

Herpes zoster: review of evidence

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on behalf of the
SAGE Working Group on varicella and herpes zoster

SAGE meeting
WHO, Geneva, Switzerland
April 2nd, 2014



Context

- SAGE VZV Working Group tasked to review evidence to formulate recommendations on the use of herpes zoster vaccines
 - Update the 1998 varicella vaccine position paper
- Evidence included:
 - Epidemiology & global disease burden
 - Vaccine safety & efficacy
 - Effectiveness & cost-effectiveness

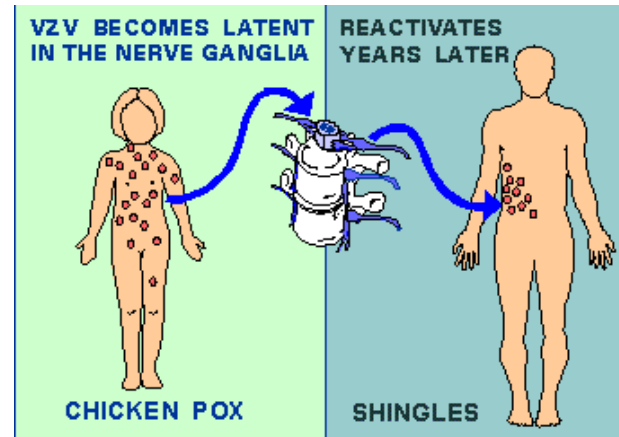
Objective

- Present the available evidence related to herpes zoster

Herpes zoster

Definition

- Herpes Zoster: reactivation of varicella zoster virus (VZV), leading to blisters in a dermatomal distribution
 - Following initial infection (varicella), VZV establishes permanent latent infection in dorsal root ganglia
 - Years to decades later VZV reactivates
 - VZV virions reappear & spread to skin through peripheral nerves



Prodromal pain

Manifestations & Symptoms

- ~74% herpes zoster patients have pain prior to rash onset
- Mean pain severity: 6/10
- Median duration: 4 days
- % overall herpes zoster burden of illness: 9%
- Starts as abnormal skin sensation, itching or tingling
 - Precedes rash by about 4 days
 - Results in medical consultations

Ref: Drolet *Human Vaccines* 2013, Benbernou *European Journal of Pain* 2011 Mean pain severity (ZBPI worst pain score) estimated among individuals reporting clinically significant pain (i.e., worst ZBPI score \geq 3) during each phase of the disease

Herpes zoster

Manifestations & Symptoms

- 30% lifetime risk
- 95% of patients have pain at rash onset
- Mean pain severity at rash onset: 6/10
- Median duration of herpes zoster episode: 33 days
- % overall herpes zoster burden of illness:
 - Acute/subacute: 70%

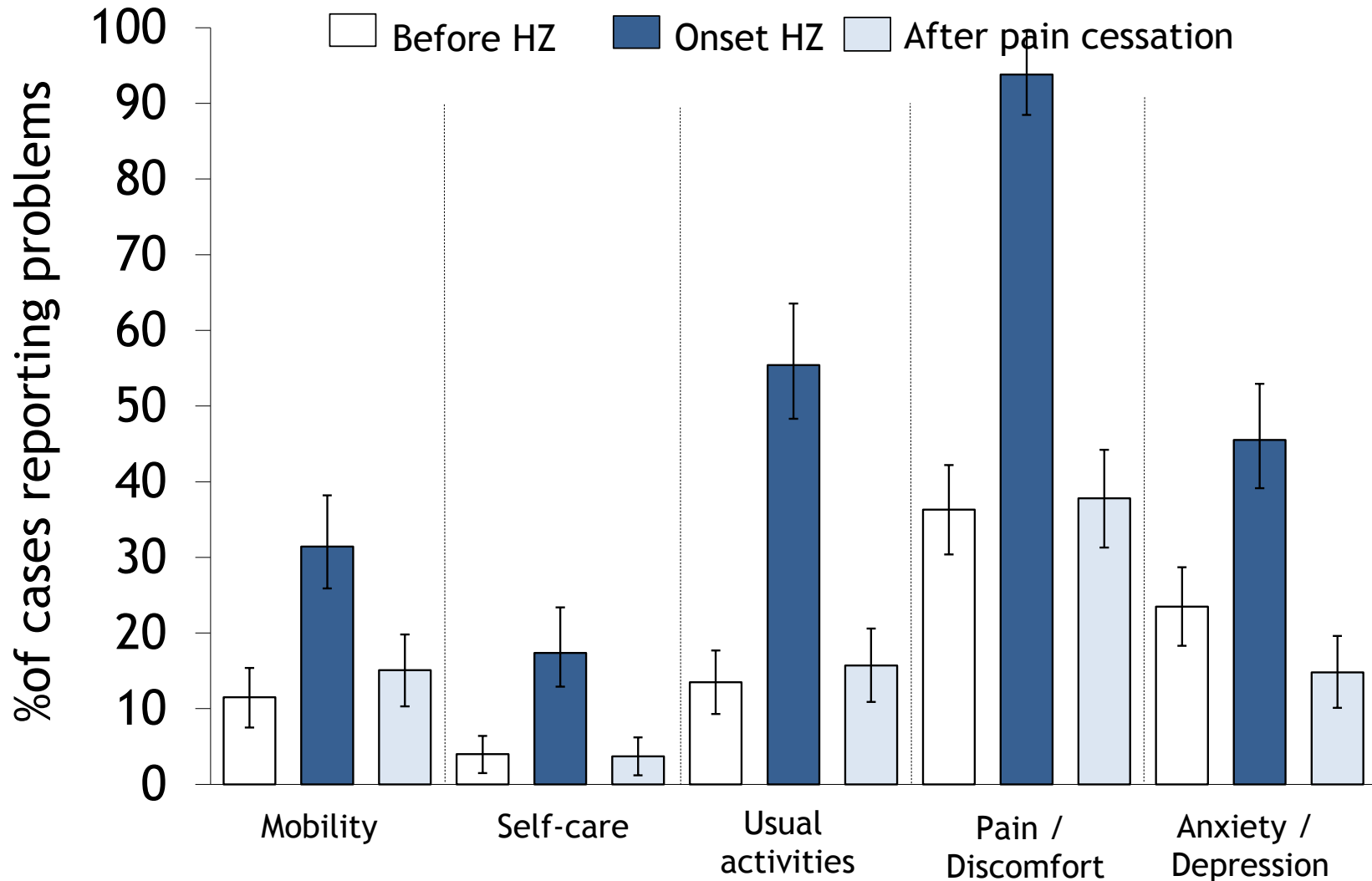
Herpes zoster

Manifestations & Symptoms

- Rash:
 - Dermatomal distribution: 1) thoracic > 2) lumbar, trigeminal, & cervical > 3) sacral, other cranial dermatomes
- Key symptom: Pain
 - Can be excruciating
 - Described as aching, burning, stabbing, shock-like
 - Often associated with:
 - Altered or painful sensitivity to touch
 - Provoked by trivial stimuli like bed sheets or breeze
 - Exaggerated, prolonged response to pain
 - Unbearable itching

Herpes zoster

Impact on quality of life (patients 50+ years old)



Post-herpetic neuralgia (PHN)

Definition, Manifestations & Symptoms

- PHN: Pain persisting more than 90 days after rash onset
 - Definition may vary, linked to long-lasting pain
- 22% (8-26%) of herpes zoster patients develop PHN
 - proportion very dependent on definition
- Mean severity at PHN onset: 6/10
- Median duration from rash onset: 170 days
- % overall herpes zoster burden of illness: 20%

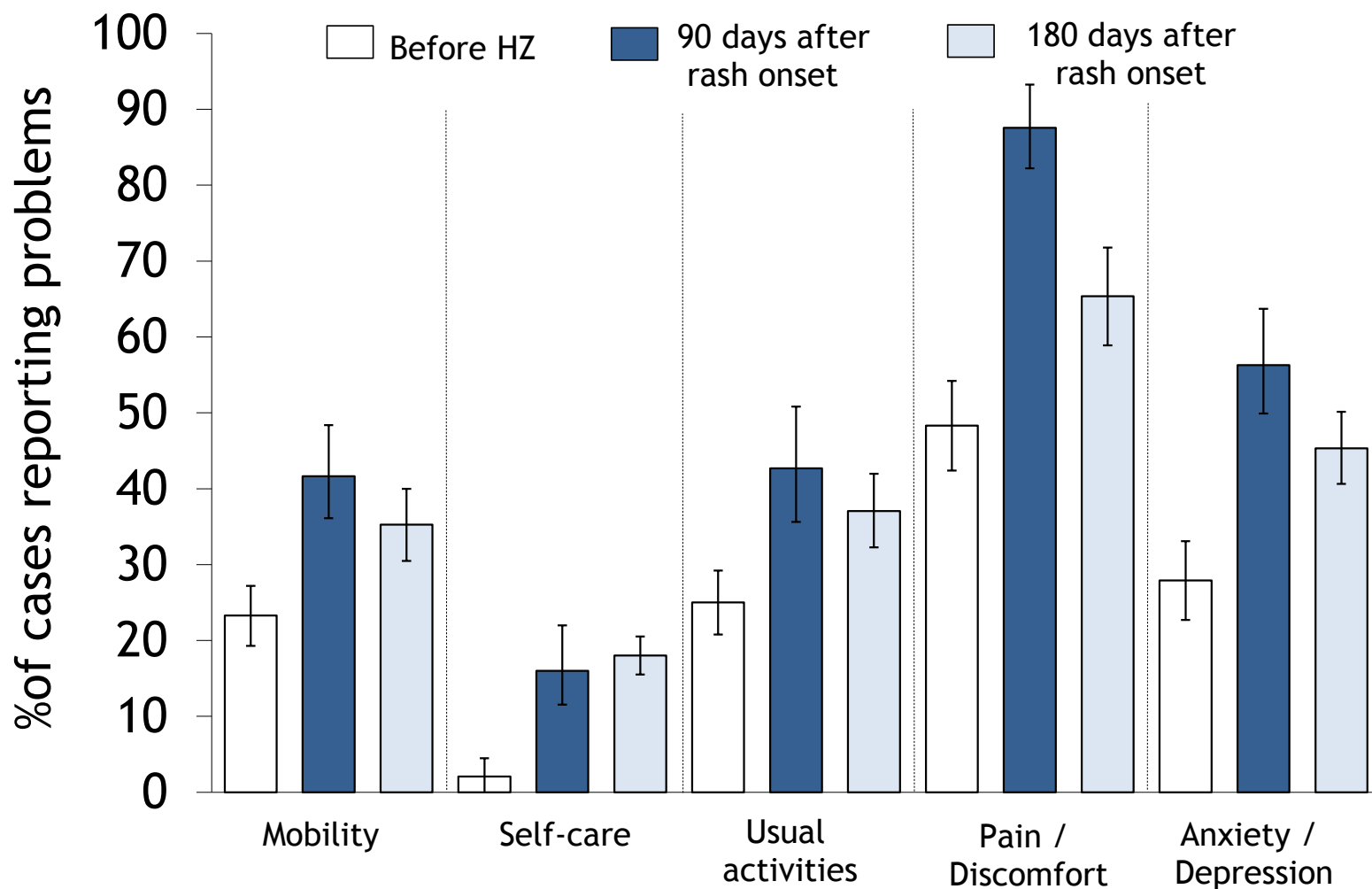
Post-herpetic neuralgia (PHN)

Definition, Manifestations & Symptoms

- Pain persists months and even years (median=6 months)
- PHN prevention with antivirals (<72 hrs after rash onset):
 - reduces acute pain
 - hastens rash resolution
 - ability to prevent PHN remains controversial
- PHN treatment:
 - Tricyclic antidepressants, anticonvulsants, topical agents, opioids, nerve blocks, others
 - Partial or inconsistent efficacy
 - Important side effects

Post-herpetic neuralgia

Impact on quality of life (patients 50+ years old)



Ref: Drolet, *Human Vaccines* 2013; Schmader *CID* 2001: **Physical** (Chronic fatigue, Weight loss, Inactivity, Insomnia), **Social** (change in social life), **Psychological** (Anxiety, Depression, Suicidal ideation), **Functional** (Interferes with dressing, eating, bathing, cooking)

Other Herpes zoster complications

Manifestations & Symptoms

- Herpes zoster Ophthalmicus (HZO):
 - Ophthalmic division of trigeminal nerve
 - ~15% of cases
 - If untreated, 50-70% develop acute ocular complications
 - chronic complications, reduced vision, even blindness
- Neurologic:
 - Invasion by VZV of vascular or neurologic structures
 - Encephalitis, myelitis, optic neuritis, palsies, stroke syndromes
 - Hearing impairment, vertigo, loss of taste sensation
- Deaths mostly occur among the immunocompromised
 - 0.25-0.51 per 1 million population^[1]
 - 7-25 per 100,000 case^[1,2]

Epidemiology & Burden of Disease

Global Burden of Herpes zoster

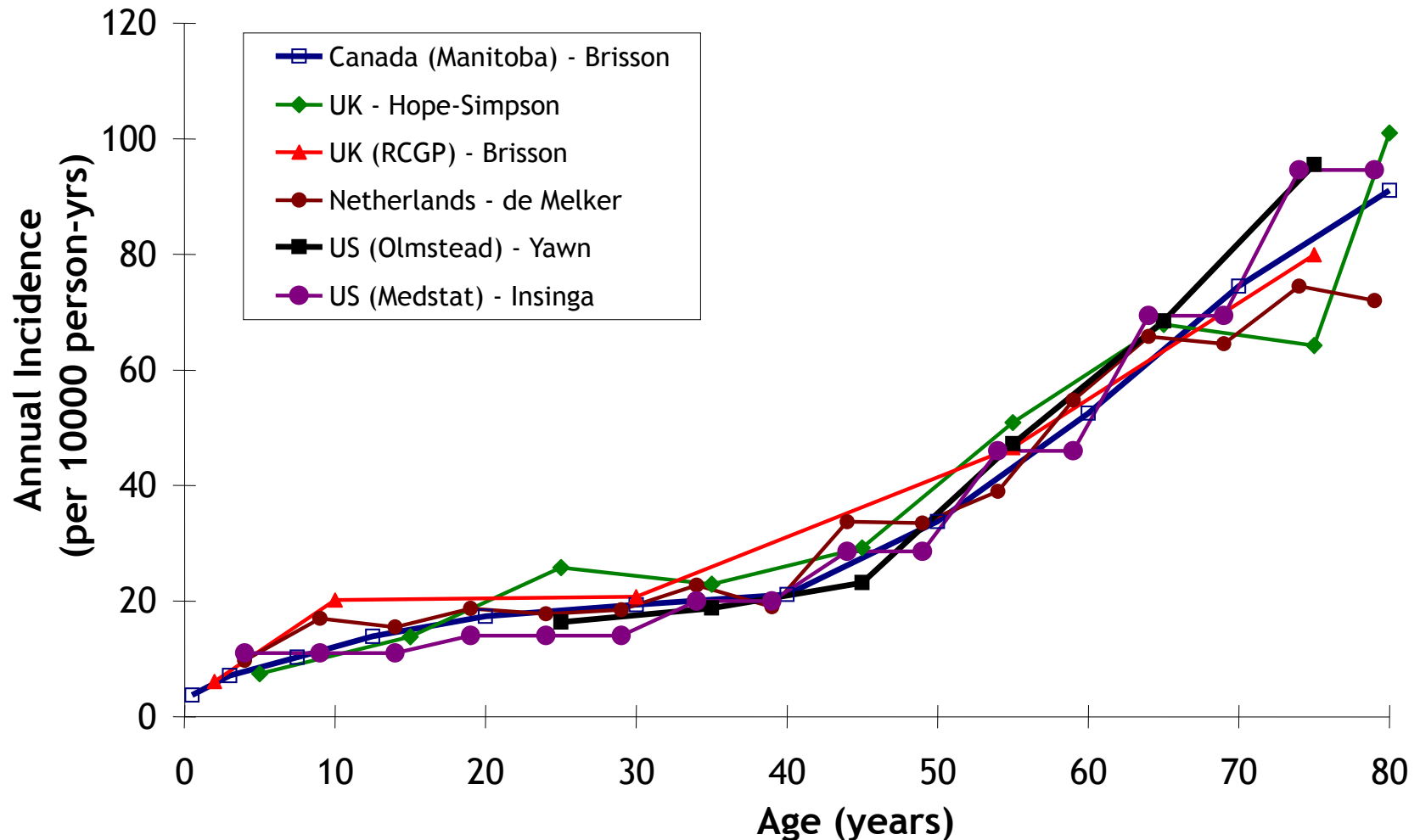
Data availability

- Incidence of Herpes zoster and mortality data
 - Most data from Europe, North America and Australia
 - No data from low and low-middle income countries (LMIC)^[1]

Herpes zoster incidence by age

Highly consistent findings between high income countries

Lifetime risk=20-35%, Steep increase in incidence with age

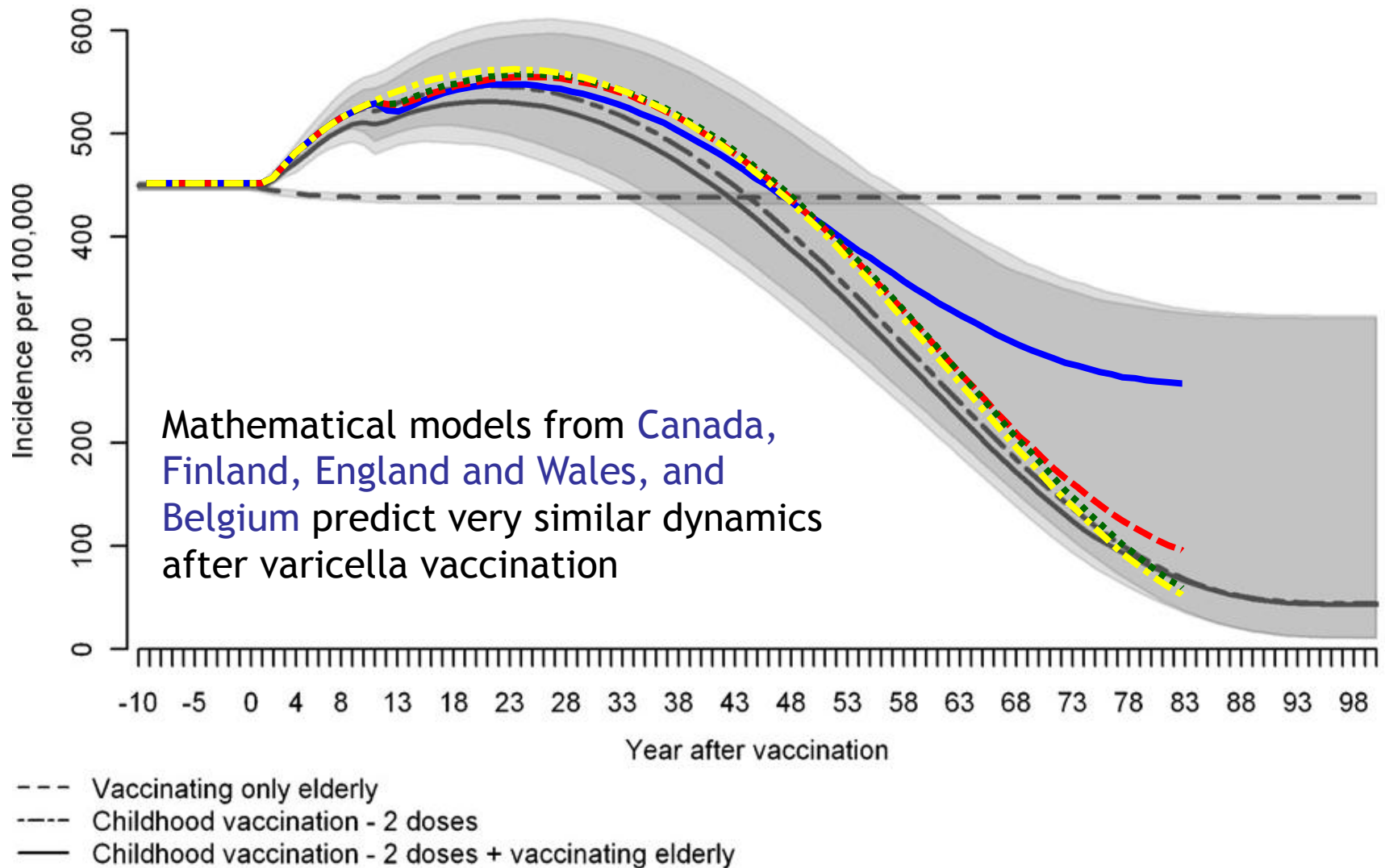


Main concern about varicella vaccination

Unknown impact on the epidemiology of zoster

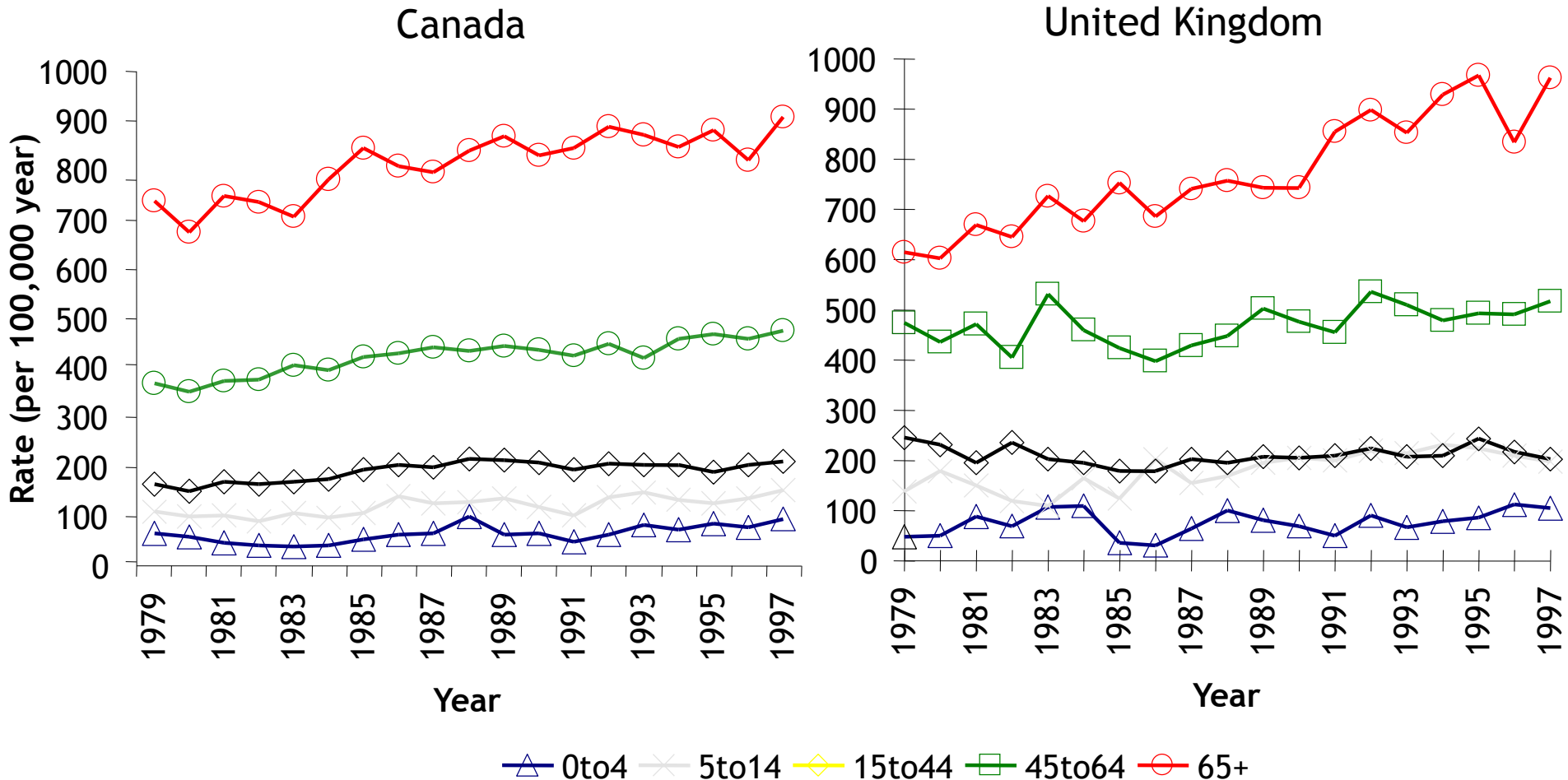
- Herpes zoster may occur more frequently in adults who have not been boosted by varicella contacts
 - Individuals with > 3 exposures to varicella have 1/5th risk of zoster compared to unexposed [1]
 - Adults living with children have higher exposure to varicella and significantly lower herpes zoster incidence [2]
- If this is so then reduction of varicella incidence after mass vaccination could increase zoster incidence
- Note: Evidence of the impact of exposure to varicella on risk of zoster is still inconclusive [3]

Predicted impact of varicella vaccination on Herpes zoster



Increase in Herpes zoster

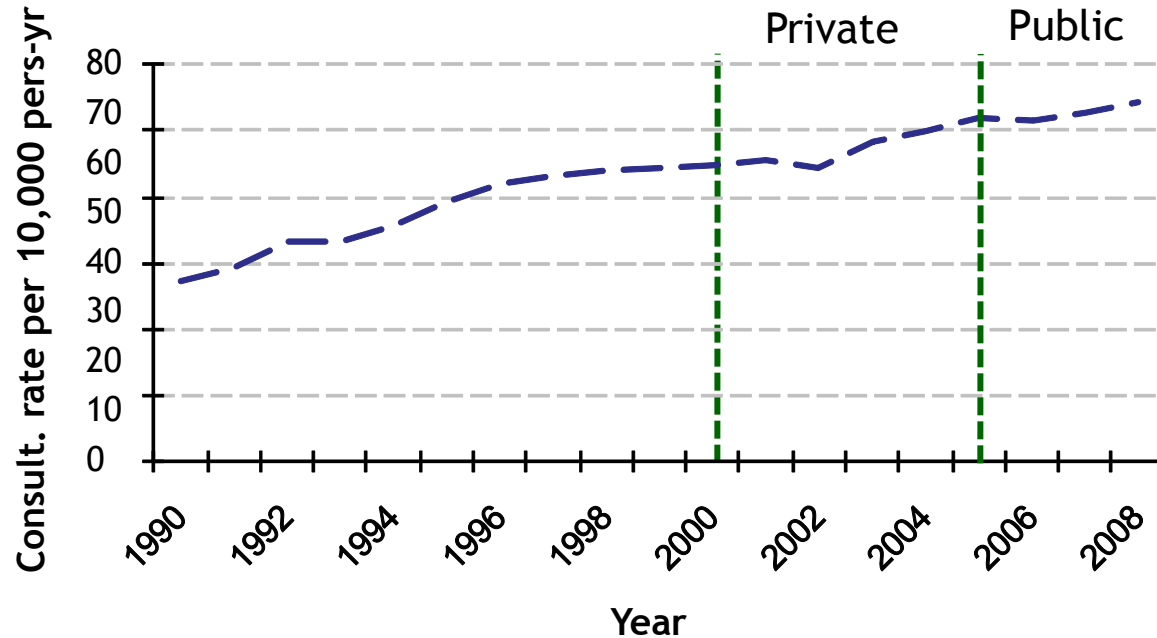
Prior to varicella vaccination in high income



Herpes zoster after varicella vaccination

Increase in herpes zoster in most high income countries

Example from Québec



⌘. Private=23%, Public= 52% (2006), 89% (2007) and 90% (2008);

Herpes zoster after varicella vaccination

Increase in herpes zoster in most high income countries

Example from Canada and US

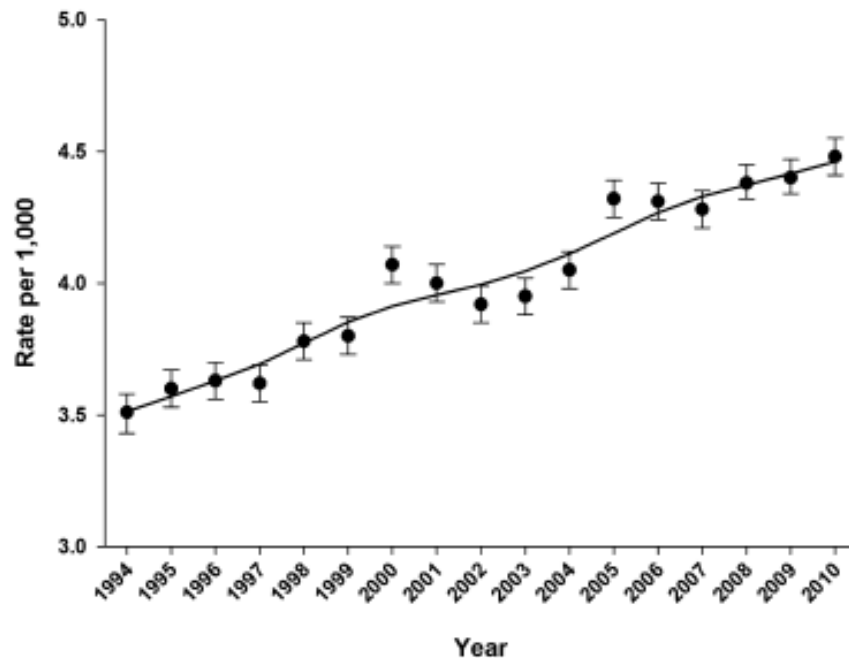
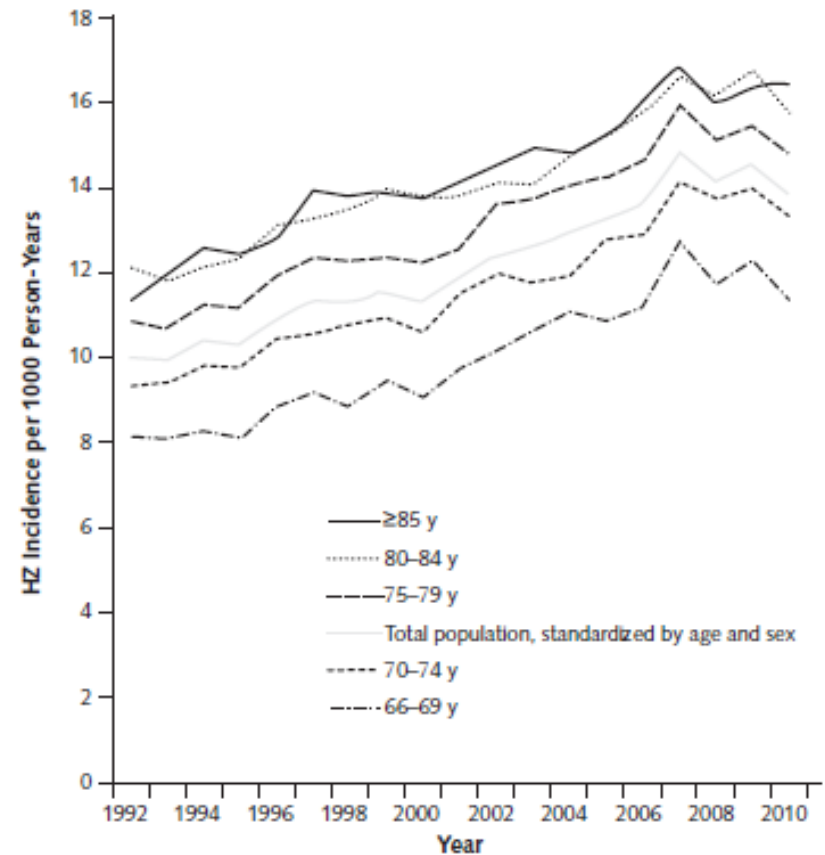


Fig. 1. Crude rates of medically attended shingles per 1000 population (with 95% confidence intervals and LOESS fit curve), 1994–2010.

Figure. HZ incidence among Medicare beneficiaries older than 65 years, by age group, 1992–2010.



Increase in Herpes zoster

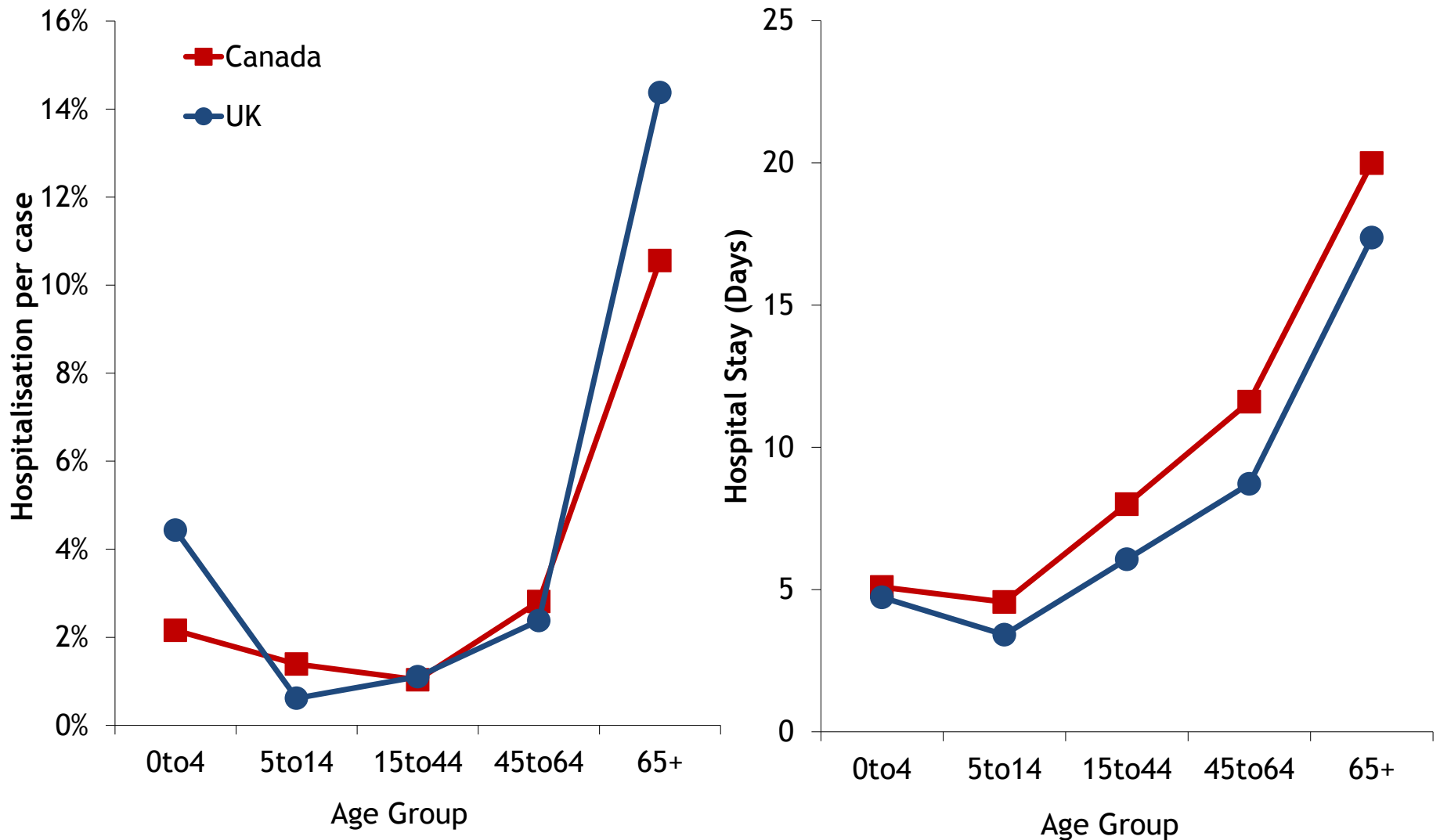
Evidence from high income countries (HIC)

- Herpes zoster is increasing in HIC
 - cannot directly attribute the increase to varicella vaccination
 - herpes zoster was increasing prior to vaccination programs
- Why is herpes zoster increasing?
 - reduced exposure to VZV?
 - varicella vaccination
 - demographic/societal changes in HIC[&]
 - more immunocompromised?
- Too early to determine whether increase in herpes zoster is partially due to varicella vaccination

[&]. decreasing % women with ≥ 1 child and numbers of children per woman, increasing # single-parent families and decreasing contact between grandparents and grandchildren

Herpes zoster severity increases with age

Hospitalizations and Length of Stay



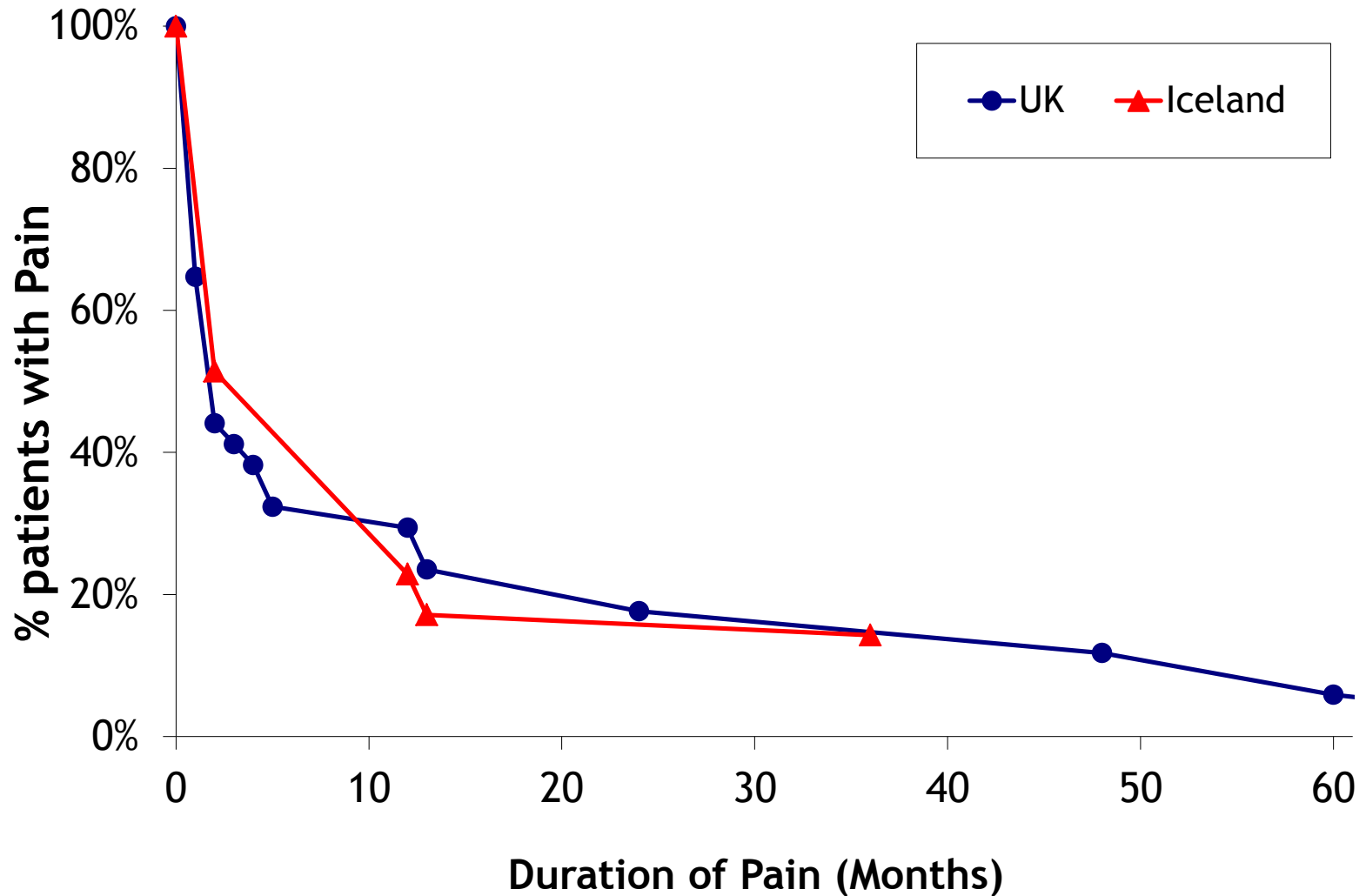
Herpes zoster

Risk factors

- Immunosuppression from any cause
 - hematologic malignancies, HIV and immunosuppressive medications
 - relative risk (RR) vs. non-immunosuppressed > 10-fold^[1-2]
- Race
 - Blacks (vs whites) RR=0.35-0.46^[3-4]
 - People born in countries with late varicella onset RR=0.56^[4]
- Sex
 - Women (vs men) RR=1.1, placebo arm zoster vaccine trial^[5]
 - Results not consistent between studies^[4]
- Exposure to children
 - Studies suggest protective effect of exposure to children ^[4,6,7]
 - Results are not consistent between studies^[4,8]
- Stress or trauma, diabetes and higher social class^[9,10]

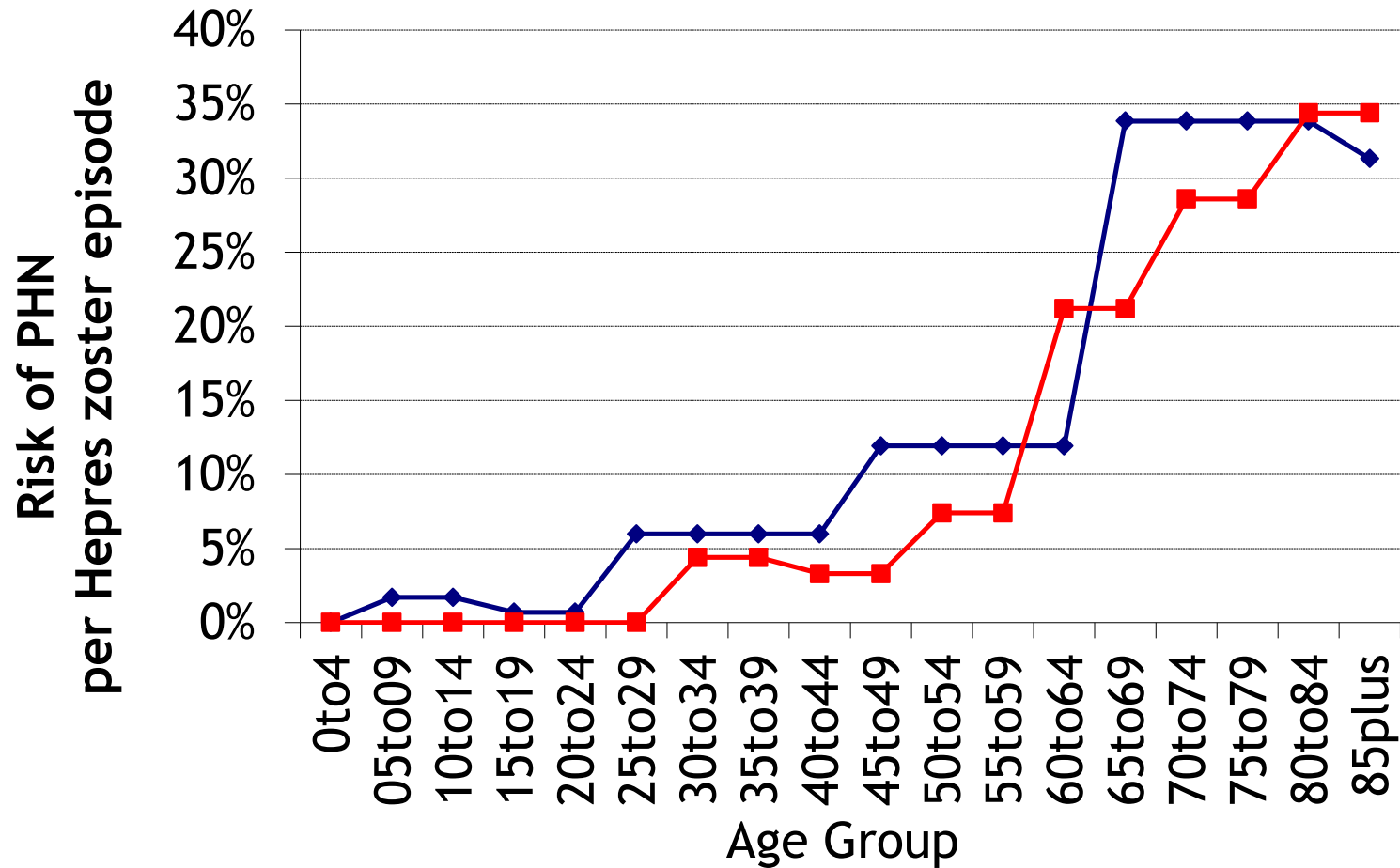
Post-herpetic neuralgia

Duration of pain



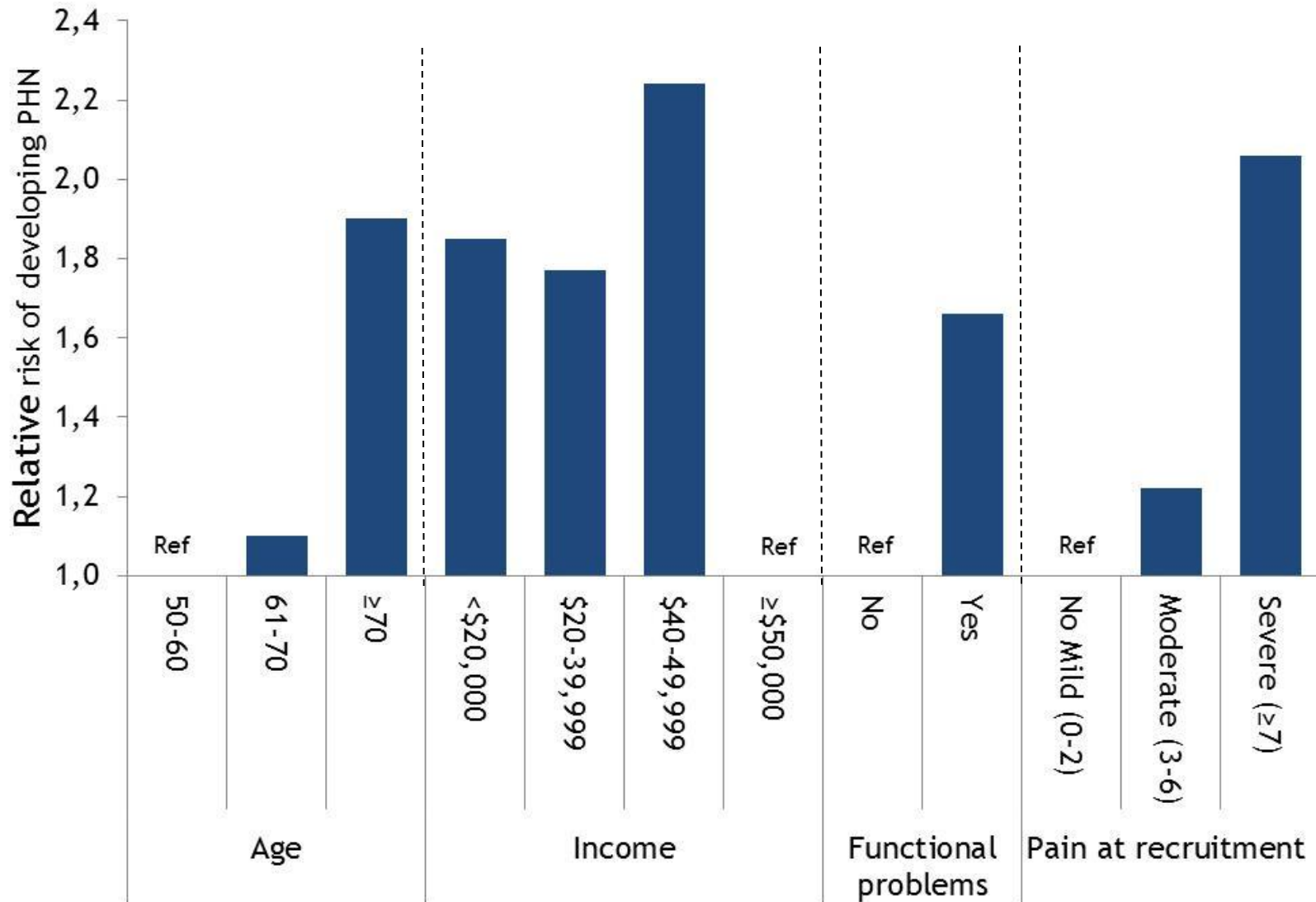
Post-herpetic neuralgia

Incidence by age, UK



Post-herpetic neuralgia

Risk factors



Ref: Drolet *Journal of Pain* 2010

Vaccine efficacy, duration & safety

Herpes zoster vaccine characteristics

- Currently available - Merck live Oka/Merck VZV vaccine
- Licensed in over 60 countries
- Indicated in immunocompetent individuals aged ≥ 50 years
- Live vaccine - contraindicated in immunosuppressed
- Potency 18,700-60,000 PFU per dose
 - Median potency 24,600 PFU
 - 14 x as potent as varicella vaccine

Clinical studies

- Shingles Prevention Study (SPS)^[1]
 - Randomized clinical trial
 - 38,546 individuals aged ≥ 60 years
- Randomized trial among younger subjects^[2]
 - 22,439 individuals aged 50-59 years
- Short-term Persistence Study^[3]
 - Continuation of follow-up of 14,000 SPS subjects

Efficacy of herpes zoster vaccine (VE)

Clinical trials (short term) [1,2]

	Incidence of HZ			Burden of illness			Incidence of PHN		
	V	P	VE (95% CI)	V	P	VE (95% CI)	V	P	VE (95% CI)
Age	-----			-----			-----		
50-59 yrs	2.0	6.6	70 (54-81)	0.1	0.5	73 (53-85)	NA	NA	NA
60-69 yrs	3.9	10.8	64 (56-71)	1.5	4.3	66 (52-76)	0.3	0.7	66 (20-87)
≥ 70yrs	7.2	11.5	38 (28-52)	3.5	7.8	55 (40-67)	0.7	2.1	67 (43-81)

V: Vaccine group; P: Placebo group; VE: Vaccine efficacy

Burden of illness score is a composite measure of HZ incidence, severity and duration of pain

Vaccine effectiveness US post-licensure studies (≥60 years):

- Herpes zoster = 55%^[3] and 48%^[4]
- Ophthalmic herpes zoster = 63%^[3]
- Hospitalizations coded as herpes zoster = 65%^[3]
- PHN = 59%^[4]
- Immunosuppressed = 37% (95%CI: 6-58)^[4]

Duration of herpes zoster vaccine efficacy (VE)

Shingles Prevention Study (SPS), Short-Term Persistence Substudy (STPS), and the Combined SPS and STPS

	Incidence of HZ	Burden of illness	Incidence of PHN
	VE, % (95% CI)	VE, % (95% CI)	VE, % (95% CI)
Time since randomization			
Years 0.0-4.9	51 (44-58)	61 (51-69)	67 (48-79)
Years 3.3-7.8	40 (18-56)	50 (14-71)	60 (-10-87)
Years 0.0-7.8	49 (52-55)	59 (49-67)	65 (47-77)

Safety of herpes zoster vaccine

Immunocompetent adults \geq 50 years

- The vaccine was well-tolerated in the SPS^[1,2]
 - Similar proportions (1.4%) of participants who received the vaccine (n=19,270) or the placebo (n=19,276) reported serious adverse events
 - Varicella-like rash at the site of injection was the only adverse event statistically more frequent among vaccinated
- Safety of the vaccine was confirmed in the RCT among younger subjects (50-59 years) ^[3]
 - 0.6% and 0.5% of participants who received the vaccine (n=11,211) or the placebo (n=11,228) reported serious adverse events
- Vaccine safety has been demonstrated in post-licensure studies^[4-7]

Concomitant administration of Herpes zoster vaccines with other vaccines

- Concomitant administration of inactivated influenza and herpes zoster vaccines:
 - No reduction in immunogenicity^[1]
- Concomitant administration of pneumococcal polysaccharide and herpes zoster vaccine:
 - no significant difference in adverse events between arms concomitantly or non-concomitantly vaccinated^[2]
 - Herpes zoster vaccine efficacy not affected^[3]

Safety of herpes zoster vaccine

Immunocompromised adults

- Herpes zoster vaccine is contra-indicated in persons who are immunosuppressed from any cause
- Safety in immunocompromised persons has been examined in post-licensure studies^[1-5]:
 - Authors claim no significant increased risk in serious adverse effects in these studies
 - However, studies are limited, particularly in terms of sample size

Ref: 1. Chakravarty *Arthritis & Rheumatism* 2012; 2. Chakravarty Annual Scientific Meeting 2012; 3. Naidus *Am J Hematol* 2012; 4. Zhang *Arthritis Res Ther* 2011; 5. Parrino *ACR/ARHP Scientific Meeting* 2011

Cost-effectiveness

Literature review

Cost-effectiveness of herpes zoster vaccination

- Review from Szucs & Pfeil^[1], including new publications^[2]
- 12 studies:
 - All from Europe and North America
 - 5 out of 12 funded by industry
- Consistent Results:
 - All studies except one considered vaccination to be cost-effective
 - Van Lier (2010) because of low CEA threshold (€20,000) in Netherlands
 - Herpes zoster vaccination is cost-effective when:
 - the vaccine is given at about 65-70 years of age, and
 - vaccine protection against PHN is longer than 10-15 years^[2]

Cost-effectiveness of herpes zoster vaccination

Quality of the evidence

- Study quality - Generally good
 - 'moderate' to 'moderate to good' according to the BMJ criteria^[1]
- Consistency of findings - Cost-effective
 - if vaccine is given at about 65-70 years of age
 - dependent on duration of protection
 - if vaccine protection against PHN is longer than 10-15 years
- Magnitude of effect - Variable
 - Studies vary from very cost-effective to not cost-effective
- Evidence - Indirect
 - All are modeling studies

Key remaining issues

- Duration of protection of the zoster vaccine?
 - Recent trial results indicate possible waning of protection^[1]
 - Key issue is long-term protection against severe zoster and PHN, which is unclear^[1]
 - Burden of Illness (BOI): $VE_{0-5yrs}=61\%$ (51 to 69) vs $VE_{3-8yrs}=50\%$ (14 to 71)
 - PHN: $VE_{0-5yrs}=67\%$ (48 to 79) vs $VE_{3-8yrs}=60\%$ (-10 to 87)
- Increase in herpes zoster after varicella vaccination?
 - Could have an impact on age at vaccination
 - May be cost-effective to vaccinate at younger age
- Epidemiology and burden of disease of herpes zoster in low to middle income countries?

Thanks!