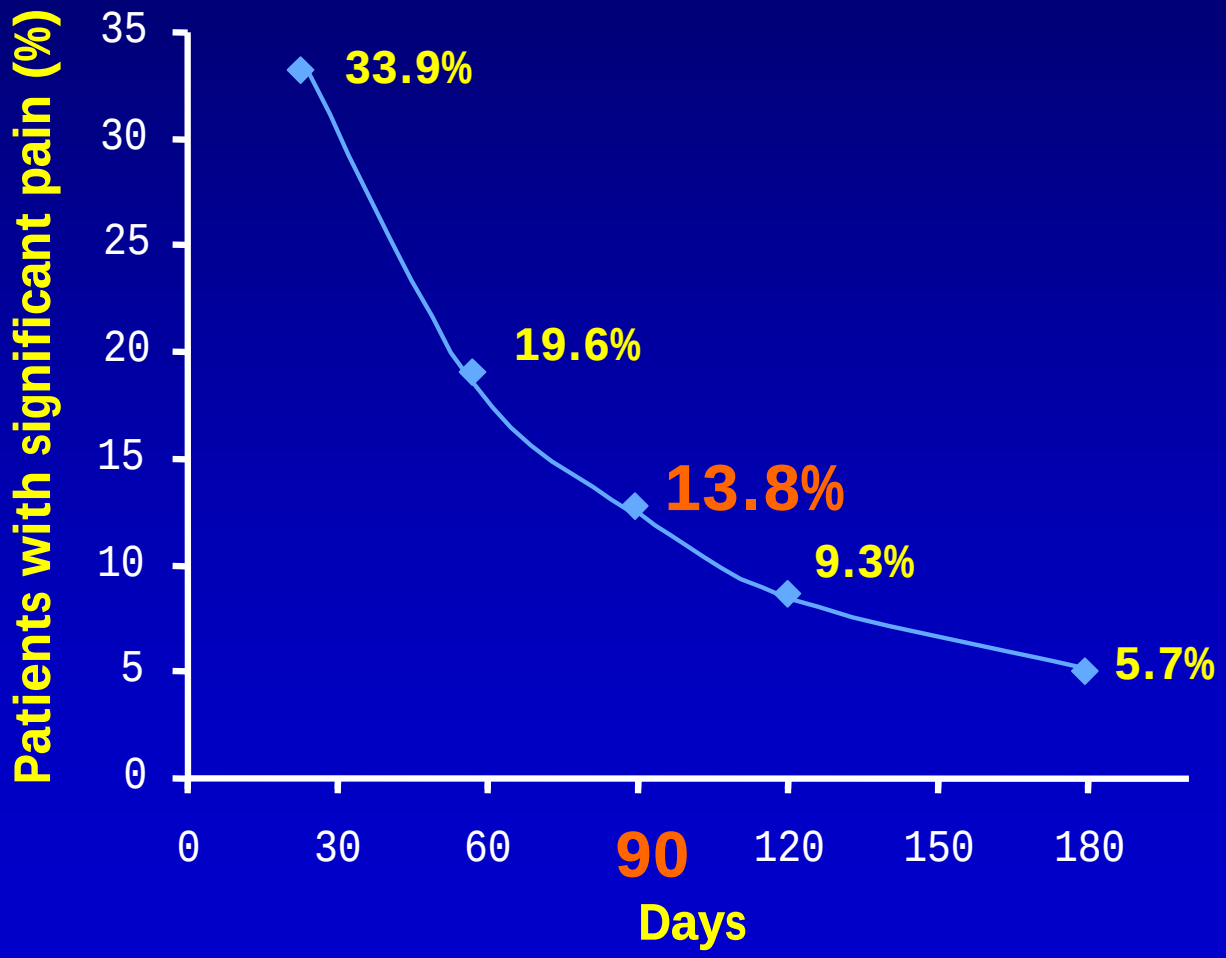
Vaccine Efficacy for the Incidence of PHN



Success required a VE_{PHN} point estimate of ≥ 62% and a lower bound of the 95 percent confidence interval >25%

Persistent Pain After Rash Healing (Postherpetic Neuralgia)

642 Placebo Recipients with Herpes Zoster



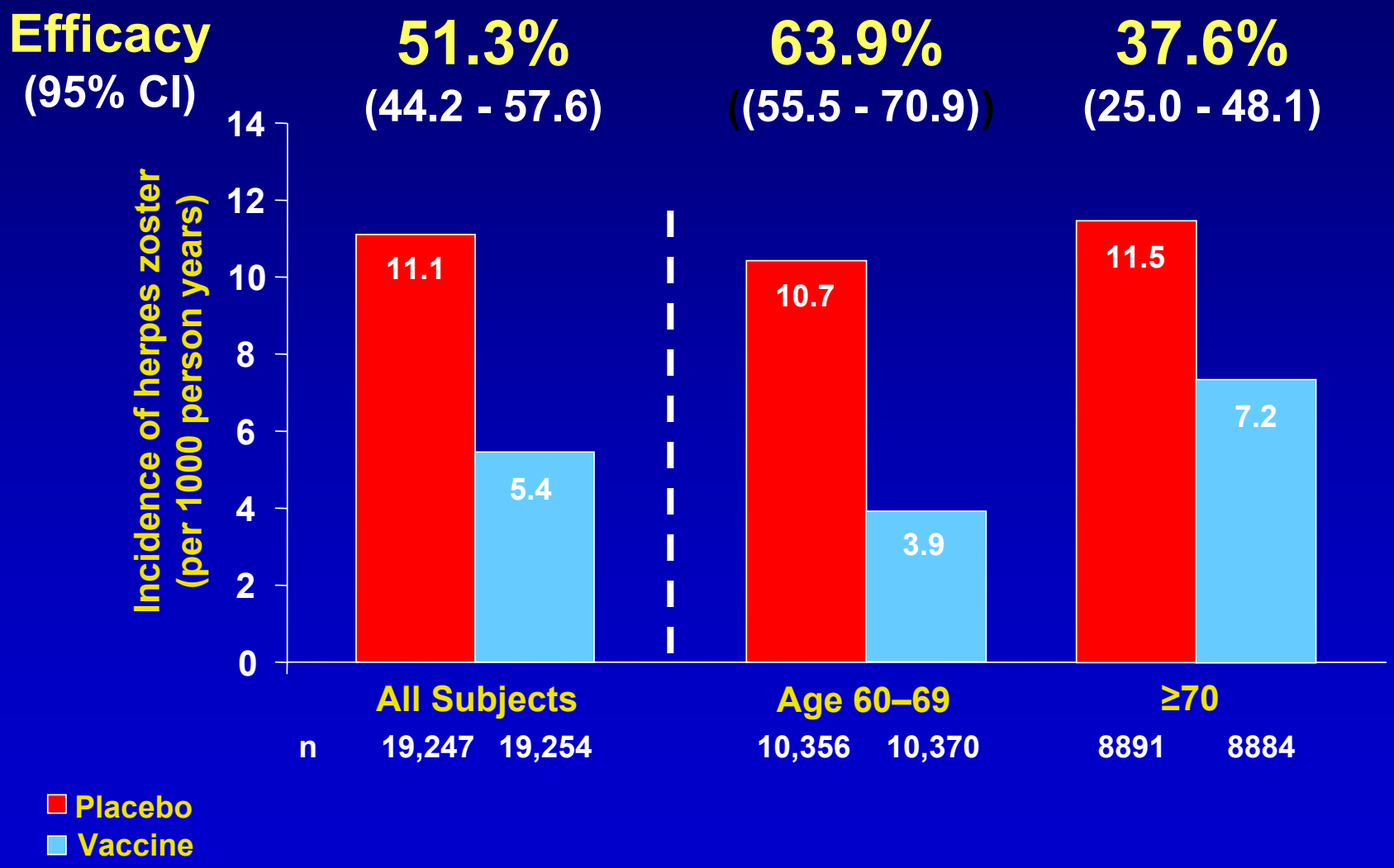
Oxman MN et al. *New Engl J Med.* 2005;352:2271-2285.

The Incidence of PHN was Reduced Even When Alternative Definitions of PHN Were Used

PHN Defined by Cutoff Day	Zoster Vaccine (N=19,254)		Placebo (N=19,247)		Vaccine Efficacy VE_{PHN} (95% CI)
	Evaluable Cases of HZ with PHN (n)	Incidence of PHN (Per 1000 Person-Years)[c]	Evaluable Cases of HZ with PHN (n)	Incidence of PHN (Per 1000 Person-Years)[c]	
30	81	1.39	196	3.39	58.9% (46.6, 68.7)
60	45	0.77	113	1.96	60.4% (43.6, 72.6)
90	27	0.46	80	1.38	66.5% (47.5, 79.2)
120	17	0.29	54	0.93	68.7% (45.2, 83.0)
180	9	0.16	33	0.57	72.9% (42.1, 88.6)

Success required a VE_{PHN} point estimate of $\geq$ 62% and a lower bound of the 95 percent confidence interval >25%

Vaccine Efficacy for the Incidence of Herpes Zoster



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

The Shingles Prevention Study Provides a Low Estimate of HZ Severity and of the Efficacy of Zoster Vaccine

- **All Study Subjects were seen as soon as possible after HZ Rash Onset and provided with State-of-the-Art treatment, including Famciclovir and pain management, without cost.**
  - **86-87 % of Subjects with HZ received Antiviral Treatment; 64-66% within 72 hours of rash onset**
  - **Average duration of opioid usage and average quantity of opioids used in Subjects with HZ were greater in the placebo group than in the vaccine group**

The Shingles Prevention Study SAFETY

The investigational zoster vaccine was well tolerated

Deaths and percent with ≥1 SAE were the same in the vaccine and placebo groups

Detailed Analysis shows no difference between the Zoster Vaccine and the Placebo Recipients in the number or distribution of Cardiovascular Severe Adverse Events

The Shingles Prevention Study SAFETY

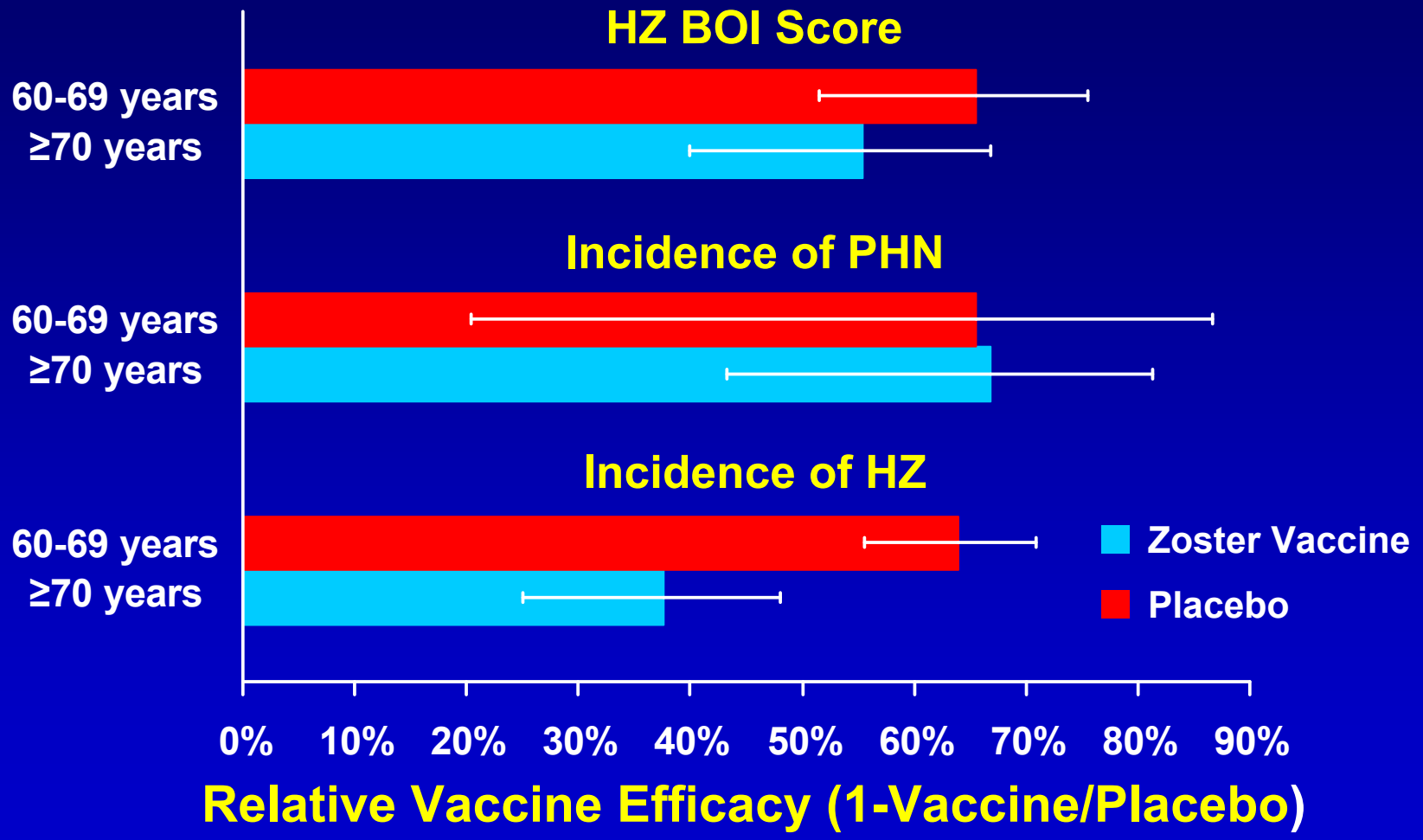
Zoster vaccine did not cause or induce shingles

- Shingles during the 30 days post vaccination
  - Placebo group → 18 cases
  - Vaccine group → 6 cases
- Vaccine virus DNA was not detected in any of 919 PCR-confirmed cases of shingles

CRITICAL QUESTION

What Was the Influence of the Age of the Subjects on the Results?

Zoster Vaccine Efficacy



Oxman M et al. Presented at the 43rd Annual Meeting of the Infectious Diseases Society of America; October, 2005; San Francisco, CA.

Summary

- Zoster vaccine maintains its efficacy regardless of the age of the subject
  - The effect in "younger" subjects is mediated mostly by preventing HZ
  - The effect in "older" subjects is mediated mostly by attenuating HZ

Current Status

- The Shingles Prevention Study provided zoster vaccine without charge to ~14,000 placebo recipients, including 380 who had documented herpes zoster during the Study

- A Long-Term Persistence Substudy has been initiated to assess the durability of zoster vaccine efficacy

Zoster Vaccine: Where Do We Stand?

- On May 25, 2006, based upon the results of VA Cooperative Study #403: The Shingles Prevention Study, the FDA licensed zoster vaccine (ZOSTAVAX™, Merck) for the prevention of herpes zoster in immunocompetent adults aged ≥60 years
- On October 25, 2006, the ACIP made a provisional policy recommendation to administer a single dose of zoster vaccine to adults aged ≥60 years for the prevention of herpes zoster and postherpetic neuralgia — whether or not they report a prior episode of herpes zoster (MMWR June 6, 2008)
- This recommendation has now been incorporated into the CDC's Adult Immunization Schedule

Adult Vaccine Schedule

Vaccine	Specifications
Tetanus, diphtheria, pertussis (Td/Tdap)	1 dose Td booster every 10 years (substitute Tdap for Td if 60-64 years old)
Zoster**	**1 dose ≥60 years of age**
Influenza	1 dose annually
Pneumococcal polysaccharide	1 dose ≥65 years of age

Recommended for all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack of documentation of vaccination or no evidence of prior infection).

CDC. Recommended Adult Immunization Schedule United States, October 2006 – September 2007. Available online at http://www.cdc.gov/nip/recs/adult-schedule.htm. Accessed January 25, 2007.
CDC. Adult Immunization 2006 Satellite Broadcast. December 7, 2006. Available online at http://www.cdc.gov/nip/ed/AdultUpdate2006/adultim06_zoster.ppt. Accessed January 25, 2007.

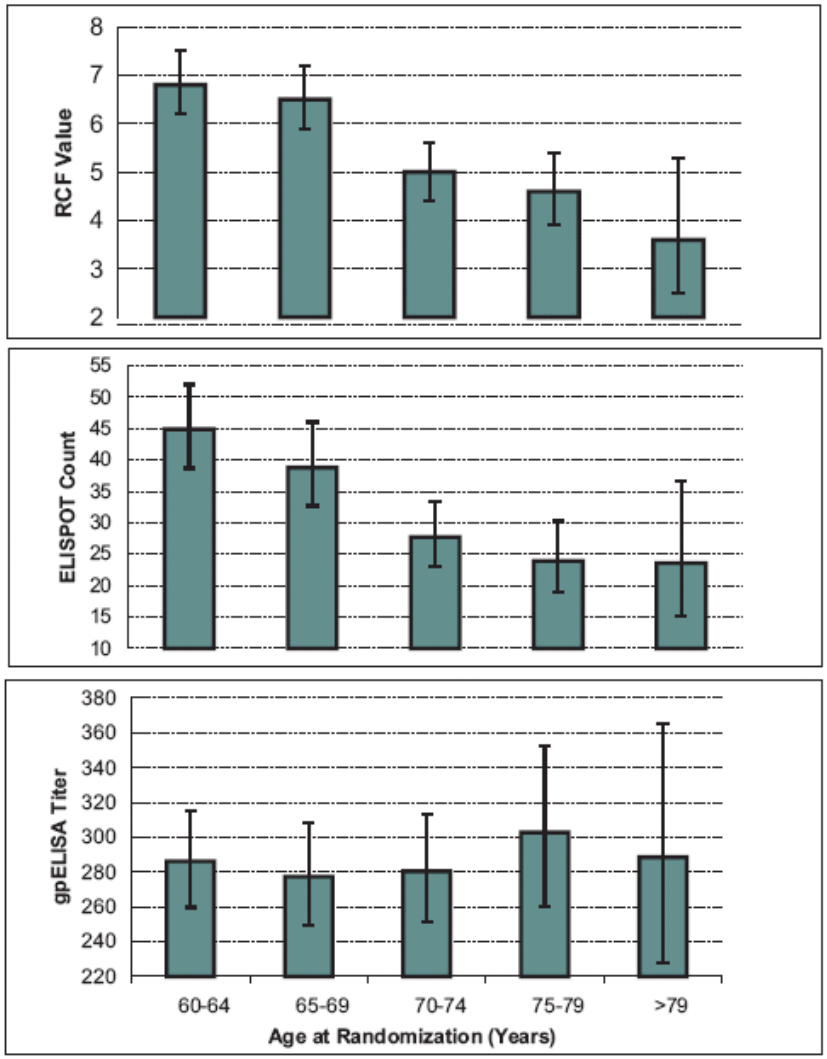
Results of Vaccinating All Persons ≥60 Years of Age

	Herpes Zoster	PHN (>90 d)
Cases per year without vaccine*	556,200	69,600
Cases eliminated by vaccination†	283,700	46,400
Remaining cases	272,500	23,200

*Based on incidence data from Oxman MN et al. *N Engl J Med*. 2005;352:2271-2284.
†Calculated reduction in number of cases based on Zoster Vaccine efficacy data from Oxman MN et al. *N Engl J Med*. 2005;352:2271-2284.

Immunology Substudy
Baseline by Age

Figure 3. VZV- Specific Immune Responses at Baseline by Age



VZV-CMI declines with increasing age

Begins in early adulthood and continues with increasing age

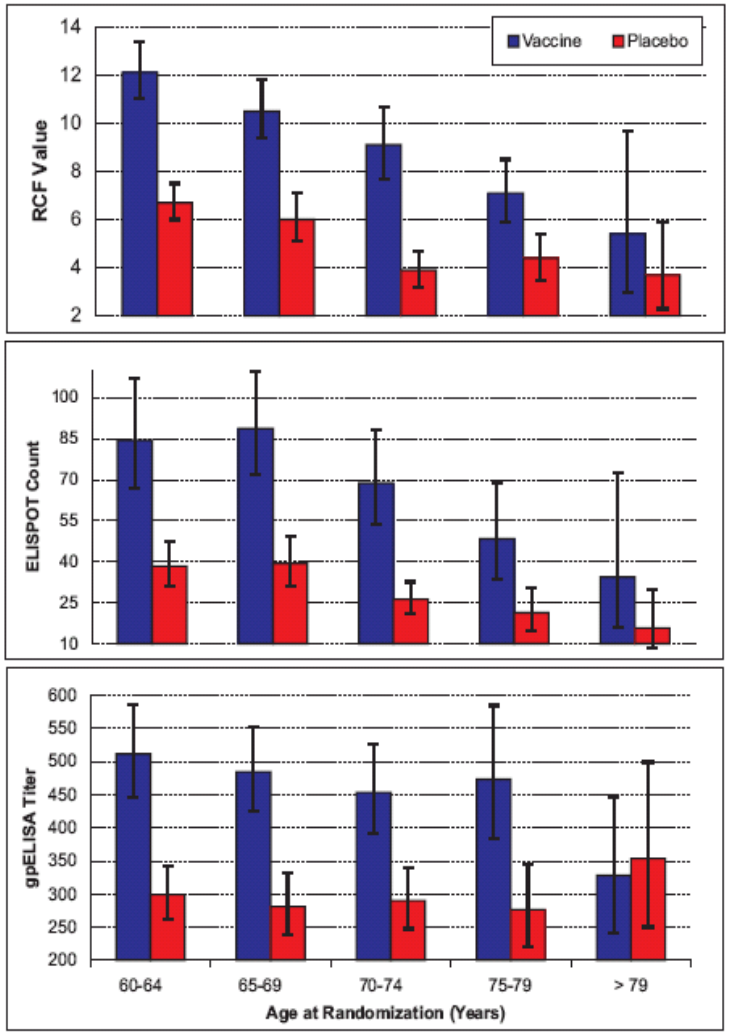
VZV antibody does not decline with age

Levin, M., et al. JID 2008:197 825-835

Immunology Substudy

VZV-Specific Immune Responses at 6 weeks post-vaccination

Figure 4. VZV- Specific Immune Responses at 6-weeks after Vaccination by Age



- At 6 weeks after vaccination, immune responses in vaccine recipients measured by all three assays were significantly increased, compared with placebo

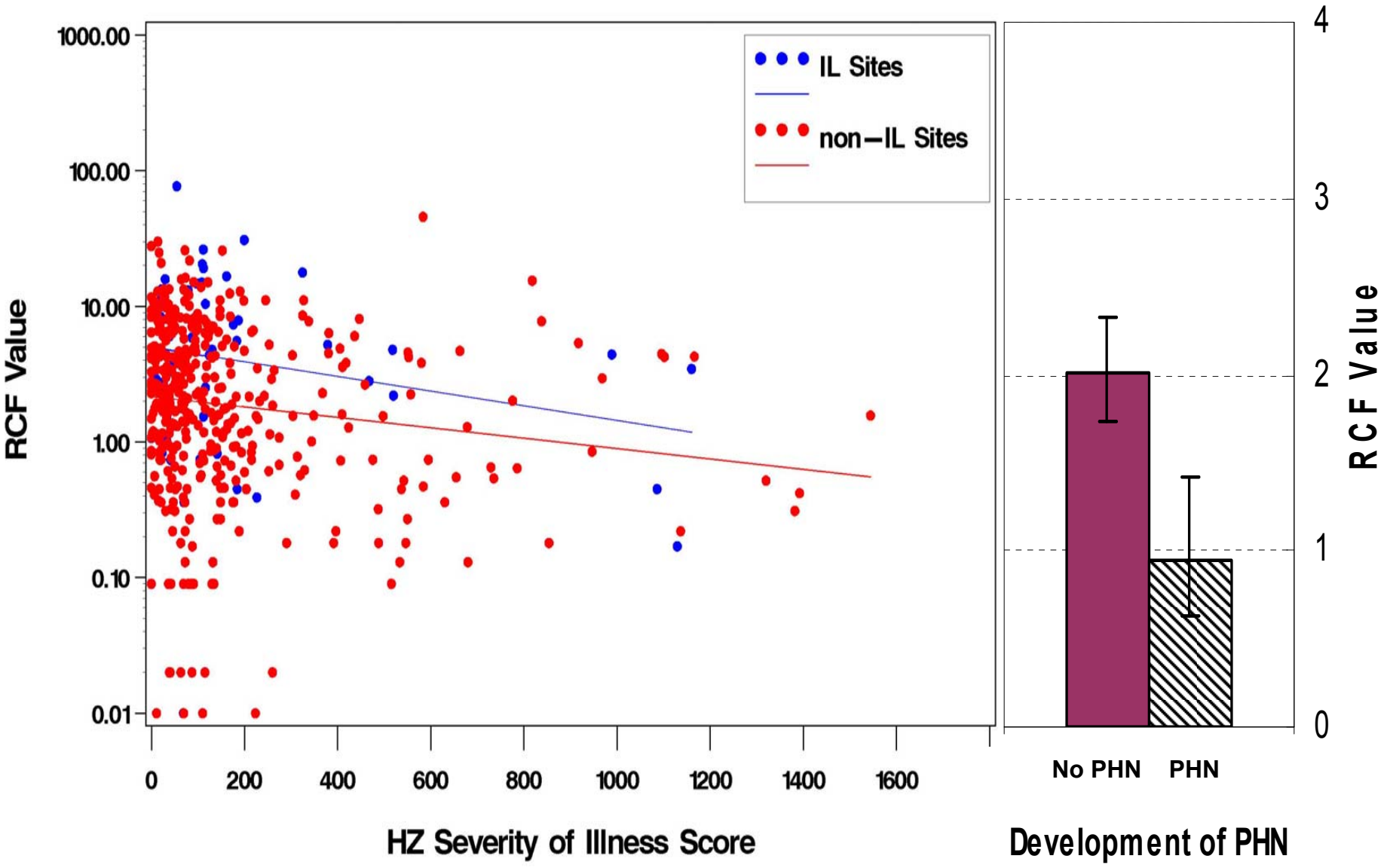
- The magnitude of the VZV CMI response to the vaccine was greater in subjects 60 - 69 years of age than in those ≥70, but little difference in Antibody response

Levin, M., et al. JID 2008: 197: 825-835

- **Higher levels of cell-mediated immunity to VZV correlate with reduced severity of disease and with a lower incidence of PHN**

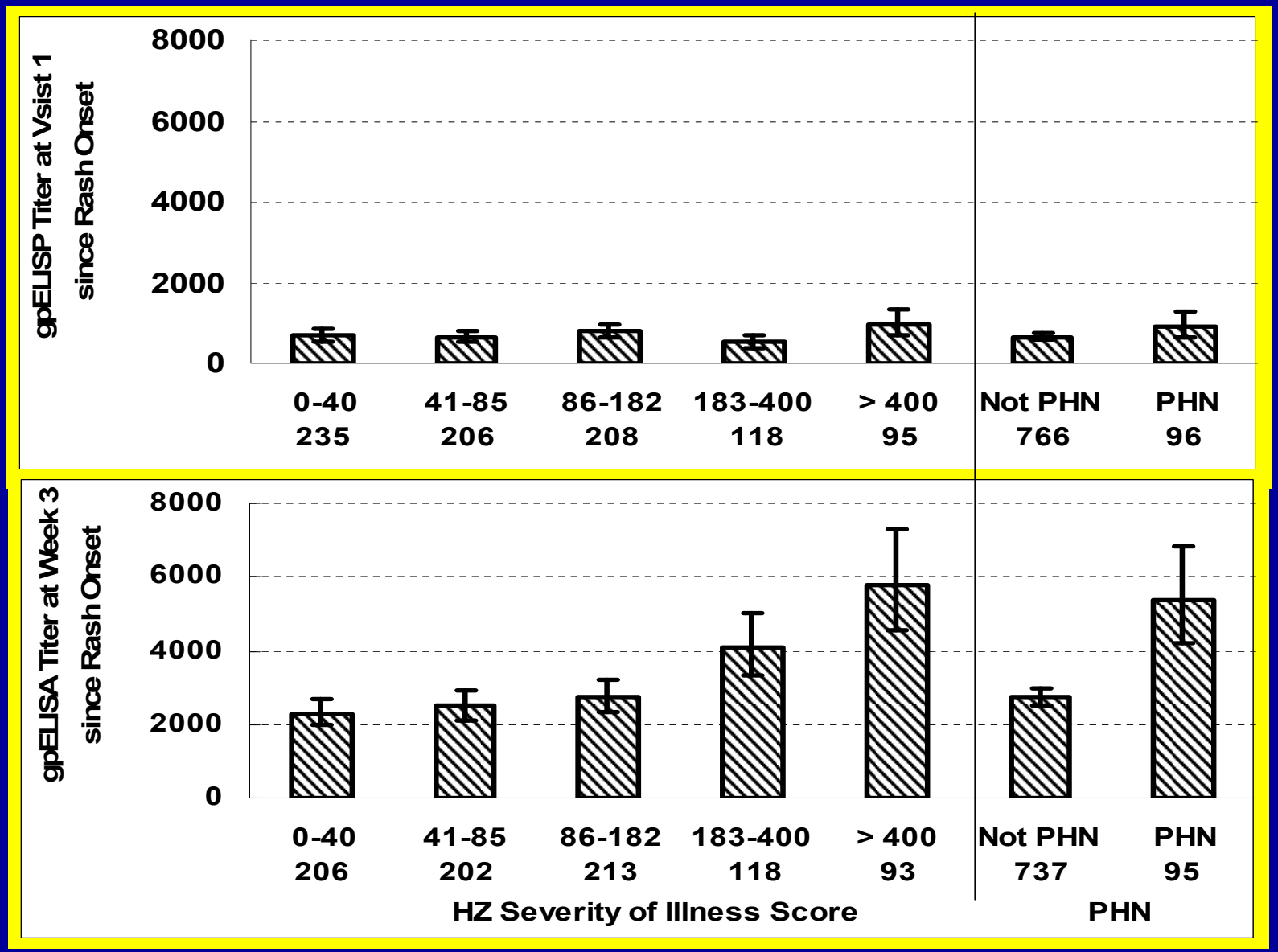
- **Higher levels of antibody to VZV do not**

RCF at First Visit vs. *HZ Severity of Illness* and Development of PHN



Weinberg A, et al. JID 2009, In Press

CMI Substudy: Increased Antibody to VZV Correlated with Increased Herpes Zoster Severity of Illness and PHN

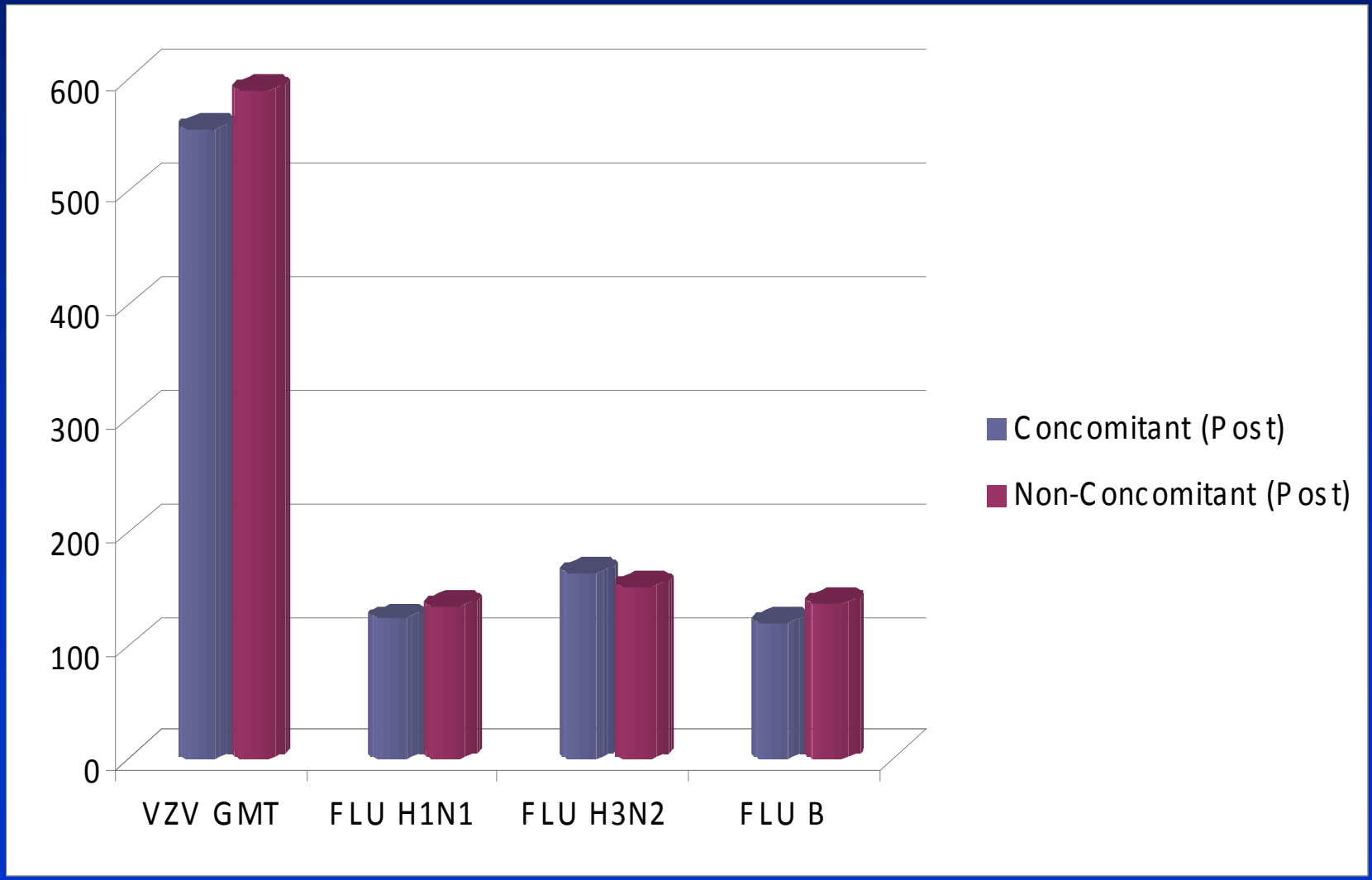


Unanswered Questions

- the rationale for the ACIP recommendation to administer zoster vaccine to persons with a history of HZ
- the risk that recipients of zoster vaccine will transmit vaccine virus to susceptible contacts
- safety and efficacy in persons ≥80 years of age
- the potential use of zoster vaccine in persons <60 years of age
- the duration of zoster vaccine efficacy (? booster dose)
- the simultaneous administration of zoster vaccine and other vaccines recommended for adults, such as influenza vaccine
- the potential use of zoster vaccine in immunocompromised persons
- The impact of childhood Varicella Vaccination on the incidence and severity of Herpes Zoster in adults
- the Cold Chain and Medicare Part D

Antibody Response to ZOSTAVAX™ plus INFLUENZA VACCINE

(Kerzner et al. *JAGS* 55:1499, 2007)



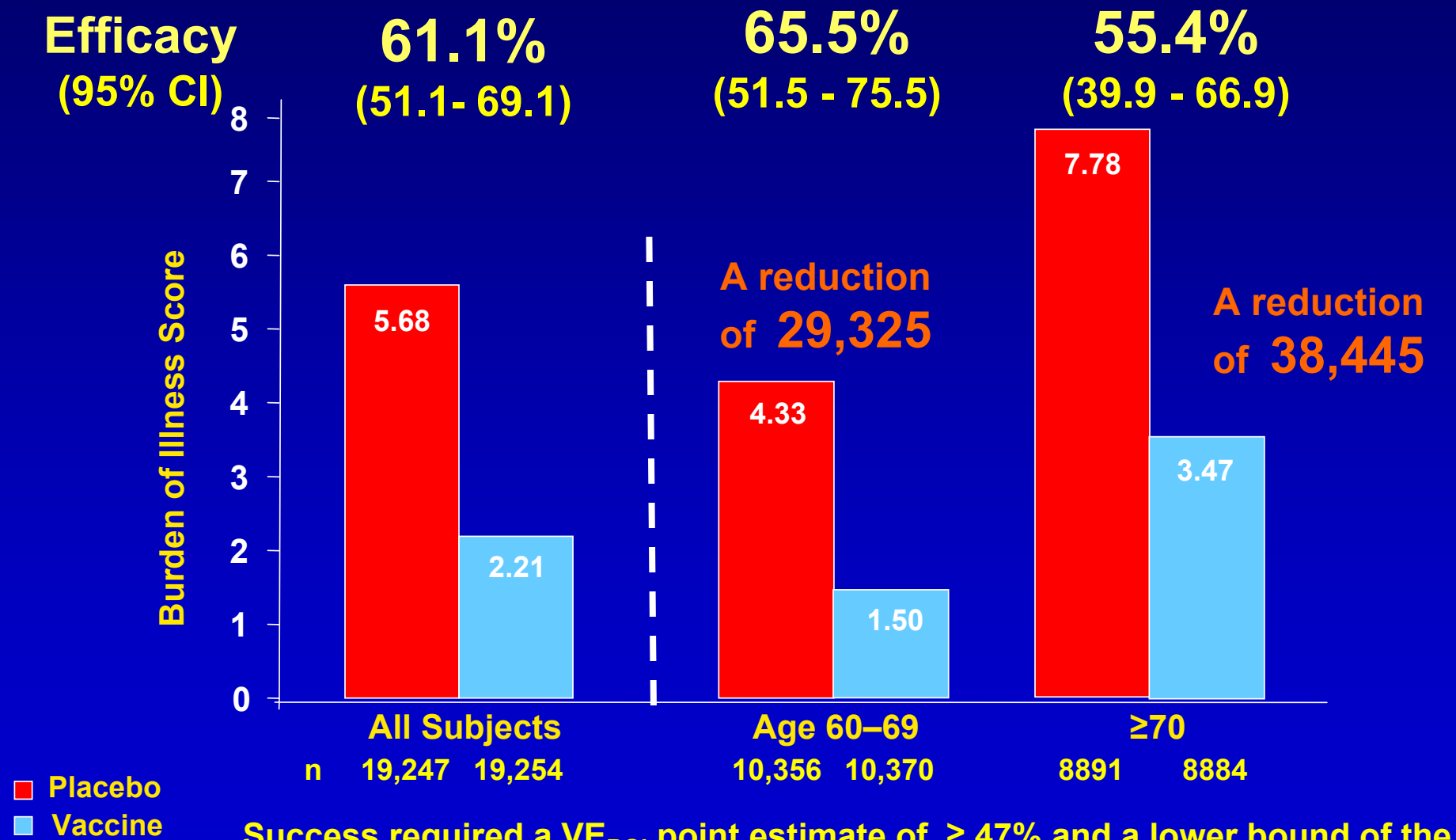
Antibody Response to Zostavax + Pneumovax

(MacIntyre CR, et al. Poater presented at the 2008 ICAAC-IDSA Meeting)

Endpoint	Concomitant Group (N=235)			Non-Concomitant Group (N=236)		
	n	Response	95% CI	n	Response	95% CI
						VZV
GMT Week 4	217	371.6	(328.7, 420.0)	225	448.5	(400.3, 502.4)
GMFR	217	**1.9**	(1.7, 2.1)§	222	**3.1**	(2.8, 3.5)
			PnPs Serotype 3			
GMT Week 4	219	1.1	(1.0, 1.2)	228	1.2	(1.1, 1.4)
GMFR	219	**2.1**	(1.9, 2.4)	227	**2.3**	(2.1, 2.5)
			PnPs Serotype 14			
GMT Week 4	219	25.7	(21.8, 30.3)	228	26.5	(22.9, 30.8)
GMFR	219	**3.9**	(3.4, 4.5)	227	**4.3**	(3.7, 5.0)
			PnPs Serotype 19A			
GMT Week 4	219	10.5	(8.7, 12.7)	228	10.5	(8.7, 12.6)
GMFR	219	**5.3**	(4.6, 6.1)	227	**5.1**	(4.4, 6.0)
			PnPs Serotype 22F			
GMT Week 4	219	2.5	(2.1, 3.0)	228	2.8	(2.3, 3.3)
GMFR	219	**7.5**	(6.3, 8.8)	227	**9.6**	(8.2, 11.2)

The Concept of Relative vs. Absolute Benefit

Vaccine Efficacy for the Herpes Zoster BOI



Success required a VE_{BOI} point estimate of ≥ 47% and a lower bound of the 95 percent confidence interval >25%

Relative vs. Absolute Benefit

- Frequency and Severity of HZ and PHN increase with increasing age
- Thus even if vaccine efficacy is reduced in persons ≥80 years of age, the absolute benefit may be as great or greater than in persons 60-69 years of age
- For example, a 40% reduction in a HZ Severity of Illness Score of 800 (=320) is greater than a 60% reduction in a HZ Severity of Illness Score of 400 (=240)