

Herpes Zoster & Postherpetic Neuralgia

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- Is there a need?
- Will the need change?
- Does vaccination satisfy the need?
- Will the public seek/want it?
- Is it cost effective?

- *At least the vaccine will not encourage sexual promiscuity!!*

Topics

- The varicella zoster virus
- Primary & secondary infection
- Epidemiology & anticipated change
- VZV immune mechanisms
- Cost of HZ and PHN
- PHN – prediction, mechanisms & management
- Vaccination against HZ
- Cost effectiveness of HZ vaccine

Varicella Zoster Virus (VZV)

- Primary infection
 - Varicella
- Persistence with clinical latency
- Reactivation
 - Herpes zoster



Diagnosis of HZ

- Clinical diagnosis
 - Up to 20% error rate
 - Most common confusion – HSV
(cold sores, genital herpes, MI, cholecystitis)
- Laboratory diagnosis
 - Usually unnecessary
 - PCR
 - Culture



HZ & PHN – the problems ...

- HZ is common with greater incidence in older adults and immunocompromised individuals:
~3% hospitalized
- PHN is the most common complication of HZ
Other, serious, complications are more rare
- HZ & PHN are costly to the individual and society
- Until now no preventive strategy for HZ

Dworkin RH, Johnson RW., Breuer J et al. Management of herpes zoster. CID 2007;44(Suppl 1);S1-S25

Who gets Herpes Zoster ?

- Normal older adults
 - Immunesenescence

- Immunocompromised individuals
 - Malignancy & its treatment
 - Lymphoma
 - Chemotherapy, radiotherapy

 - Immunocompromising disease
 - HIV

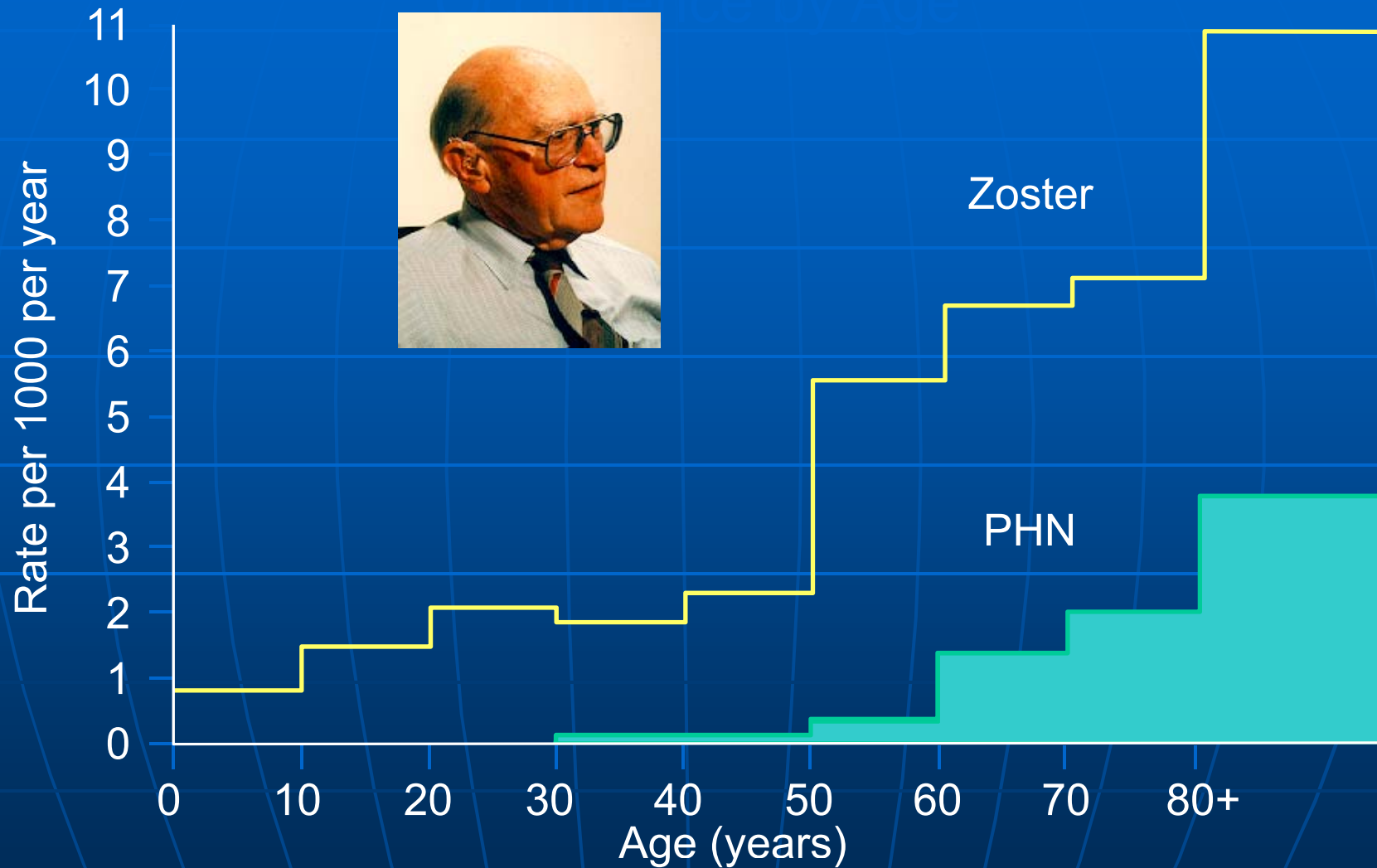
 - Therapeutic immune suppression
 - Organ transplant
 - Steroids etc.

- Normal children and younger adults

Dworkin RH, Johnson RW., Breuer J et al. Management of herpes zoster. CID
2007;44(Suppl 1);S1-S25

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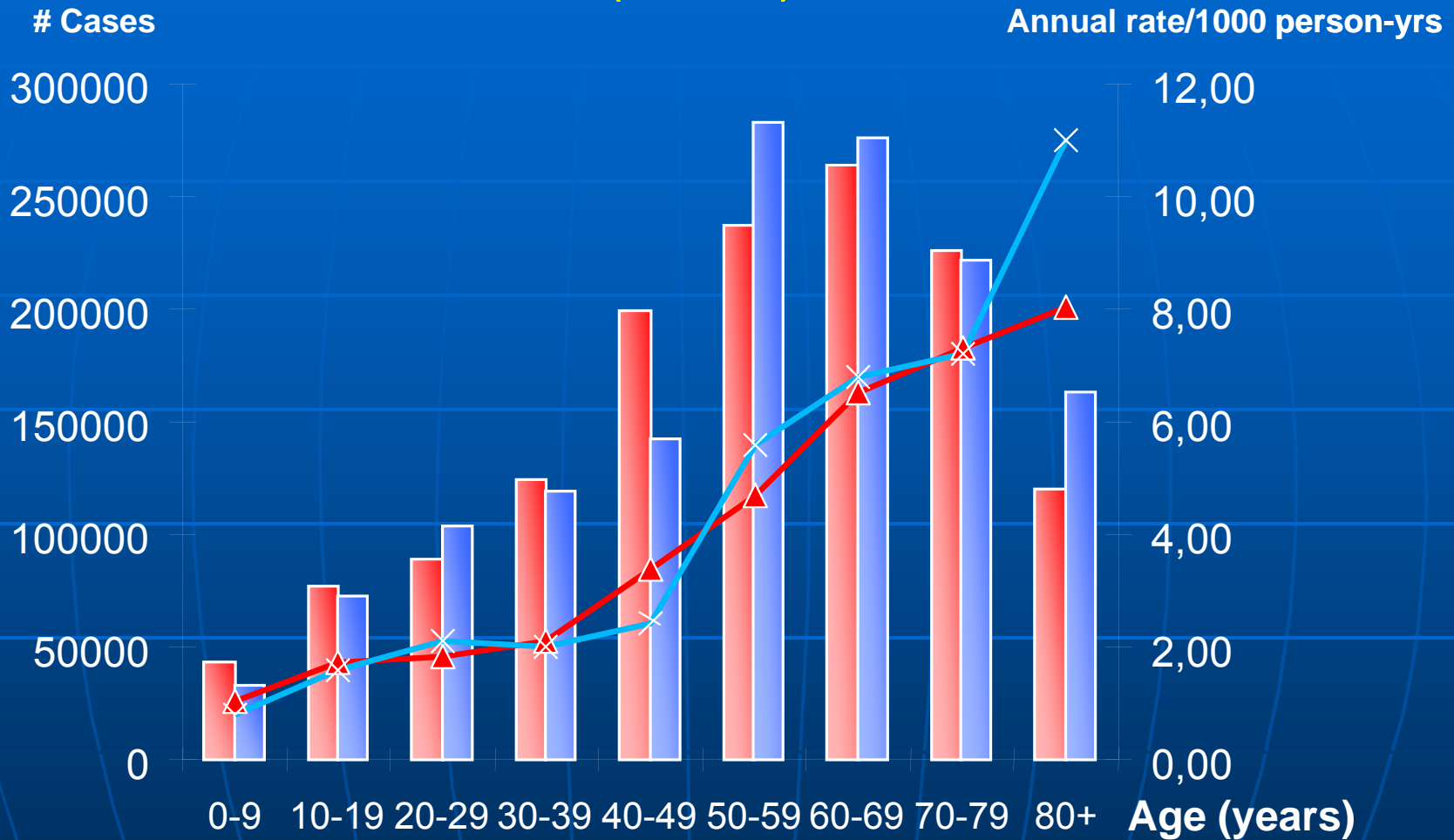
Age related incidence of HZ and PHN



Hope-Simpson RE. *J R Coll Gen Pract.* 1975; 25:571-575

Anney, July 2008

Incidence and absolute numbers of Herpes Zoster (EU 25)



EU cases (The NLs incidence, 2006*)

EU cases (UK incidence, 1975)**

The Netherlands 2006

UK 1975

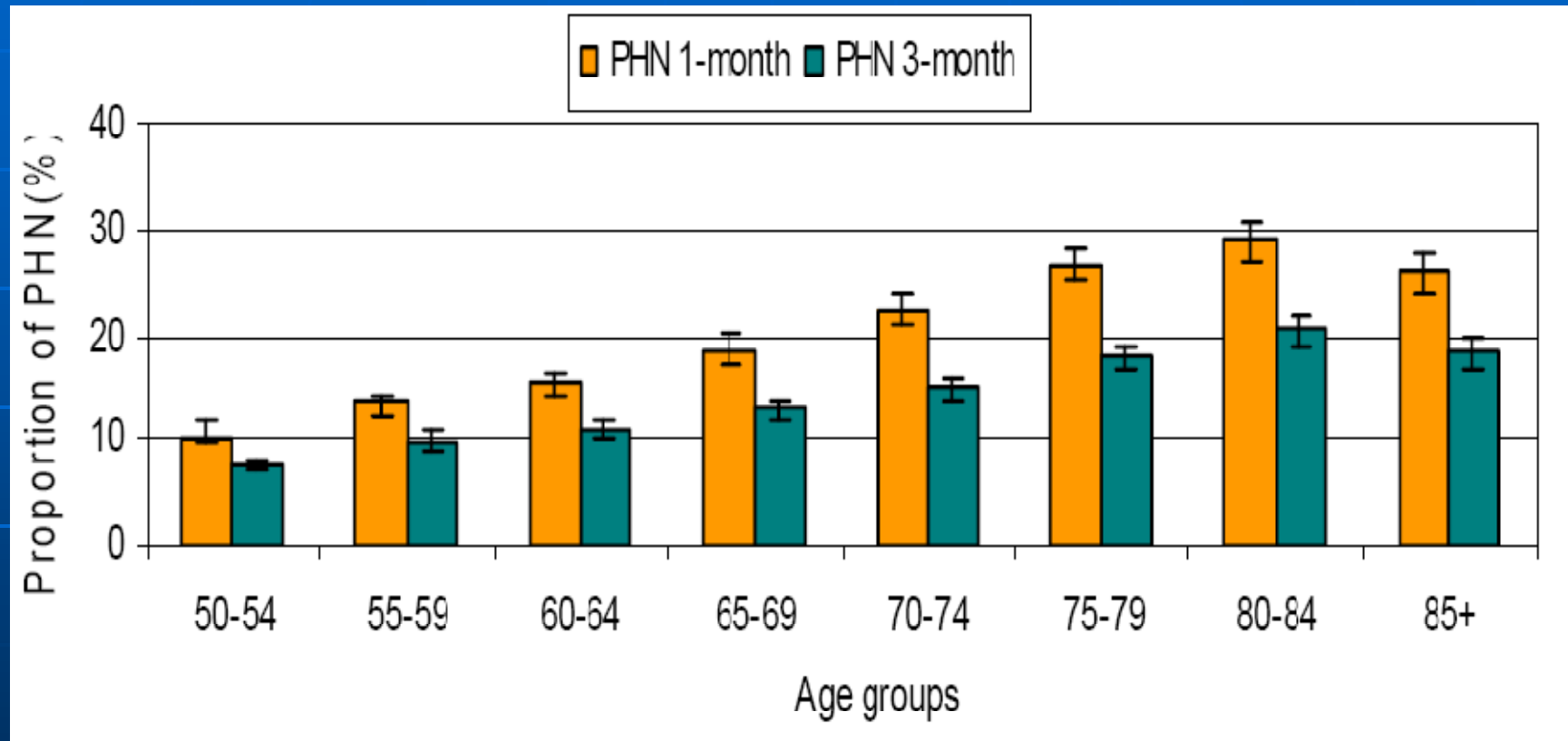
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* de Melker et al. The epidemiology of varicella and herpes zoster in The Netherlands: Implication for Varicella Zoster Virus vaccination. Vaccine, 2006, in press

** Hope-Simpson R.E. The Nature of Herpes Zoster: A Long-term Study and a New Hypothesis. Proc R Soc Med, 58:9-20, 1965

Proportion of Patients with PHN by age group

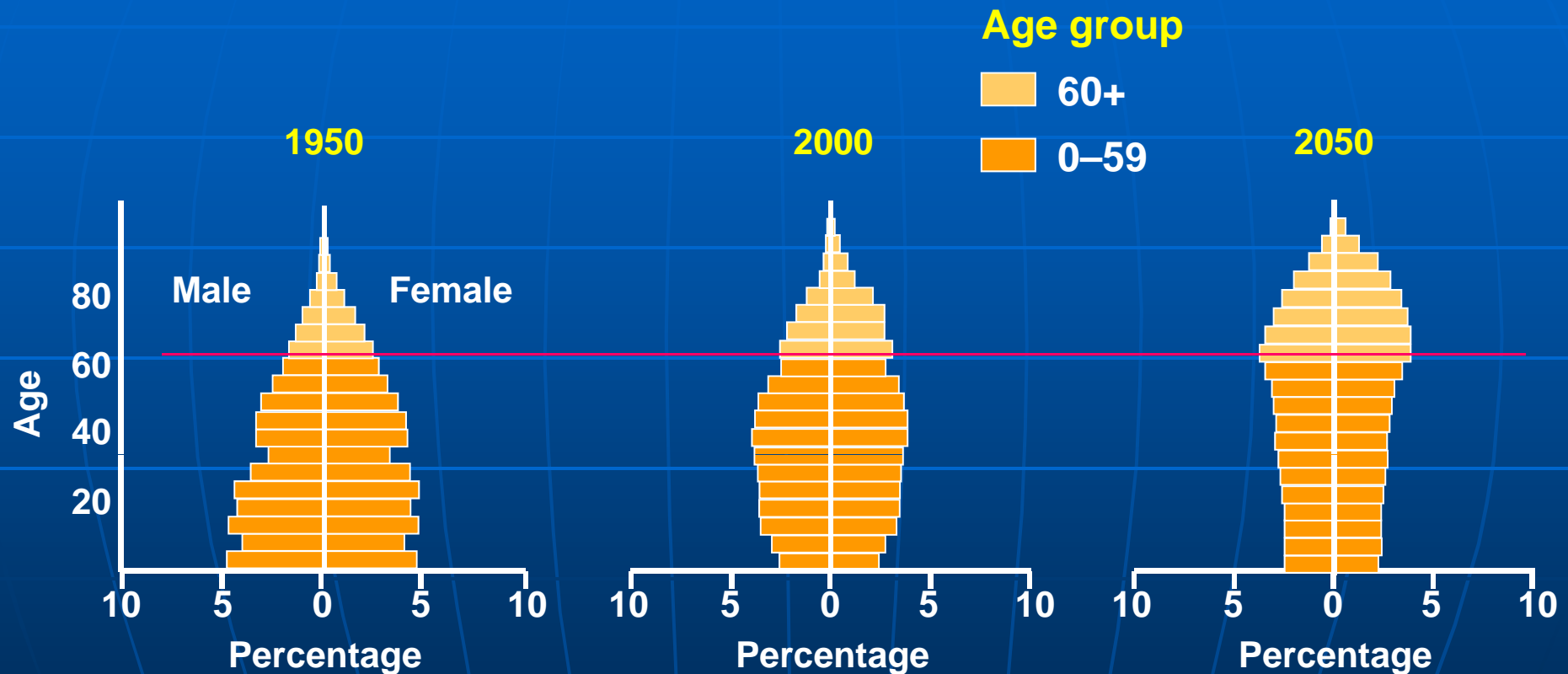


Epidemiology and management costs of Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN) in the UK. Remy et al

The future ...

- Population demography
- Disease and its treatment
- Antiviral drugs
- Varicella vaccine
- Herpes zoster vaccine

European population distribution by age: population pyramids



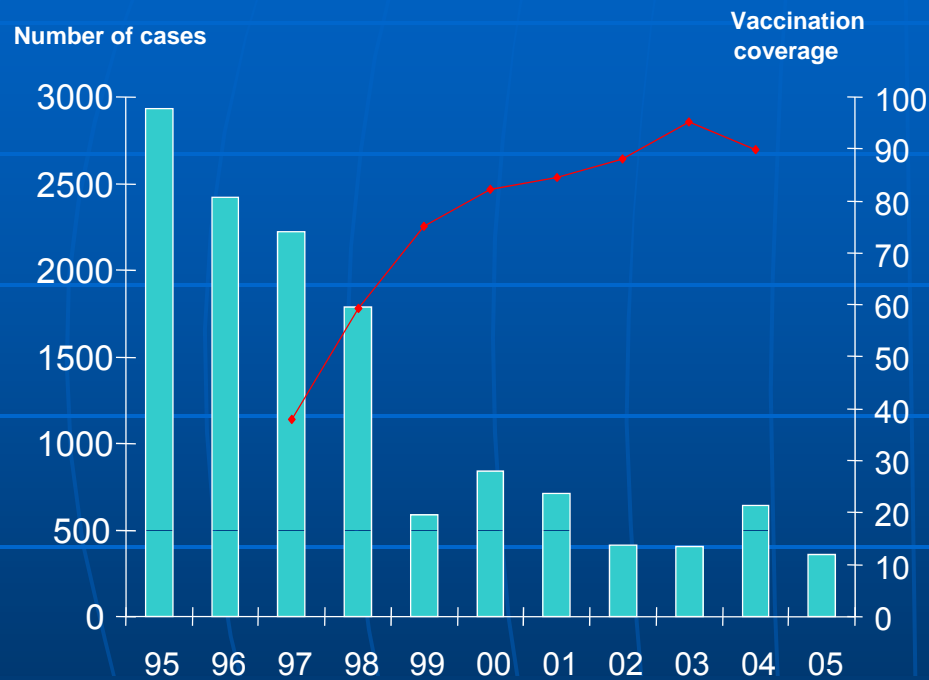
Source: UN World Population Ageing: 1950-2050

Facts about ageing

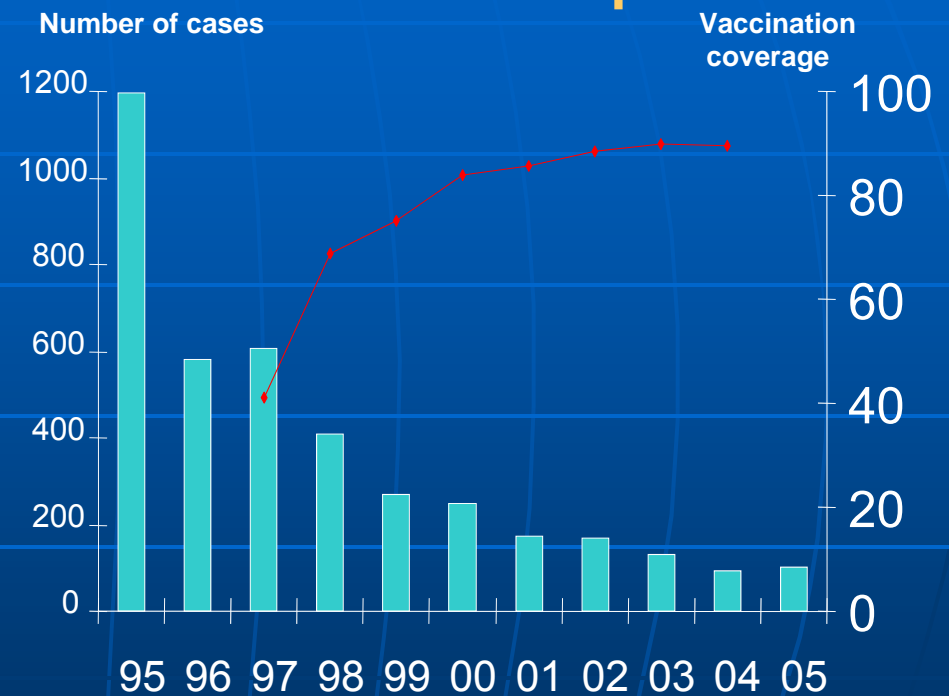
- Social and medical advances have added 'years to life' but not 'life to years'
- Short-term debility leads to prolonged detriment to ADL and independence
- Zoster-specific CMI declines with advancing age
- Neurosenescence may add to PHN susceptibility

Reported varicella cases and vaccination coverage* by year -- *Varicella Active Surveillance Project, 1995-2005*

Antelope Valley



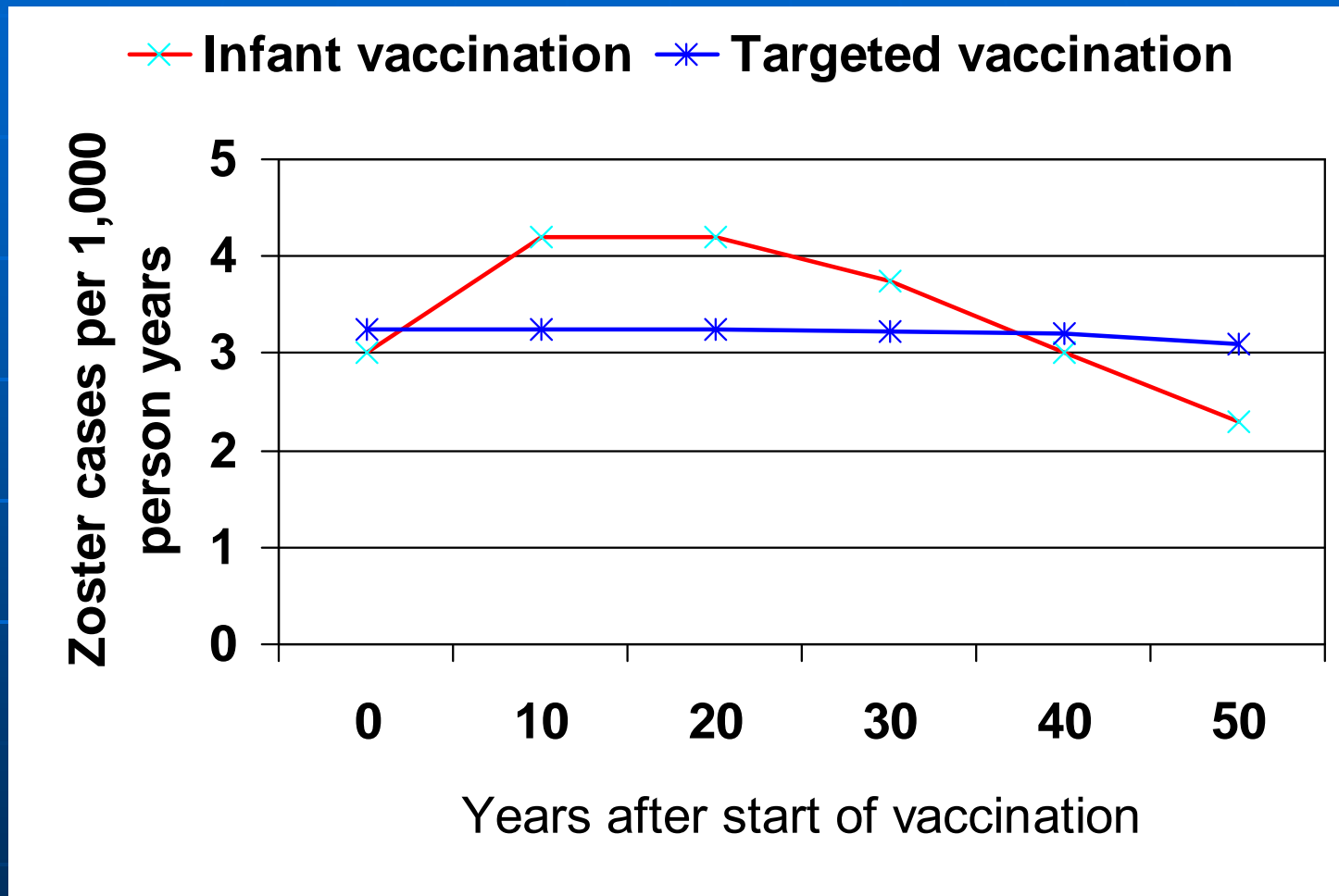
West Philadelphia



— Vaccination coverage ■ Varicella cases

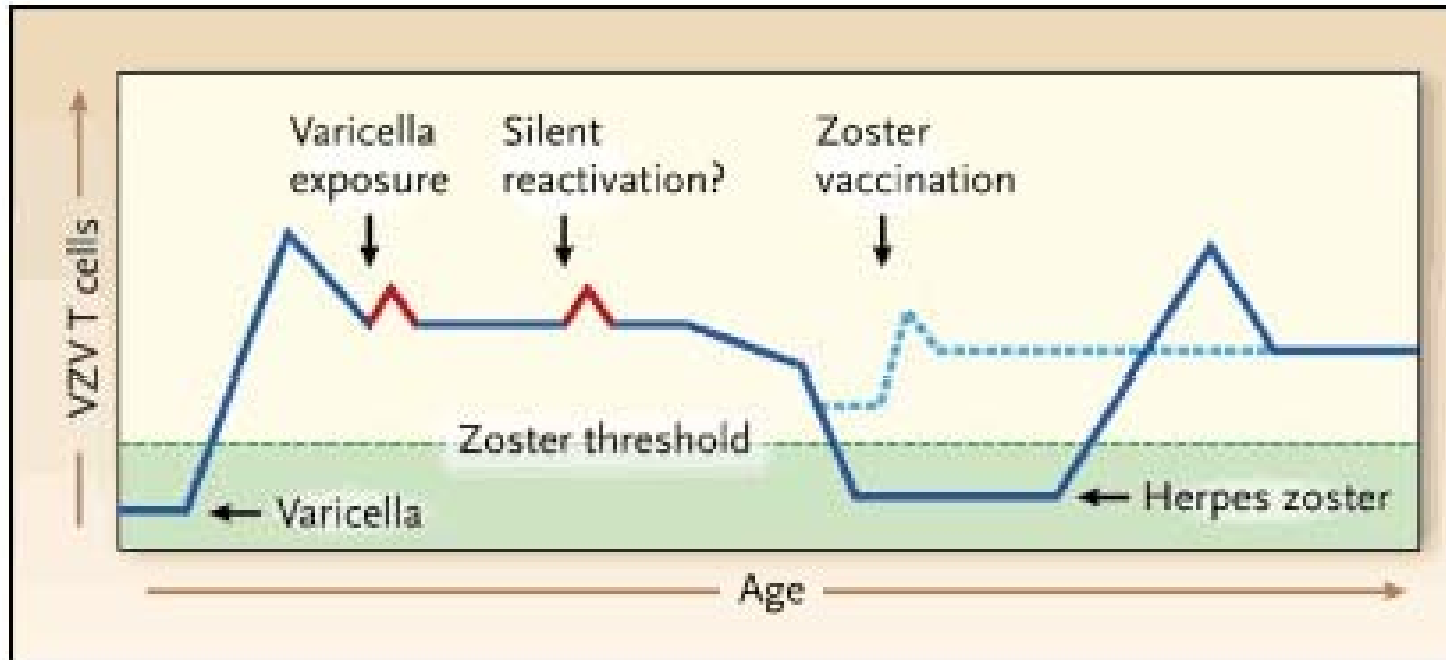
* Coverage estimates from NIS in LA and Philadelphia, among children 19-35 months of age.

Hypothesis - effects of vaccination strategies on HZ



Adapted from Edmunds W.J. & Brisson M. *J. of Infection* 4 (2002) 211-219

Lifetime changes in immune status



Aging, Immunity, and the Varicella-Zoster Virus, Ann Arvin, *NEJM*(2005) 352;22:2266-7

Prediction of PHN risk

- Baseline and follow up data from 965 HZ patients examined by univariate and multivariate analysis confirmed that:
 - Older age
 - Female gender
 - Presence of prodrome
 - Greater rash severity
 - Greater acute pain severity
 - (Diabetes)

made independent contributions to predicting which patients developed PHN

What do antivirals achieve?

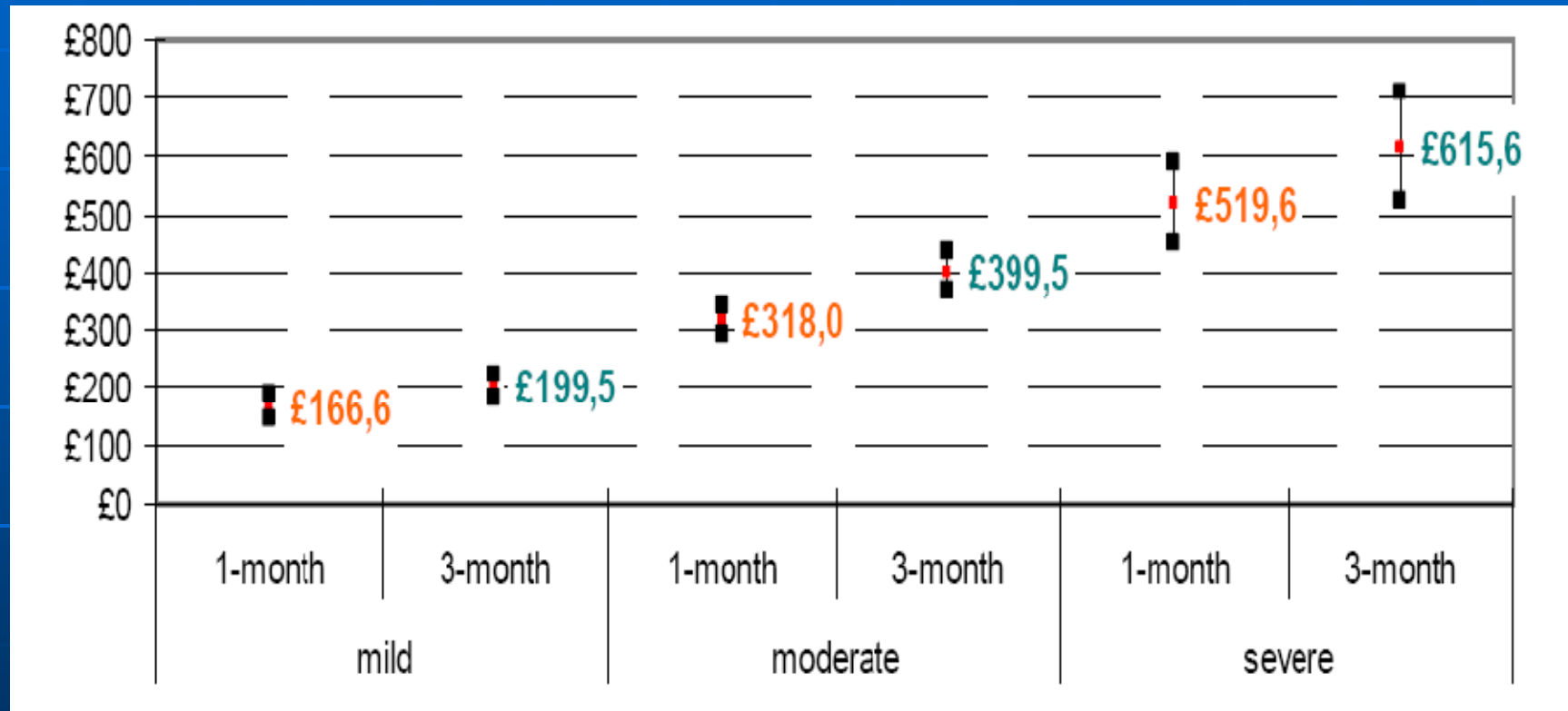
- Reduce acute pain
- Accelerate rash healing
- Reduce period of viral shedding
- **Reduce duration of pain**
- Effect on complications other than pain
- Excellent safety profile
- Reduction in overall burden of HZ

Cost of HZ – 1st 6 months

- Societal and economic burden
- Prospective observational pilot study
- 70 patients had detailed follow-up
- Average overall cost 1st 6 months £524 (min 20, med 158, max 4218)
- Medical costs highest >65
- Societal costs highest <65

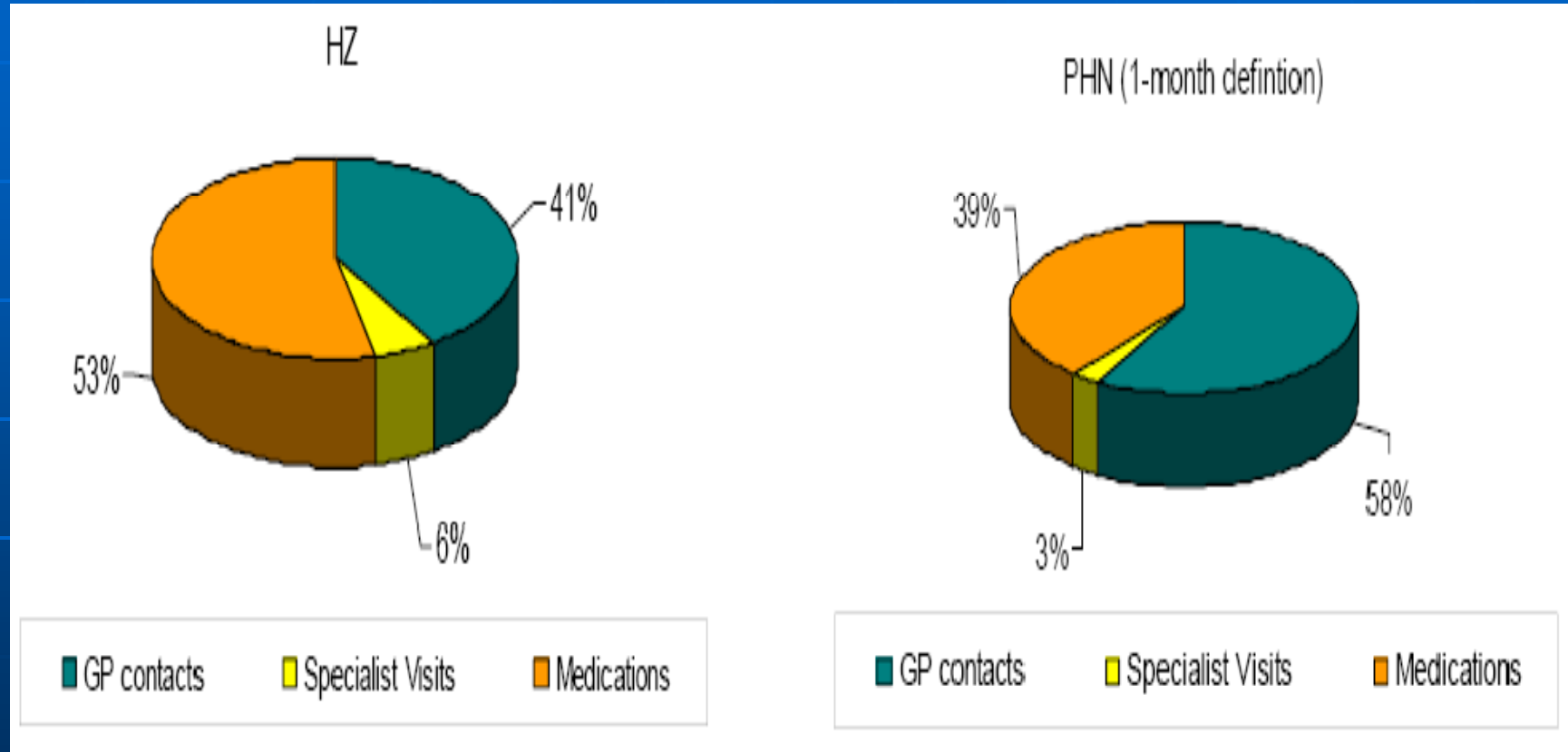
SUK study. Scott F, Johnson R, Leedham-Green M, Davies E, Edmunds WJ, Breuer J. *Vaccine* 2006

Mean cost per PHN episode by severity



Proportion of herpes zoster patients developing post-herpetic neuralgia and its management in the UK. Gauthier et al

Proportion of management costs of HZ and PHN by category

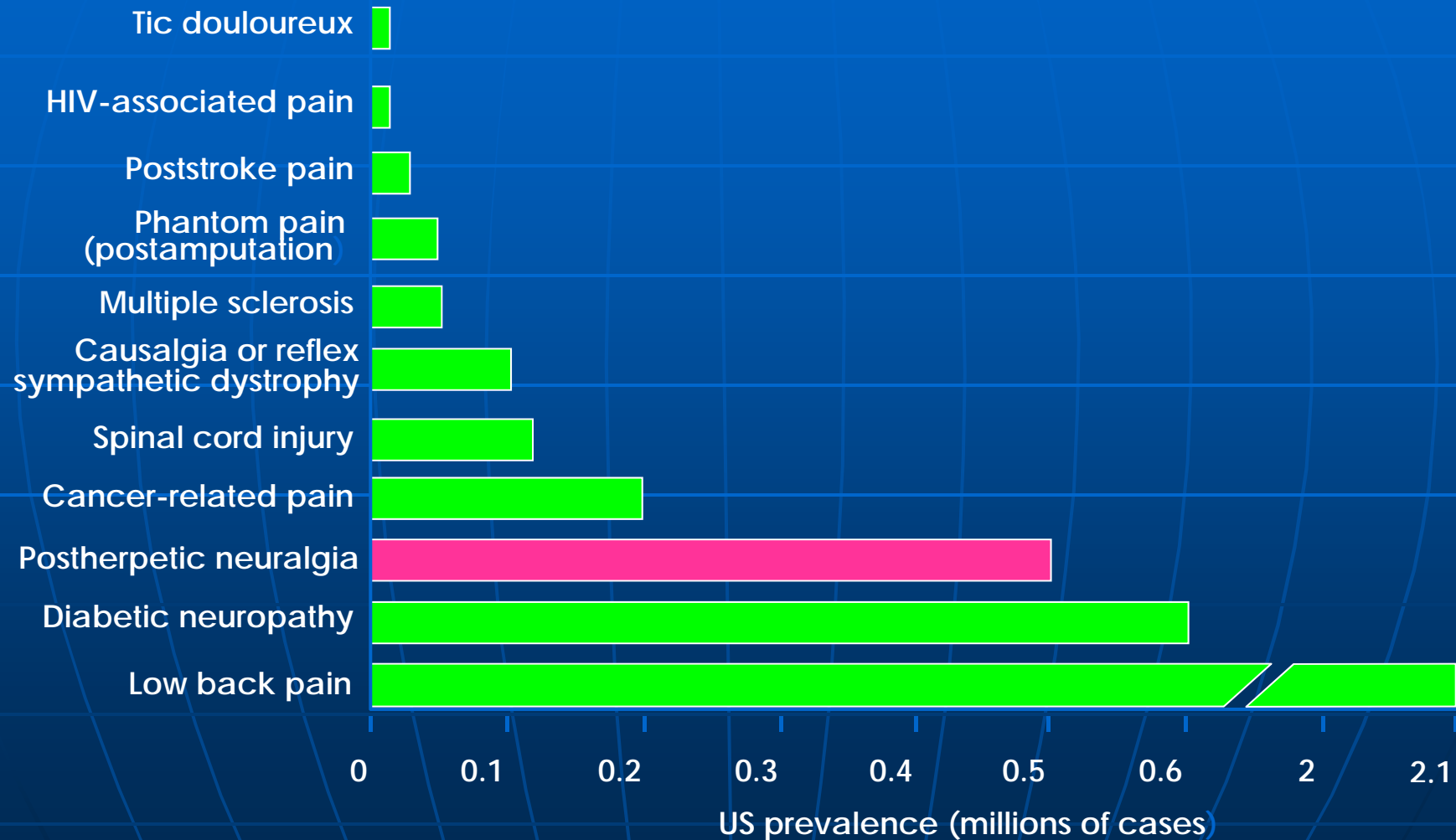


Epidemiology and management costs of Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN) in the UK. Remy et al

Facts about PHN

- Antiviral drugs (+/- steroids) have limited effect in prevention of PHN: *they do not 'bring dead neurons back to life'*
- Nerve blocks or neuropathic pain drugs: *evidence for PHN prevention limited - lacking in practicality*
- Despite significant advances <50% of PHN patients gain 50% pain relief

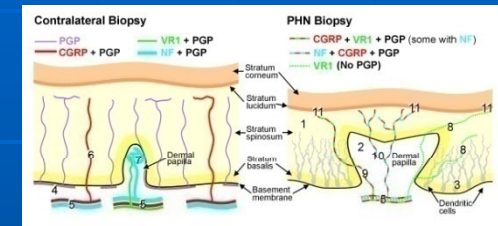
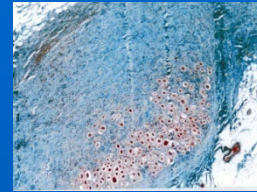
Sources of Neuropathic Pain



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Bennett G. *Hosp Prac (Off Ed)*. 1998;33:95-98;101-104;107-110.

The pain pathway



PERCEPTION

Cortex



Thalamus

Thalamocortical projections

MODULATION

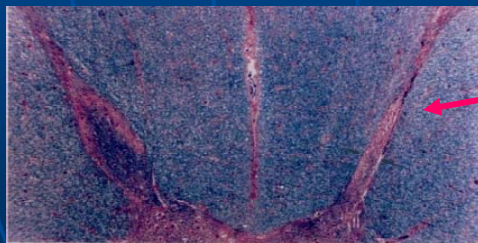
TRANSMISSION

TRANSDUCTION

NOXIOUS STIMULUS

Primary afferent nociceptor

Spinothalamic tract



Agents with NNT<5

M-prednisolone (I.t)

Aspirin(topical)

Lidocaine 5% patch

TCA's

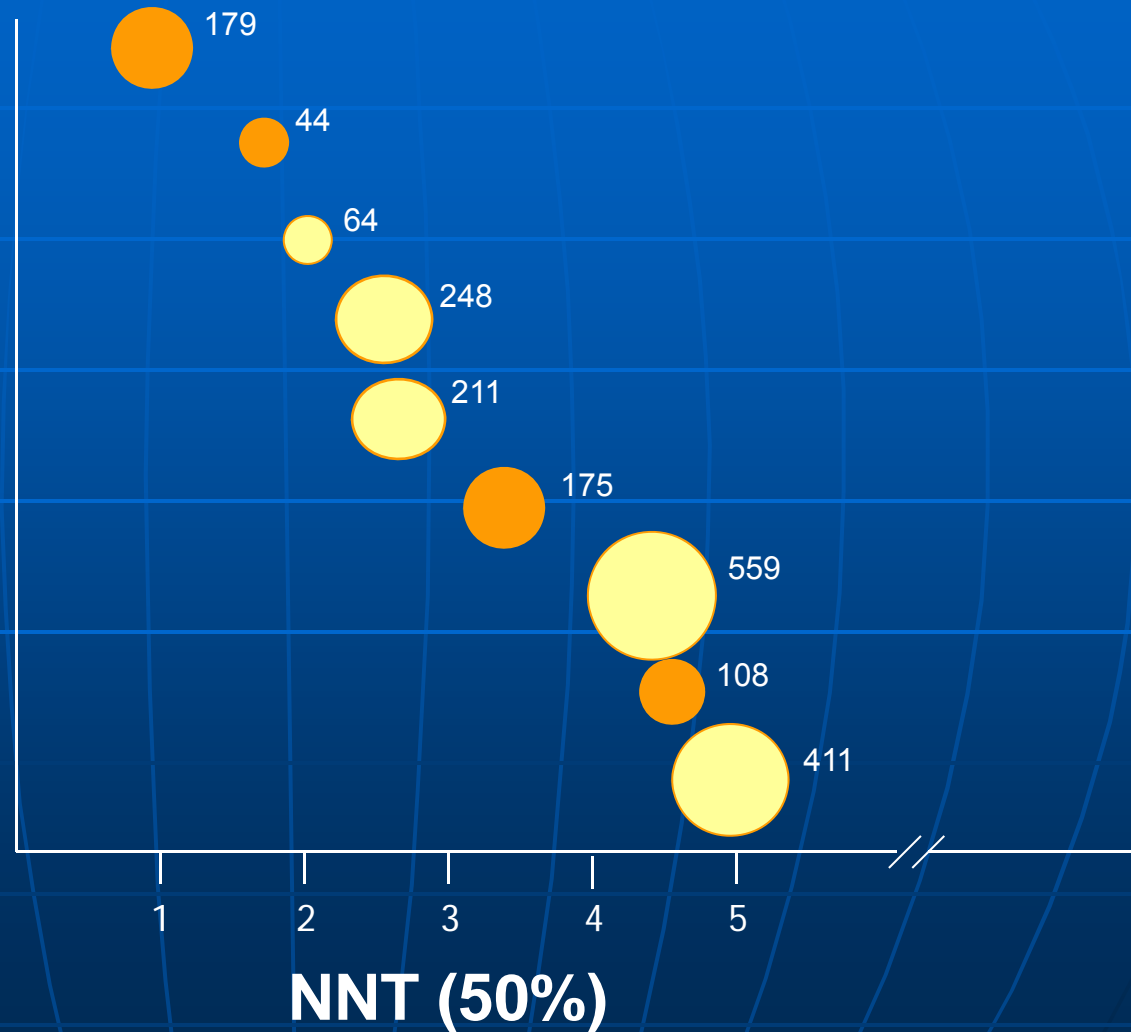
Strong opioids

Capsaicin

Gabapentin

Tramadol

Pregabalin

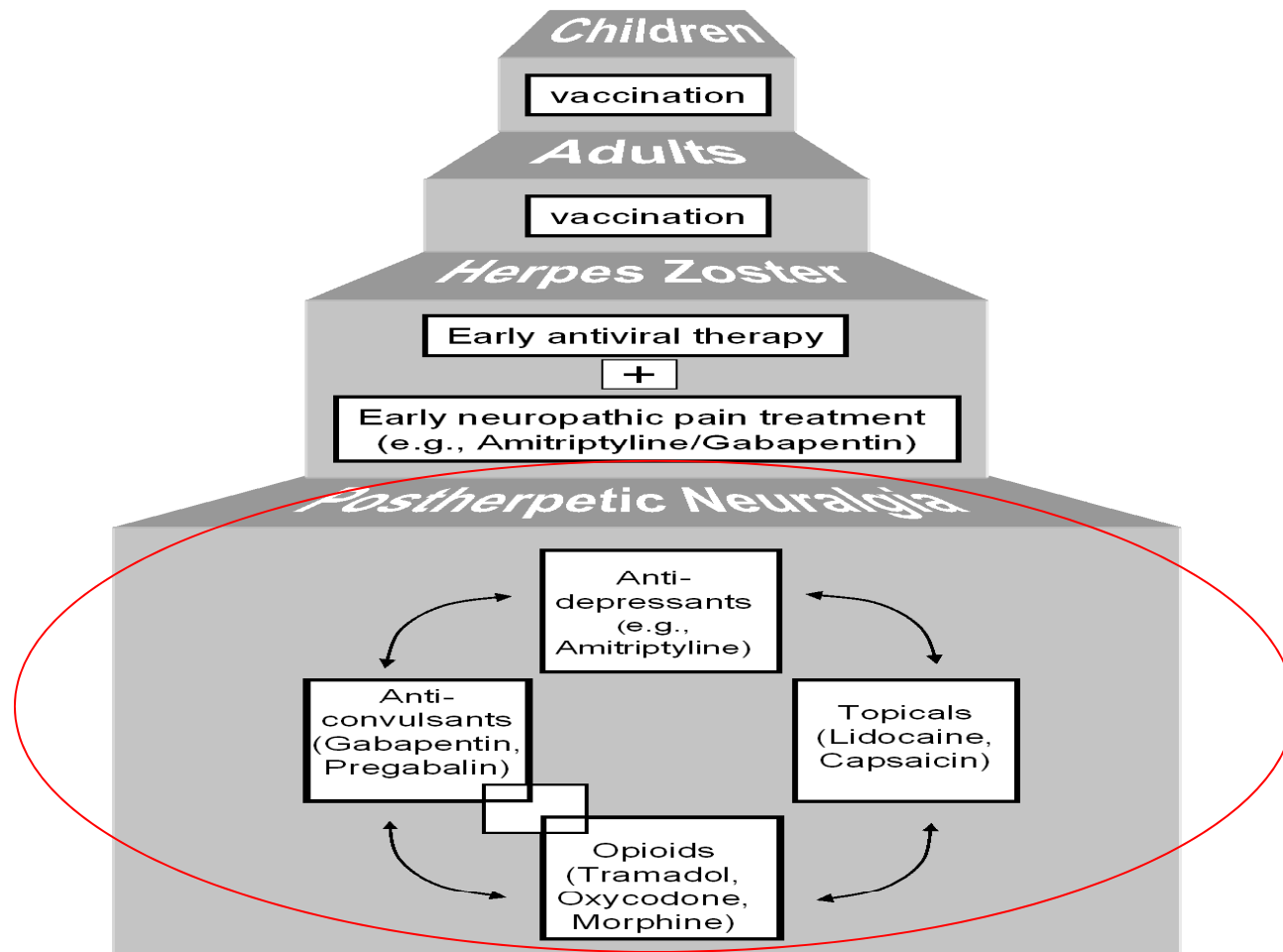


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Hempenstall et al 2005. Based on systematic review of RCTs with a Jadad score ≥ 3

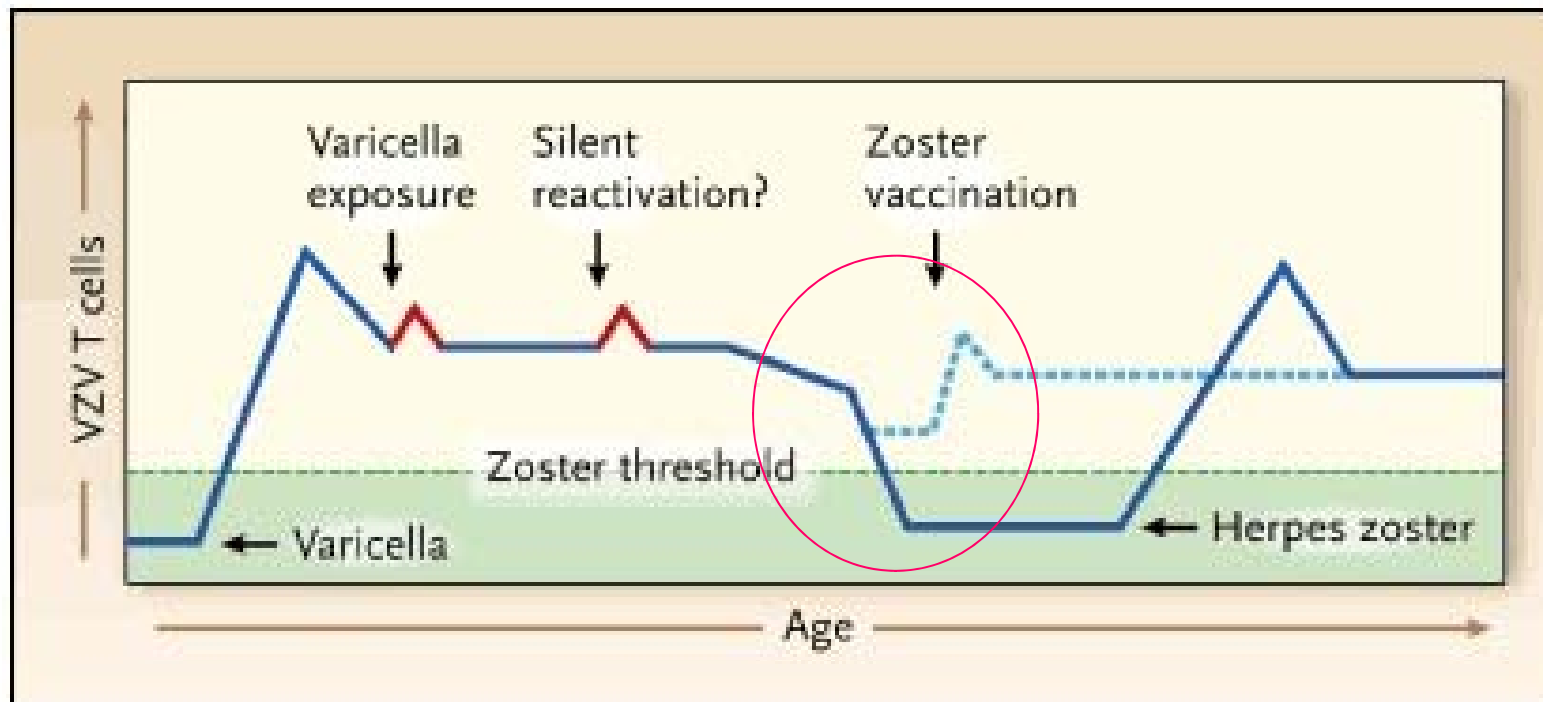
Management Plan for HZ & PHN



Prevention of Herpes Zoster by vaccination

- Reduction in number of susceptible individuals in population
 - Varicella vaccine
- Increased VZV-specific CMI of seropositive individuals
 - Relevance of exogenous boosting
 - HZ vaccine
- Unlike other vaccine-preventable diseases, HZ not directly related to exposure to exogenous infective agent

Rationale for vaccination against HZ



The Oka vaccine

- Live, attenuated, cell-free preparation of Oka strain VZV (killed virus antigen weak stimulant of CMI)
- Original 'wild type' virus isolated by Michiaki Takahashi from 3 year old Japanese child whose family name was Oka
- Three licensed preparations – Merck (stored at -15°C), GSK (stored at 2°C) and Merck (refrigerated)
- The same strain of Merck/Oka virus is used for varicella and herpes zoster protection BUT the latter contains a several fold greater (14x) titer of virus because of the reduced immune response of older adults

The New England Journal of Medicine

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., et al.

Shingles Prevention Study

- *Objective*

- To determine whether immunization with a live attenuated zoster vaccine can reduce the incidence and/or severity of HZ and PHN in persons ≥ 60 years of age

Shingles Prevention Study

■ *Design*

- Randomized, double-blind, placebo controlled trial
- 38,546 subjects
- Stratified by age group: 60 - 69 yr and >70 yr
- Active vaccine or placebo vaccine

Shingles Prevention Study

■ *Participants*

- Immunocompetent adults greater than 60 years old who had no prior history of herpes zoster
- History of varicella or ≥ 30 years residence in US
- Included male and female veterans and non-veterans
- Sample size estimate = 37,200 (18,600 each group) for 95% power, $\alpha = 0.05$ (two-sided), to detect 60% reduction in herpes zoster BOI score

Incidences of HZ and PHN

- PHN – worst pain and discomfort ≥ 3 (0-10 scale) 90 or more days from rash onset
 - $VE_{PHN} = 1 - (PHN \text{ incidence vaccine} / PHN \text{ incidence placebo})$
- HZ
 - $VE_{HZ} = 1 - (HZ \text{ incidence vaccine} / HZ \text{ incidence placebo})$

Summary of results

HERPES ZOSTER VACCINE:

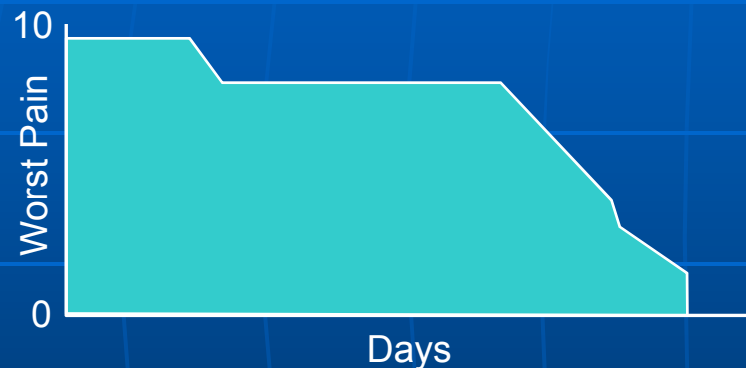
- Reduces HZ Pain BOI by 61% *

M.N. Oxman et al, N Engl J Med, 2005 Jun 2; 352 (22): 2271-84

* $p < 0.001$ versus placebo

Burden of Illness (BOI)

- Population measure
- Sensitive to the incidence, duration and severity of HZ pain over 6 months



Max. possible BOI score = 180 (days) x 10
(Max. intensity) = 1,800

- Severity-by-duration (AUC) calculated for each HZ case
- Subjects without HZ were assumed to have no HZ-associated pain (i.e., AUC=0)

Summary of results

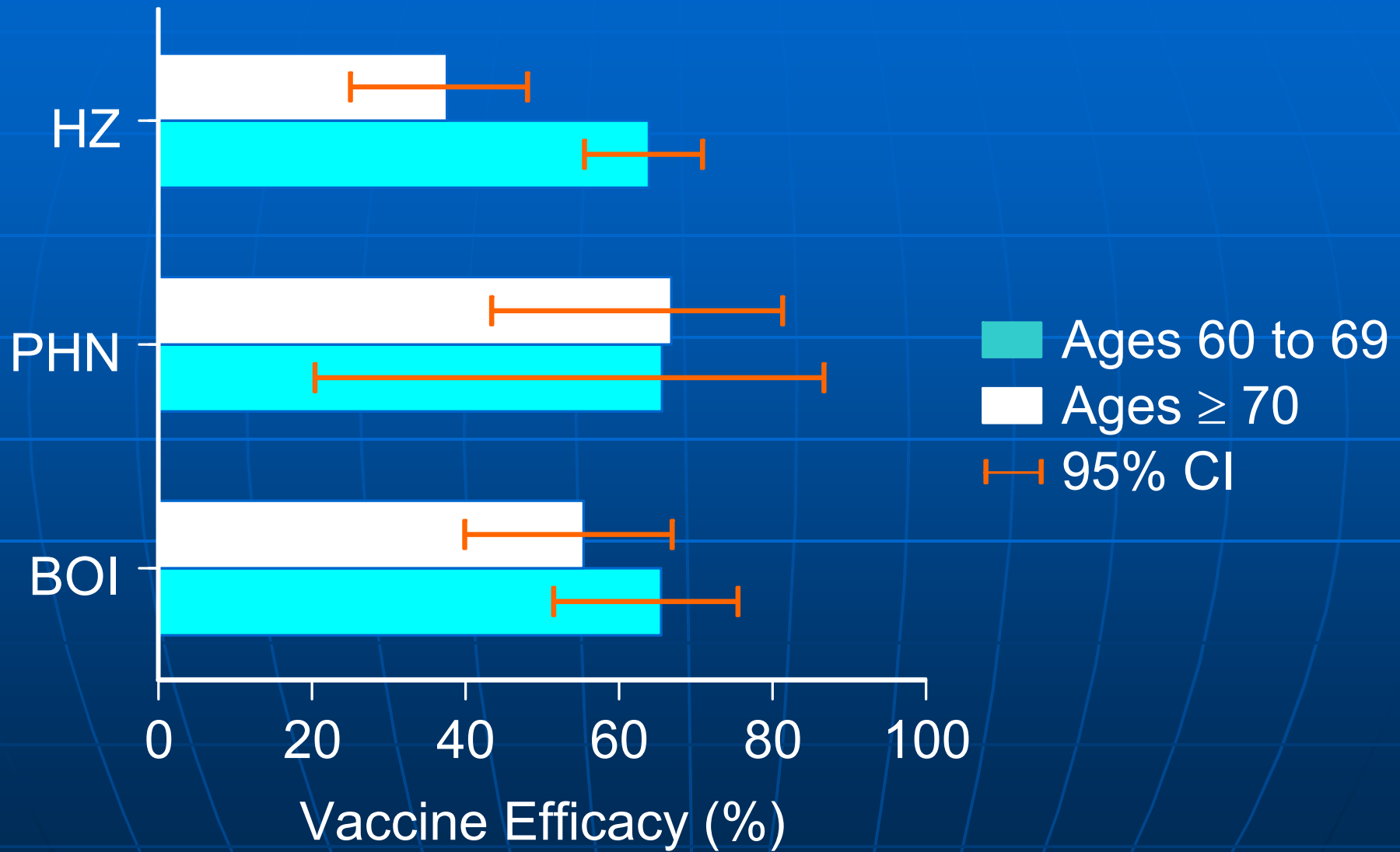
HERPES ZOSTER VACCINE:

- Reduces HZ Pain BOI by 61% *
- Prevents HZ by 51% *
- Prevents PHN by 67% *
- Elicits a VZV-specific CMI response

M.N. Oxman et al, N Engl J Med, 2005 Jun 2; 352 (22): 2271-84

* $p < 0.001$ versus placebo

ZOSTAVAX™ efficacy by age



Safety

- Serious Adverse Events (whole study population): Number and type of event similar in vaccine and placebo groups.
- SAE (safety sub-study) higher in vaccine (1.9%) than placebo (1.5%) group - RR 1.5 (95%CI=1.0-2.3).
- No temporal or clinical patterns of adverse events in vaccine recipients to suggest a causal relationship.
- Death and hospitalization similar in both groups throughout.

Safety

- Mild local & systemic reactions:
 - Injection site erythema, swelling, pain etc 48.3% in vaccine group & 16.6% with placebo ($p < 0.05$): risk higher in younger cohort
 - Headaches etc slightly more common in vaccine recipients
 - Risk of fever similar in both groups

Cost-effectiveness

- 5 studies have estimated cost-effectiveness of 1 dose vaccination ≥ 60 yr
- At vaccine cost of US\$150: -
 - \$27,000 – 112,000 per QALY
 - WHO threshold = 3x gross domestic product per capita = \$94,431 for US
 - Appears acceptable in comparison to other interventions but at intermediate-to-high end of range

Advice at this time

- Vaccinate against HZ at age 50 to 60
- In patients who develop HZ:
 - Antiviral drugs (preferably pro-drug)
 - Effective analgesia
 - Early use of TCA / pregabalin / strong opioids if required

Summary

HERPES ZOSTER VACCINE

- Reduces HZ Pain BOI by 61% *
- Prevents HZ by 51% *
- Prevents PHN by 67% *
- Elicits a VZV-specific CMI response
- Has an excellent safety profile
- Efficacy for HZ & PHN endpoints was demonstrated through 48 months of follow-up

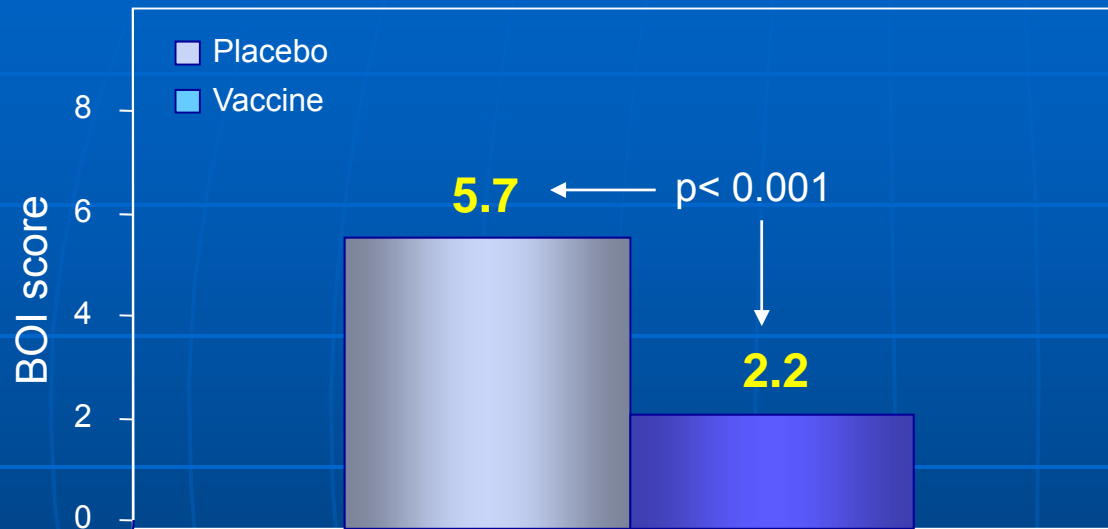
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* $p < 0.001$ versus placebo

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Efficacy on HZ Burden of Illness (BOI)

Vaccine Efficacy on HZ Burden Of Illness



EFFICACY = 61.1%*

(95% CI 51.1 - 69.1%)

* $p < 0.001$ versus placebo

- HZ BOI = Incidence x severity x duration of HZ associated pain
- Similar HZ Vaccine Efficacy when results stratified according to sex or age

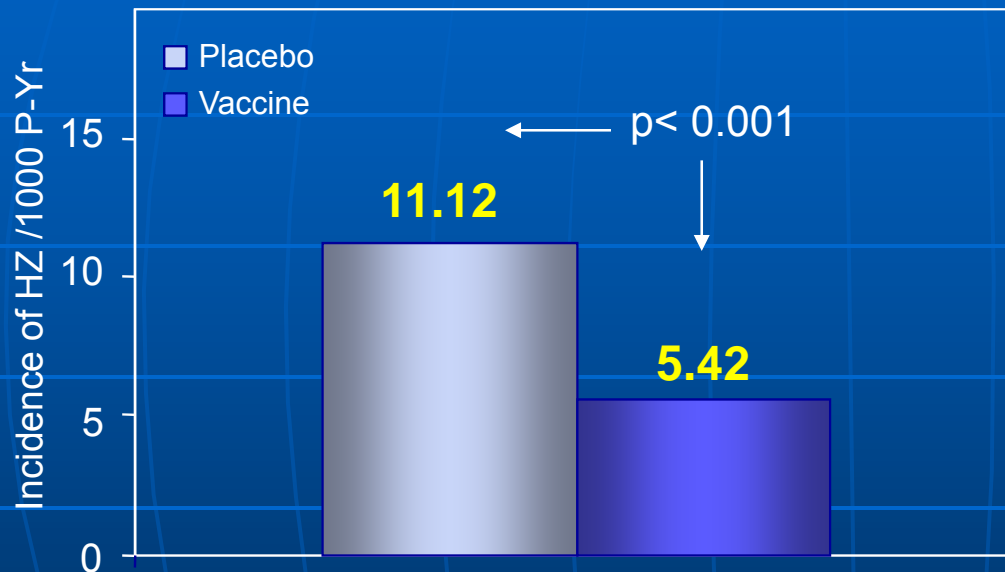
HZ Burden of Illness (BOI) Score

- Herpes zoster BOI Score is the average Area-Under-the-Curve (AUC) of zoster pain of all individual randomized subjects in a group of subjects (e.g., vaccine recipients) for 6 months
 - Subjects who do not develop herpes zoster are assigned a score of 0
- Vaccine efficacy for BOI defined as relative reduction in BOI score in vaccine vs. placebo group
 - $VE_{BOI} = 1 - (BOI \text{ score vaccine} / BOI \text{ score placebo})$

Efficacy on HZ

- HZ case definition = PCR+ or Culture + or CEC+

Vaccine Efficacy on HZ incidence



EFFICACY = 51.3%*

(95% CI 44.2 - 57.6%)

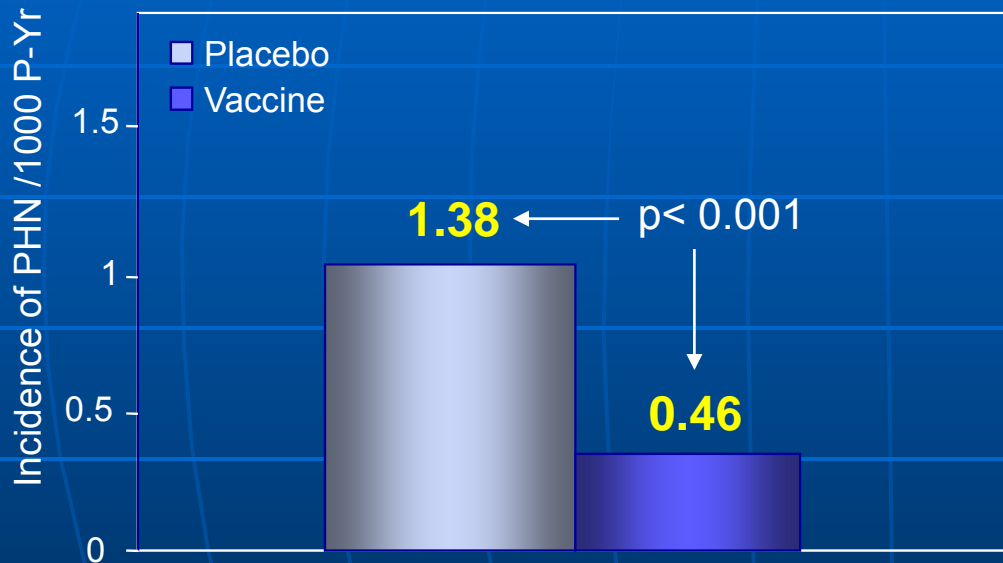
* $p < 0.001$ versus placebo

- HZ Vaccine Efficacy greater among 60-69 year old subjects than subjects > 70 years (64% versus 38%, $p < 0.001$)

Efficacy on PHN incidence

PHN = presence of pain (score 3 on 0-10 scale) beyond 90 days after HZ rash onset

Vaccine Efficacy on PHN incidence



EFFICACY = 66.5%*

(95% CI 47.5 - 79.2%)

* p < 0.001 versus placebo

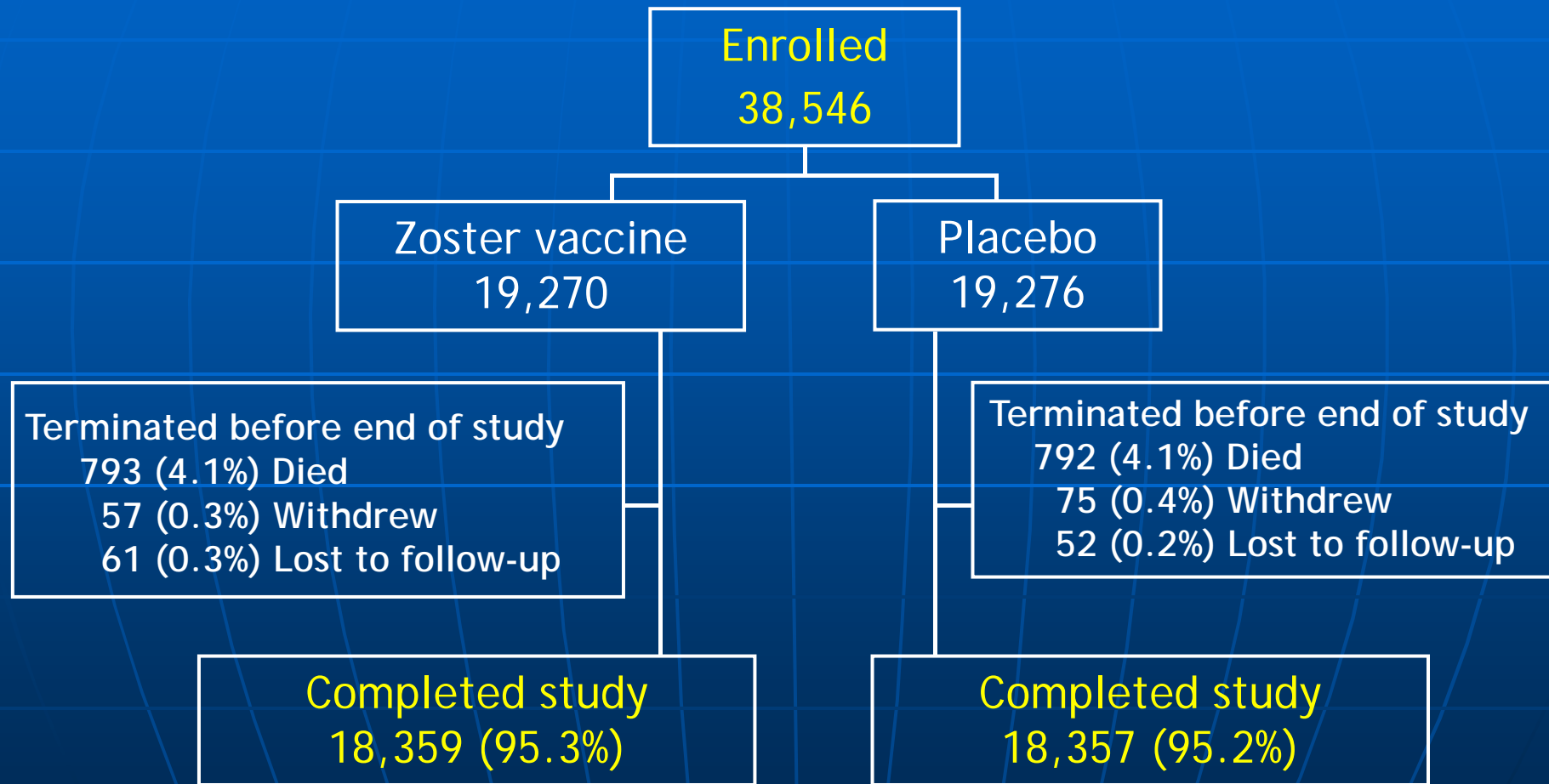
- Cases of PHN: HZ vaccine group: 27 versus Placebo group: 80
- Similar HZ Vaccine Efficacy when results stratified according to sex or age

Shingles Prevention Study

- *Intervention*

- 0.5 ml live, attenuated zoster vaccine (Oka/Merck) or placebo s.c. in non-dominant arm

Study Subjects



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Baseline Characteristics

Characteristic	Vaccine Group (N=19,270)	Placebo Group (N=19,276)
Age ≥70 yr	8,892 (46.1%)	8,907 (46.2)
Sex – Female	7,867 (40.8%)	7,919 (41.1%)
Race – White	18,393 (95.4%)	18,381 (95.4%)
Health Limits* No	9,924 (51.5%)	9,862 (51.2%)
Mild	7,440 (38.6%)	7,423 (38.5%)
Moderate	1,637 (8.5%)	1,714 (8.9%)
Severe	266 (1.4%)	273 (1.4%)

*Health-related limitations on activities

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Adapted from Table 1 in Oxman et al. NEJM. 2005;352:2271-84

Sub-study populations

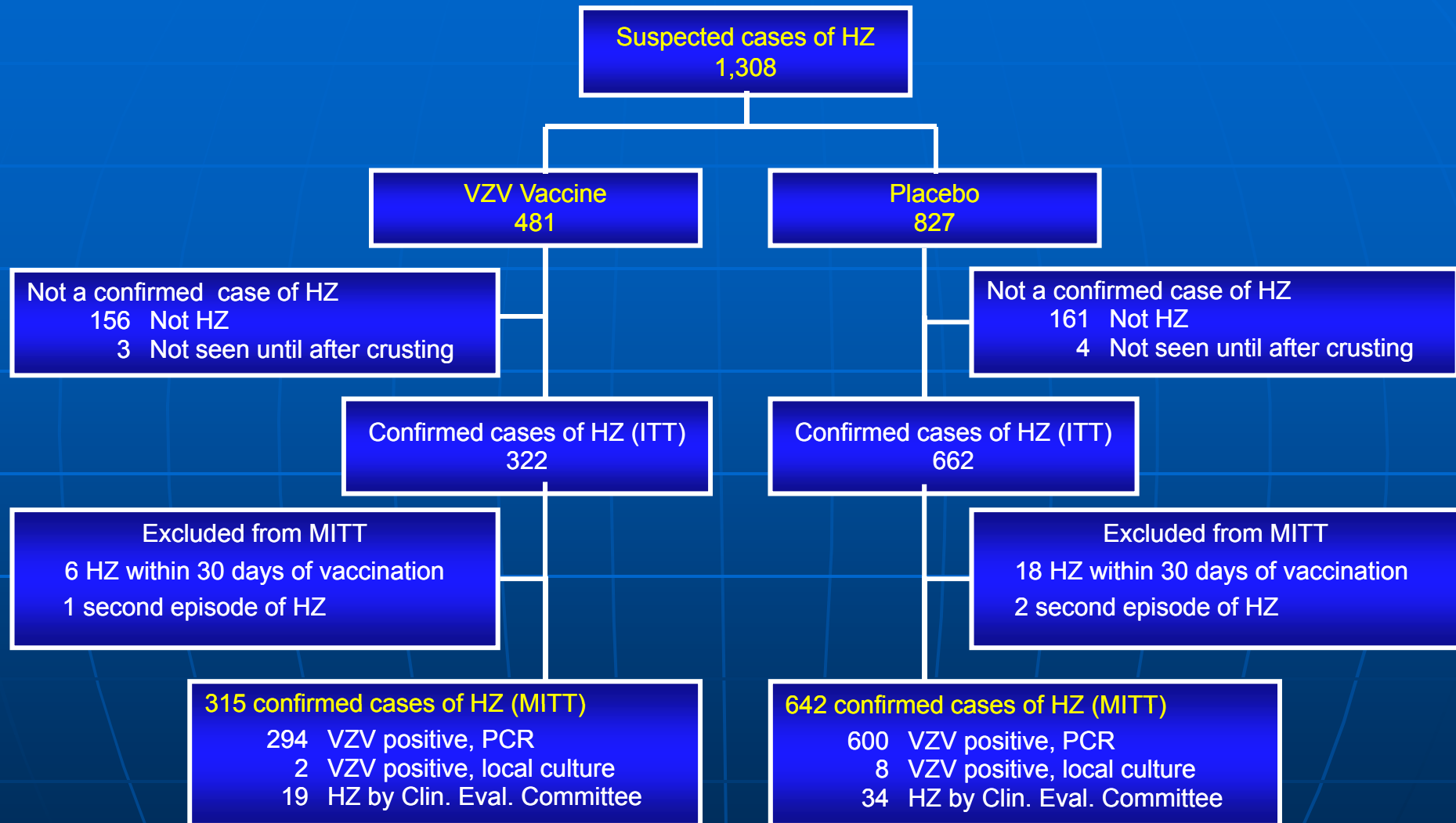
- Safety sub-study (n = 6616)
 - At all 22 study sites
 - Detailed safety assessment
 - Completed a vaccination report card through Day 42 post-vaccination
 - Followed for hospitalizations until the end of study

- CMI sub-study (n = 1395)
 - At 2 study sites
 - Specimens were obtained at baseline and post-vaccination (6 weeks; 1, 2 and 3 years)
 - Antibody level by gpELISA
 - VZV-specific CMI by ELISPOT and RCF assays

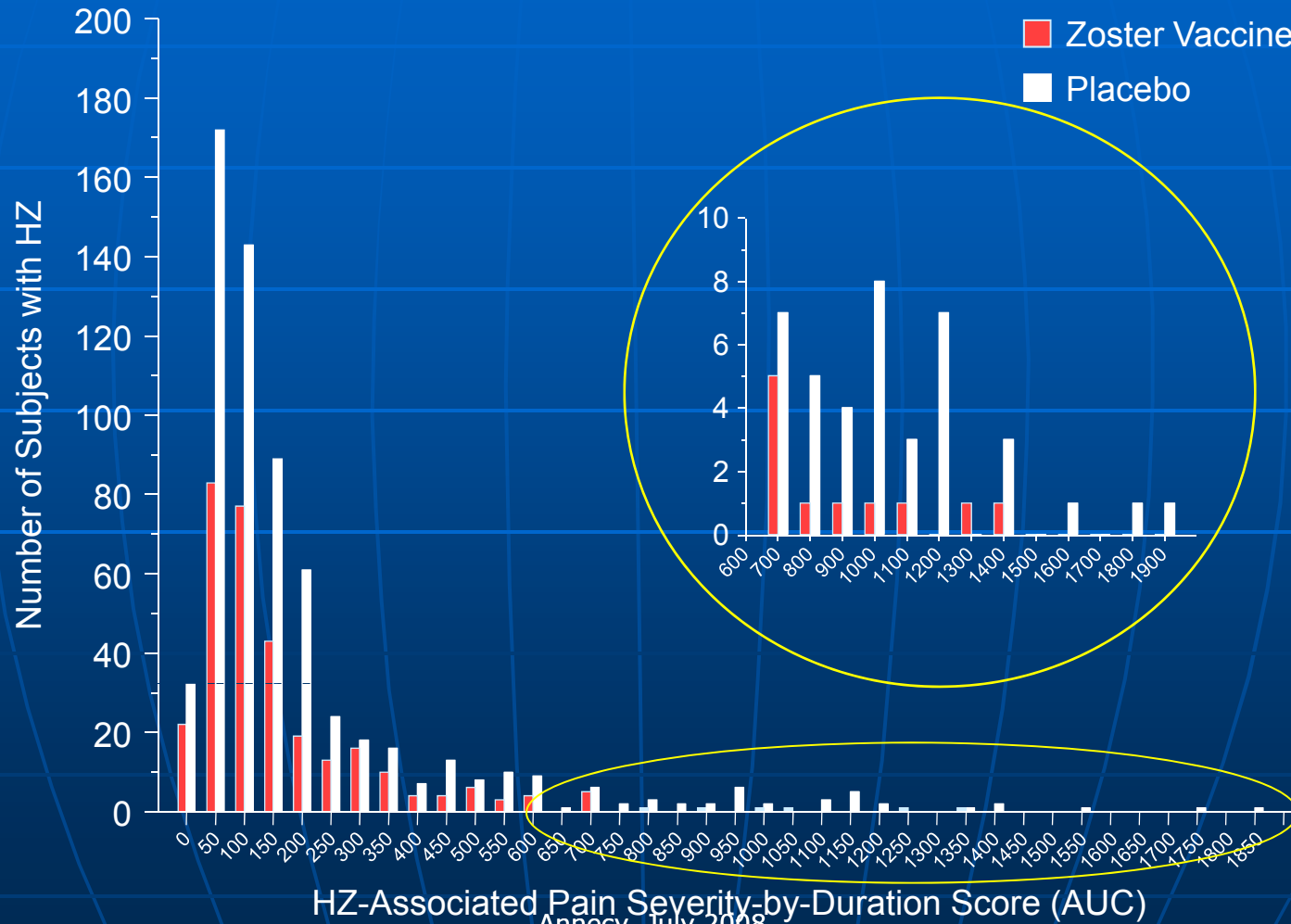
Efficacy analysis population

- Modified Intention-To-Treat population (MITT)
 - All enrolled subjects who did not develop evaluable HZ within 30 days post-vaccination
 - Analyses included only the first confirmed case
- Why exclude cases in the first 30 days?
 - Cases may have been in development at the time of vaccination
 - Vaccine-induced immune responses unlikely to be fully developed for some time after vaccination
 - Potential confusion with vaccine-induced rash

Confirmation of HZ cases



Histogram of Severity-by-Duration Score (AUC) of HZ Pain Among Evaluable HZ Cases by Vaccination Group (MITT Population)

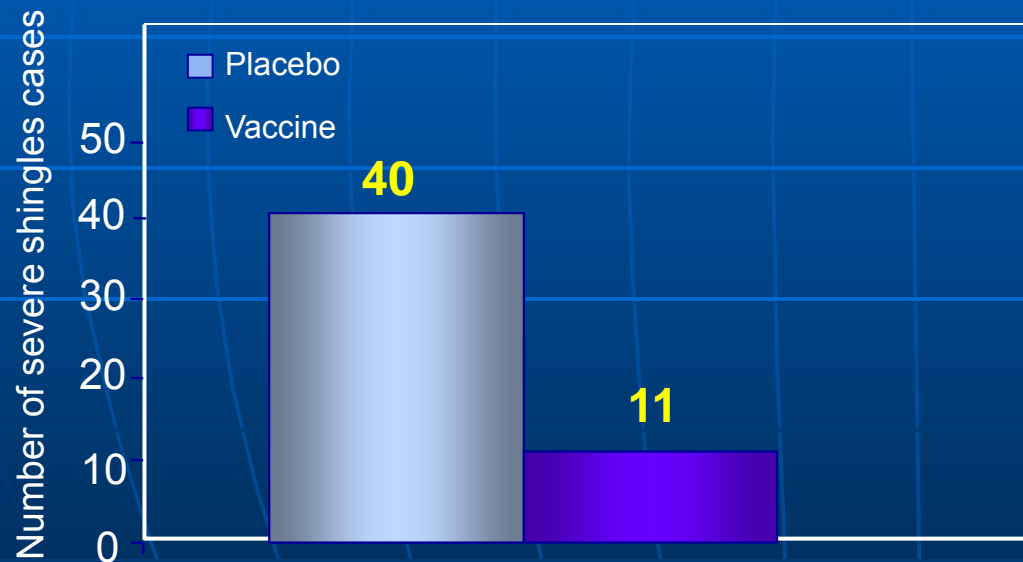


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Efficacy on all HZ severe cases

HZ severe cases = HZ with severe x duration pain score > 600

Vaccine efficacy on severe HZ cases



EFFICACY = 73%

(95% CI 46 - 87.6%)

SPS Safety Evaluation

- *All Subjects*
 - All adverse events recorded within 42 days after vaccination
 - Subjects contacted at end of 42 day period and prompted for any other unreported adverse events
 - Deaths identified by reports from family and during follow-up of missed monthly calls

Serious Adverse Events Among All Subjects

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

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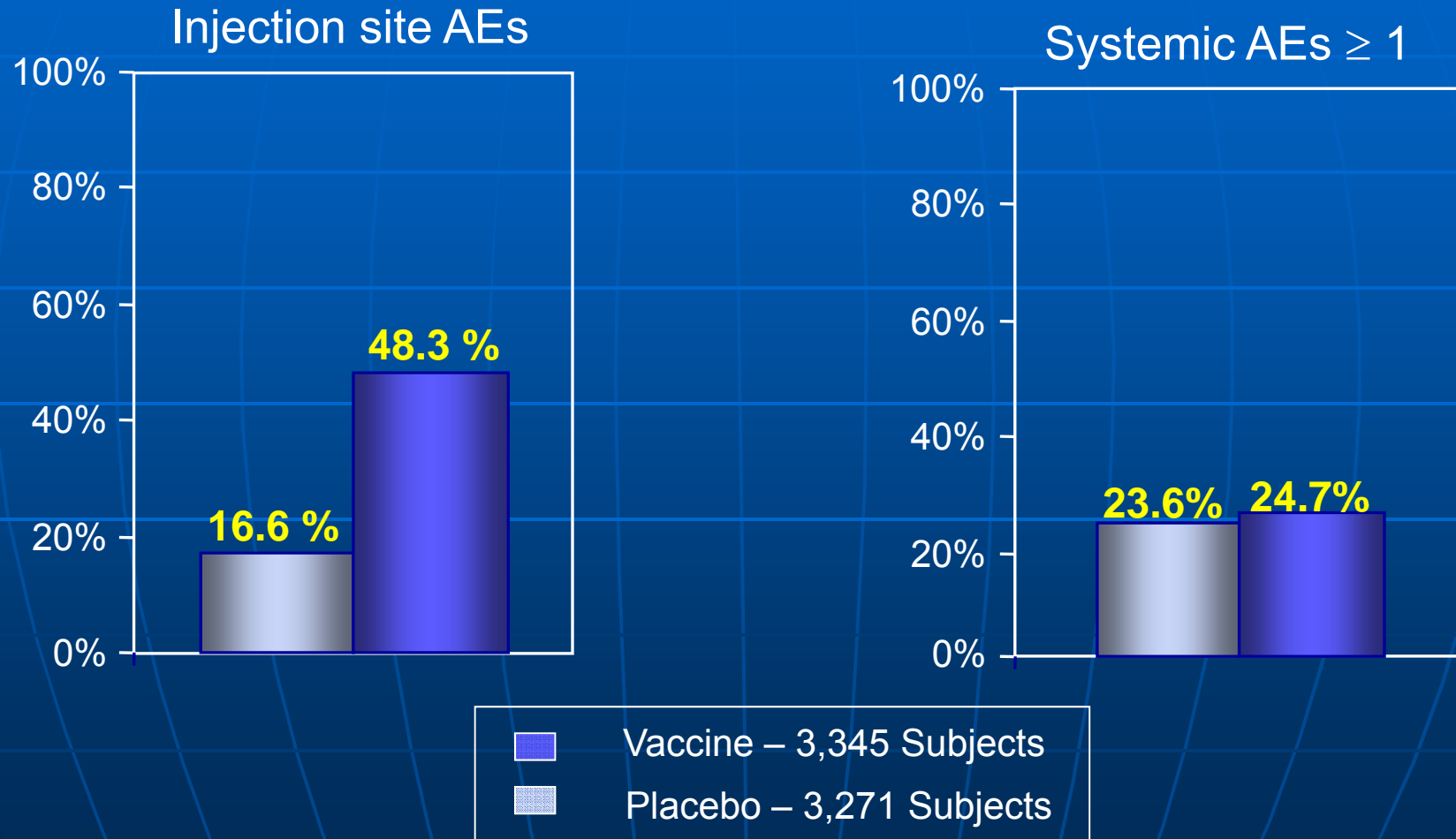
Adapted from Table 4 in Oxman et al. *NEJM* 2005;352:2271-84

SPS Safety Evaluation

- *Adverse Events Substudy*
 - Approximately 300 subjects per site enrolled
 - During 42 days after vaccination, daily log of body temperature and vaccination report card of clinical symptoms and injection site complaints
 - During remainder of study, followed by monthly calls and site personnel to identify all hospitalizations

Safety (AEs sub-study)

Day of vaccination to Day 42



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Rate of HZ Complication (MITT Population)

	ZOSTAVAX™ N=19,270		Placebo N=19,276		% Relative Reduction in ZOSTAVAX™ Recipients (95% CI)
	n	Incidence Rate*	n	Incidence Rate*	
Neurologic†	29	0.5	82	1.4	64.9 (45.8, 77.9)
Cutaneous	39	0.7	116	2.0	66.6 (51.7, 77.4)
Ocular involvement	14	0.2	40	0.7	65.3 (34.8, 82.6)
Sacral dermatome involvement	6	0.1	24	0.4	75.2 (37.7, 91.7)
Visceral complications	9	0.2	28	0.5	68.1 (30.5, 86.8)

* Incidence rate = per 1000 person years (total population).

† Excluding pain.

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Cost-effectiveness of HZ vaccine in USA

- Age-specific analytic model
- Lifetime costs and outcomes for HZ, PHN, other HZ complications
- Vaccinated and non-vaccinated cohorts aged ≥ 60 years
- Societal and payer perspectives considered

Pellissier JM et al. *Vaccine* 25 (2007);8326-8337

For 1.000,000 US vaccine recipients ≥ 60 ...

- HZ vaccine would eliminate:-
 - 75,548-88,928 cases of HZ
 - >20,000 cases of PHN
 - >300,000 outpatient visits
 - >375,000 prescriptions
 - >97,000 ER visits
 - >10,000 hospitalizations
- Saving US\$ 82-103 million annually

Pellissier JM et al. *Vaccine* 25 (2007);8326-8337

Cost-effectiveness of HZ vaccination in US

- US\$ 16,229 - 27,609 per QALY gained depending on data source and analytic perspective.
- Most sensitive to:
 - PHN costs
 - Duration of vaccine efficacy
 - Complication costs
 - QALY loss associated with pain

Pellissier JM et al. *Vaccine* 25 (2007);8326-8337

Cost-effectiveness and QALYs

- US\$ 50,000 – 100,000 per QALY gained considered cost-effective
- WHO suggests 3 X domestic product/capita = $3 \times \approx \text{£}20,000 = \text{£}60,000$ for UK
- For comparison:
 - Hypertension management US\$ 60,000/ QALY gained

Cost-effectiveness results in the 65+ UK population (40% coverage rate)

Results		Vac Policy	No Vac Policy	Difference
Costs		£505,521,469	£159,097,028	£346,424,441
Effectiveness	QALYs	74,061,721	74,031,587	30,134
	HZ Cases	634,725	779,603	144,878
	PHN Cases	133,945	184,028	50,083
ICERS	Cost per QALY gained			£11,496
	Cost per HZ Case Avoided			£2,391
	Cost per PHN Case Avoided			£6,917

A health economic evaluation of a new herpes zoster (HZ) vaccine for the prevention of Post-herpetic neuralgia (PHN) in the UK. Martin et al.

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Mean cost per case of HZ over 6-month follow-up by age

Age class	Sample size	Patient (£)	NHS (£)	Society (£)	Total (£)
<65 years	45	10.8 (0, 4, 187)	85.6 (20, 68, 696)	430.0 (0, 26, 3265)	526.3 (20, 173, 3578)
65+ years	25	42.5 (0, 0, 1000)	400.9 (48, 138, 3257)	76.6 (0, 0, 957)	519.9 (48, 138, 4218)
Overall	70	22.1 (0, 1, 1000)	198.2 (20, 86, 3257)	303.8 (0, 0, 3267)	524.0 (20, 158, 4218)

The minimum, median and maximum costs are in ()

Follow up : 146 GP consultations, 7 hospital visits, 6 emergency ambulances, 4 admissions, 6 consultations with complementary practitioners, 307 days work lost by patients, 52 by carers

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The future

- Duration of protection
- Need for booster injection(s)
- Effects in the elderly 'unfit' patient
- Vaccine suitable for immunocompromised patients
- Reduced prevalence of seropositive individuals
- More effective vaccine?
 - n.b. effectiveness of other vaccines in elderly adults