

# Herpes zoster vaccination and quality of life in ageing population

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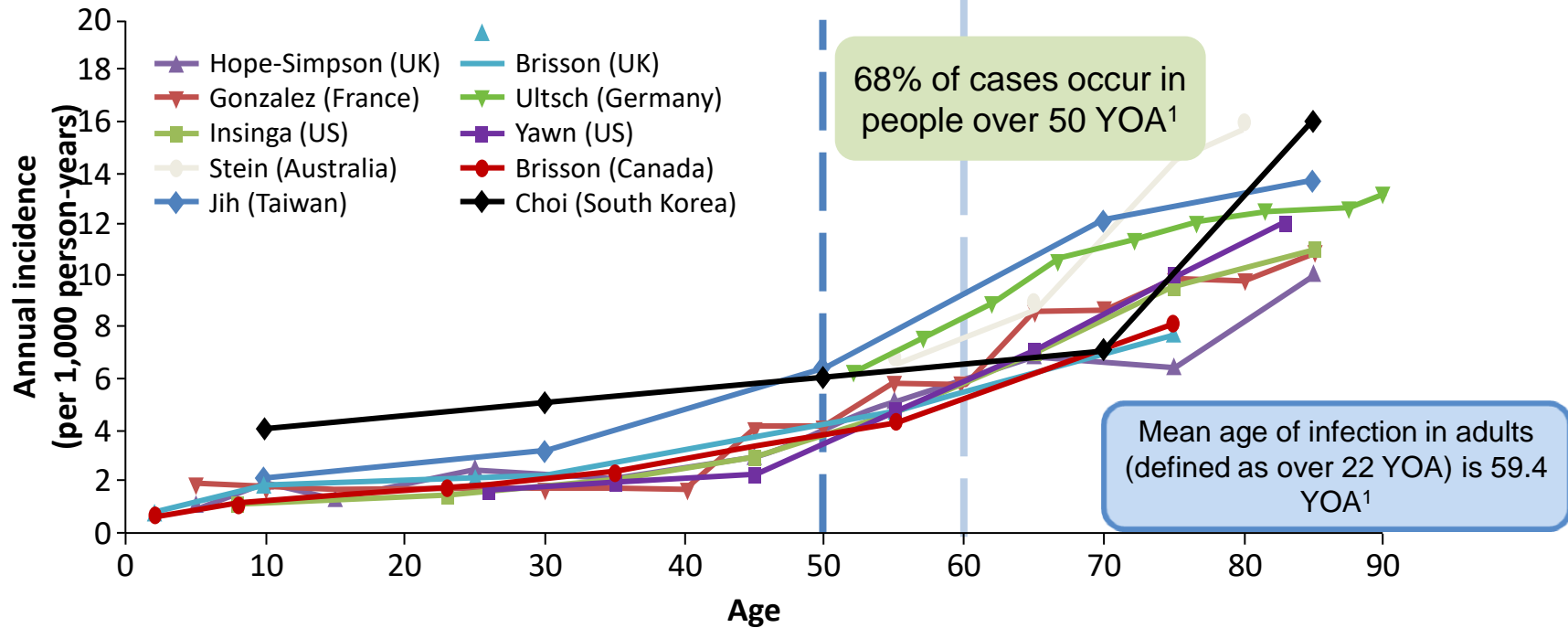
## **Conflict of Interest, 2017**

- Honoraria for lecturing or as member of advisory boards from Pfizer, GSK und Sanofi-Pasteur
- Honoraria for conducting clinical vaccine trials for GSK and Pfizer

# Zoster ophthalmicus



# Age-specific HZ incidence rates<sup>1</sup>

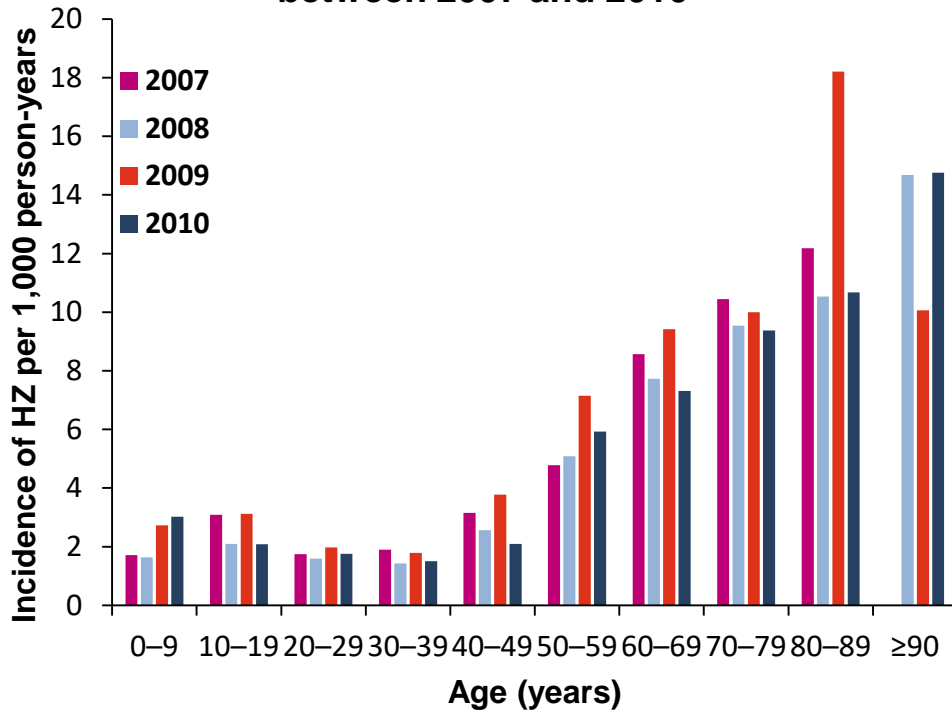


Several studies have shown that the incidence of HZ increases substantially with age<sup>1,2</sup>

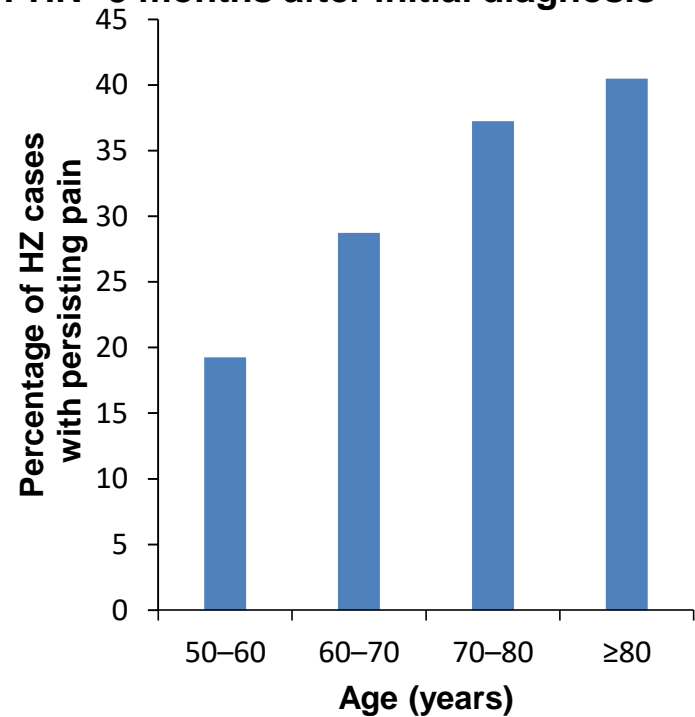
1. Yawn and Gilden. *Neurology* 2013; 81: 928930; 2. Harpaz et al. *MMWR Recomm Rep* 2008; 57: 1–30

# France: Incidence

The incidence of HZ between 2007 and 2010<sup>1</sup>



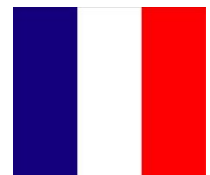
The percentage of patients with HZ who experienced PHN\* 3 months after initial diagnosis<sup>2</sup>



**HZ incidence has remained stable between 2007 and 2010 at 3.82 cases per 1,000 person-years, but HZ and PHN incidences increase with age**

\* PHN defined as persistent pain occurring at least 1 month after initial diagnosis of HZ  
 HZ, herpes zoster; PHN, post-herpetic neuralgia

1. INSERM Sentinelle. [www.sentiweb.org](http://www.sentiweb.org) [Accessed May 2014]; 2. Mick et al. *Rev Epidemiolog Sante Publique* 2010; 58: 393-401

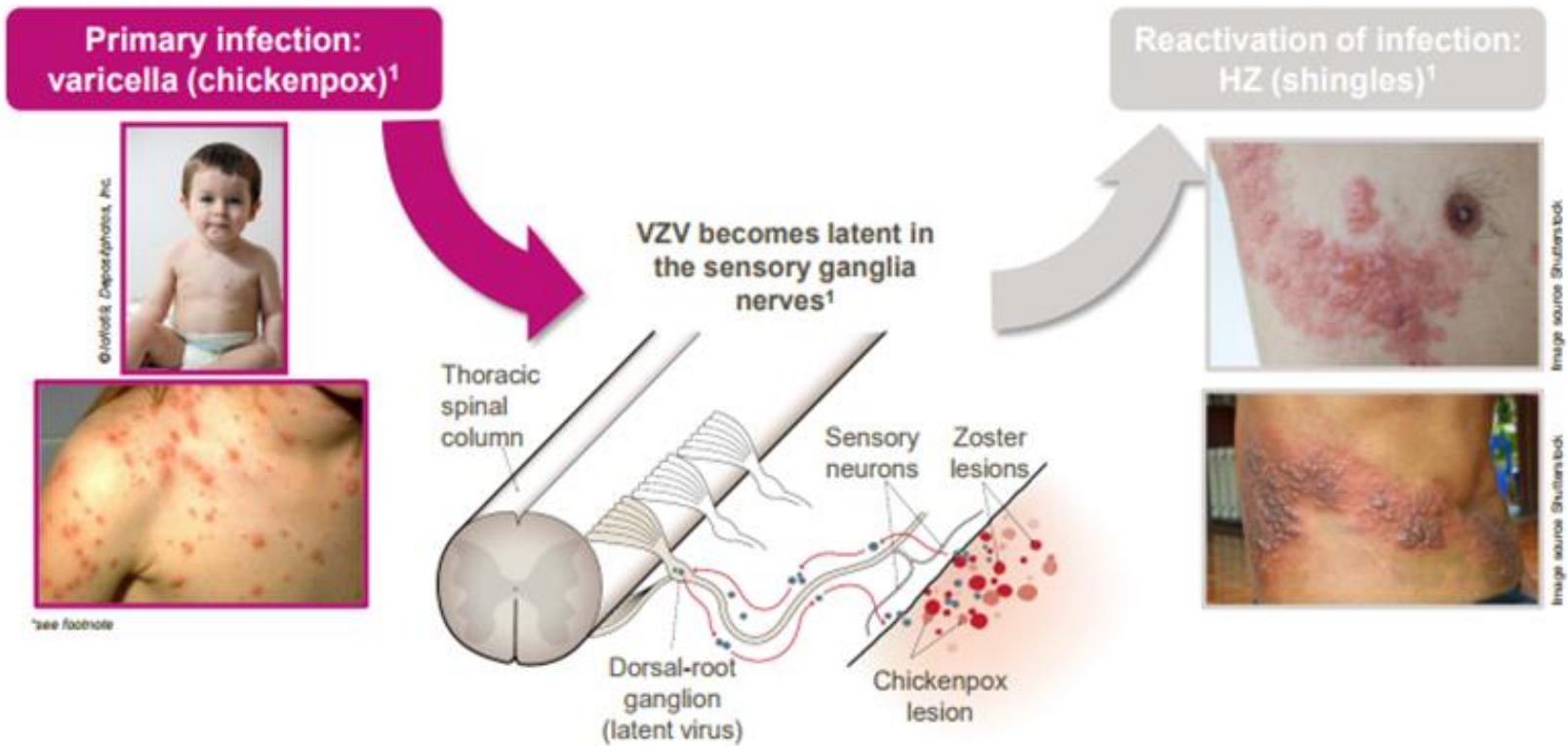


## Increase in Herpes zoster in high income countries

- May be related to an increase in varicella vaccination?
- However, incidence of HZ was increasing prior to varicella vaccination programs
- Reduced exposure to varicella zoster virus
- More immune-compromised patients
- Demographic and societal changes
  - decreasing % of women with >1 child/no of children per women
  - More single-parent families
  - decreasing contact between grandparents and grandchildren



# HZ is caused by the reactivation of varicella zoster virus



\*see footnote



Image source Shutterstock

Image source Shutterstock

Approximately 99.5% of adults ≥40 years of age show serologic evidence of VZV infection, and one in three people develop shingles in their lifetime<sup>2</sup>

1. Kimberlin DW, et al. *New Engl J Med* 2007;356:1338-43; 2. Harpaz R, et al. *MMWR Recomm Rep* 2008;57:1-30  
 \*From American Academy of Pediatrics. *Varicella-Zoster Virus Infections*. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book*© 2015 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2015:846-860. Copyright © 2015. Reproduced with permission. HZ, herpes zoster; VZV, varicella zoster virus

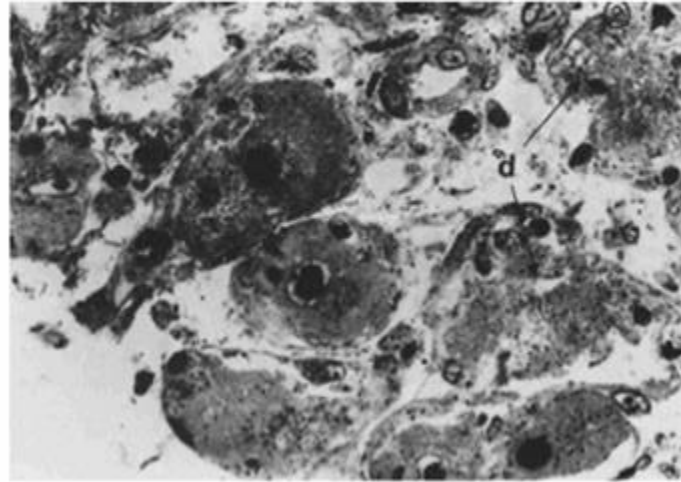


# Dorsal root ganglion

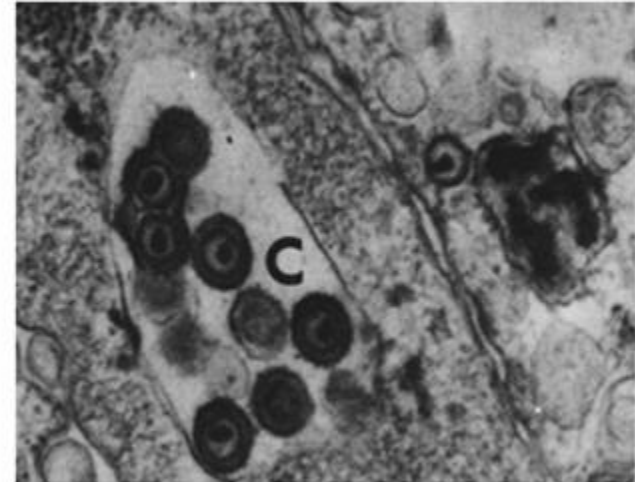
Scarring

Surviving nerve cells

Degeneration of neurons



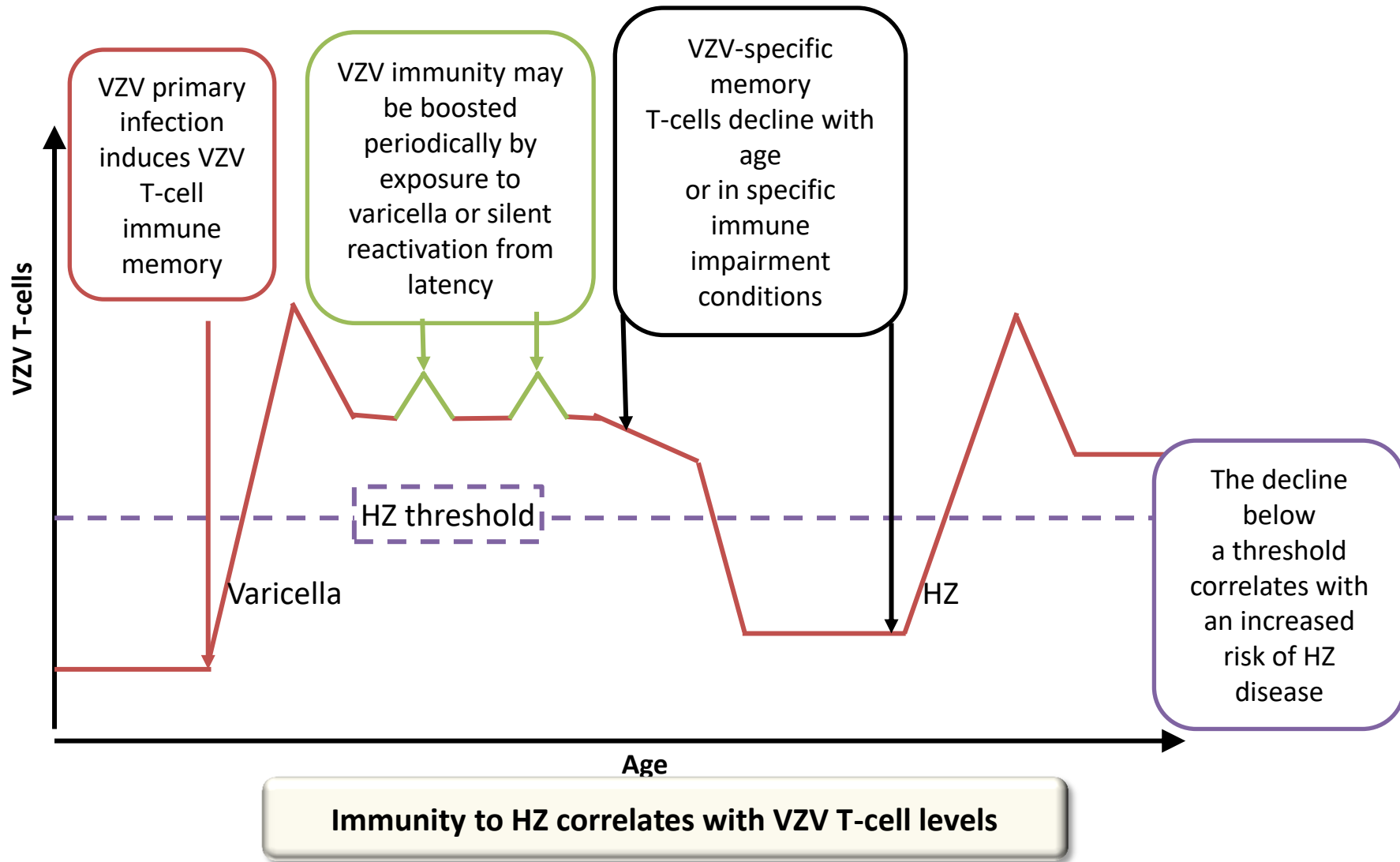
VZV virions in neurons



*Esiri and Tomlinson J Neurol Sciences 1971*



# Latent VZV infection and reactivation



## Licensed zoster vaccines

### Live-attenuated zoster vaccine (ZVL)

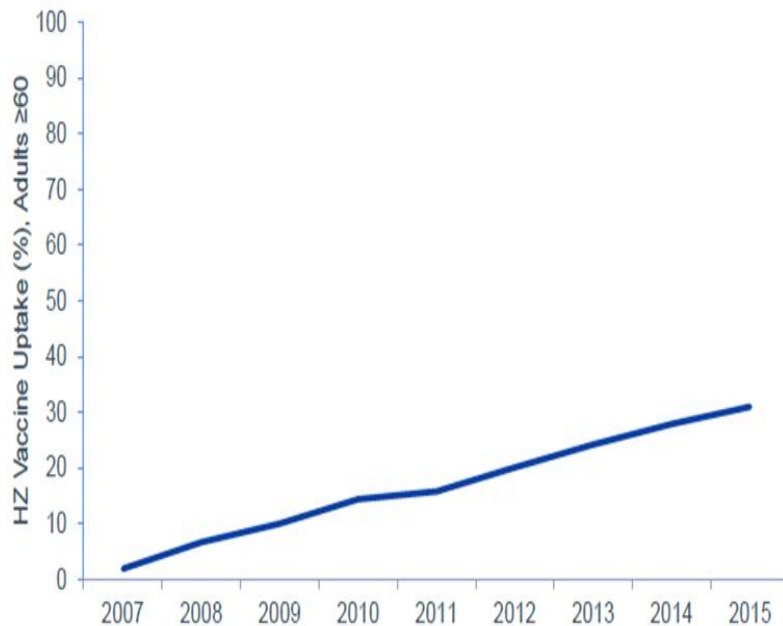
- Indicated for prevention of herpes zoster in individuals 50 years of age and older.
- First licensed 2006 (60 y) resp. 2011 (50 y)
- 1 dose

### HZ/su (adjuvanted subunit vaccine)

- Antigen: recombinant VZV Glycoprotein E (gE) + Adjuvant System AS01<sub>B</sub>
- Indicated for prevention of herpes zoster in adults aged 50 years and older.
- 2 Doses (month 0, 2)
- First licensed 10/2017 (Canada, USA)

# Current zoster vaccine recommendations

## USA, 2007-2015 Vaccination coverage



\* 2007: National immunization Survey (Lu et al, Vaccine 27:882-7); 2008-13: NHIS (Am J Prev Med 40:e1-6 & MMWR February 5, 2016 / 65(1);1-36)

## General recommendations

- UK: 70-79 y
- Canada: 60+ years
- France: 65-74 years
- Austria: 50 + years
- Saxonia (Germany): 50+
- Germany: not generally recommended
- <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/07/shingles-letter-jul16.pdf>
- <https://www.canada.ca/en/public-health/services/publications/healthy-living/update-use-herpes-zoster-vaccine.html>
- [https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-06/zostavax\\_en\\_sapub\\_ct13478\\_val.pdf](https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-06/zostavax_en_sapub_ct13478_val.pdf)
- <https://www.bmgf.gv.at/home/Impfplan>
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- [https://www.slaek.de/media/dokumente/02medien/Patienten/gesundheitsinformationen/impfen/Synopsis\\_2017\\_.pdf](https://www.slaek.de/media/dokumente/02medien/Patienten/gesundheitsinformationen/impfen/Synopsis_2017_.pdf)

## HZ/su pivotal phase III programme: ZOE-50 and ZOE-70<sup>1,2</sup>

*New England Journal of Medicine, 2015, 2016*

Study design and objectives	ZOE-50 <sup>1</sup> (Zoster-006)	ZOE-70 <sup>2</sup> (Zoster-022)
Study design	Randomised, observer-blind, placebo-controlled, multicentre, multinational (North America, Europe, Latin America, Asia-Pacific)	
Schedule	2 doses administered 2 months apart	
Primary objectives	<b>VE<sub>HZ</sub> in subjects ≥50 years of age</b>	<b>VE<sub>HZ</sub> in subjects ≥70 years of age</b>
Primary objectives (pooled analysis)	VE <sub>PHN</sub> in individuals ≥70 years of age VE <sub>HZ</sub> efficacy in individuals ≥70 years of age	
Actual enrollment	<b>16160</b>	<b>14816</b>

**ZOE-50 and ZOE-70 studies conducted at the same sites**  
**Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70**

PHN, postherpetic neuralgia; VE, vaccine efficacy



## ORIGINAL ARTICLE

## Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D.,

**ZOSTER-006 (Final Analysis): Vaccine efficacy against first or only episode of HZ during the entire study period in adults  $\geq 50$  YOA, overall and by age strata (mTVC)**

Age strata	HZ/su				Placebo				Vaccine Efficacy		
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	95% CI	
										LL	UL
$\geq 50$ YOA **	7344	6	23297.0	0.3	7415	210	23170.5	9.1	97.2	93.7	99.0
50-59 YOA *	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.6	89.6	99.4
60-69 YOA *	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.4	90.1	99.7
$\geq 70$ YOA**	1711	1	5127.9	0.2	1724	48	5083.0	9.0	97.9	87.9	100

N = number of subjects included in each group

n = number of subjects having at least one confirmed HZ episode

## HZ/su greatly reduced HZ complications, such as PHN, among all groups $\geq 50$ years of age\*<sup>1,2</sup>

### Pre-specified, pooled analyses from ZOE-50 and ZOE-70

Age, years	HZ/su		Placebo		VE <sub>HZ</sub> (95% CI) <sup>†</sup>
	PHN cases (n)	Rate (cases per 1000 person-years)	PHN cases (n)	Rate (cases per 1000 person-years)	
$\geq 50$	4 (13881)	0.1	36 (8346)	1.2	<b>91.2%</b> (75.9, 97.7)
$\geq 70$	4 (8250)	0.1	46 (14035)	0.9	<b>88.8%</b> (68.7, 97.1)

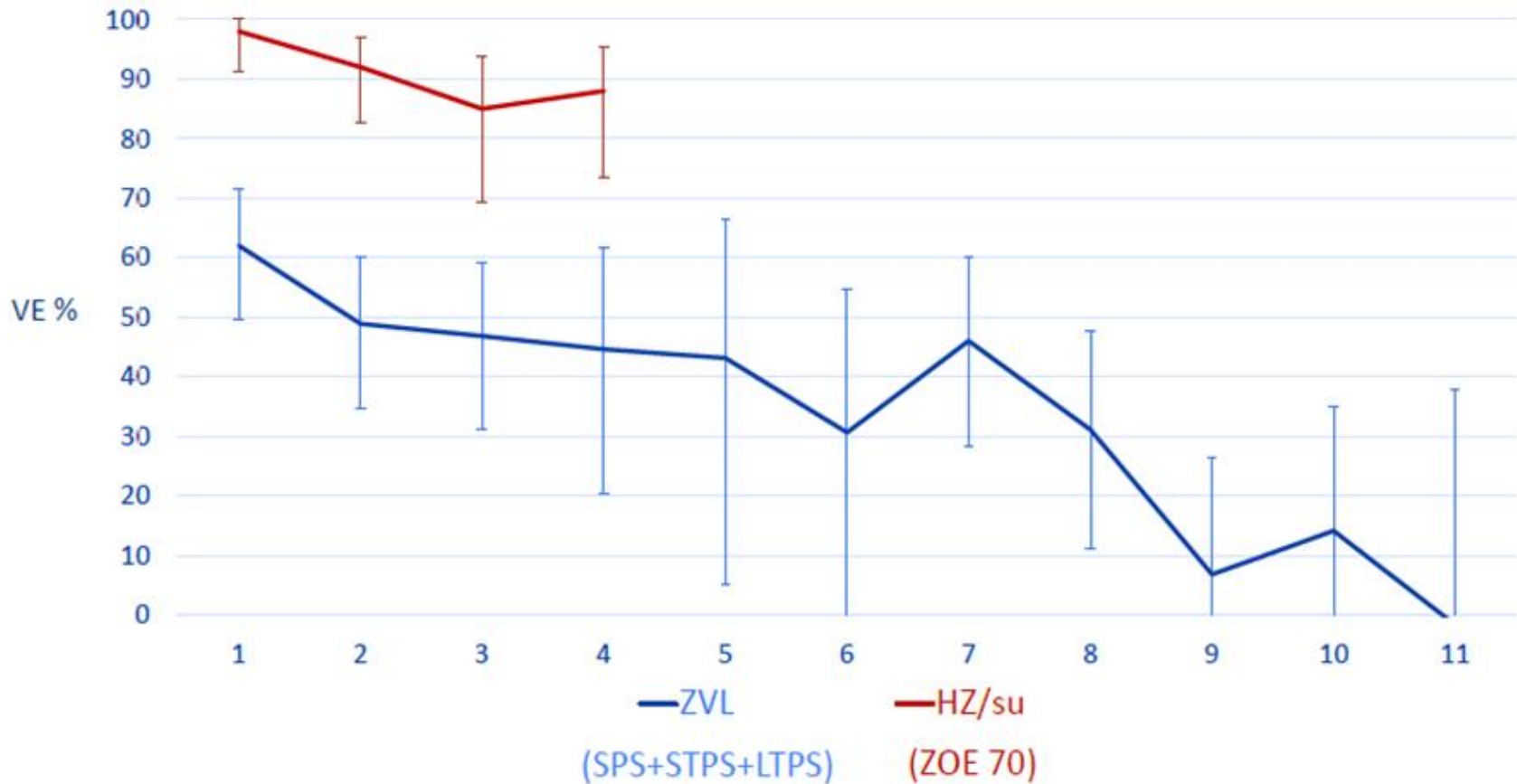
- In a post-hoc pooled analysis from ZOE-50 and ZOE-70, HZ/su also reduced non-PHN complications (HZ vasculitis, stroke, disseminated, ophthalmic, neurological and visceral disease)<sup>2</sup>
  - VE in subjects  $\geq 50$  years of age: 93.7% (95% CI 59.5, 99.9)
  - VE in subjects  $\geq 70$  years of age: 91.6% (95% CI 43.4, 99.8)

PHN defined as HZ-associated pain rated as  $\geq 3$  on a 0–10 scale, occurring or persisting for at least 90 days following the onset of rash using Zoster Brief Pain Inventory questionnaire. Pooled data from ZOE-50 (subjects  $\geq 50$  years of age) and ZOE-70 (subjects  $\geq 70$  years of age)

\*All subjects randomised in the study who received a second dose of the vaccine. Final analysis data cut-off date: July 1, 2014; mean follow-up 3.8 years;  $\dagger p < 0.001$  for both comparisons

CI, confidence interval; HZ/su, herpes zoster subunit vaccine; PHN, postherpetic neuralgia; VE, vaccine efficacy

# Vaccine efficacy against HZ for ZVL and HZ/su following vaccination



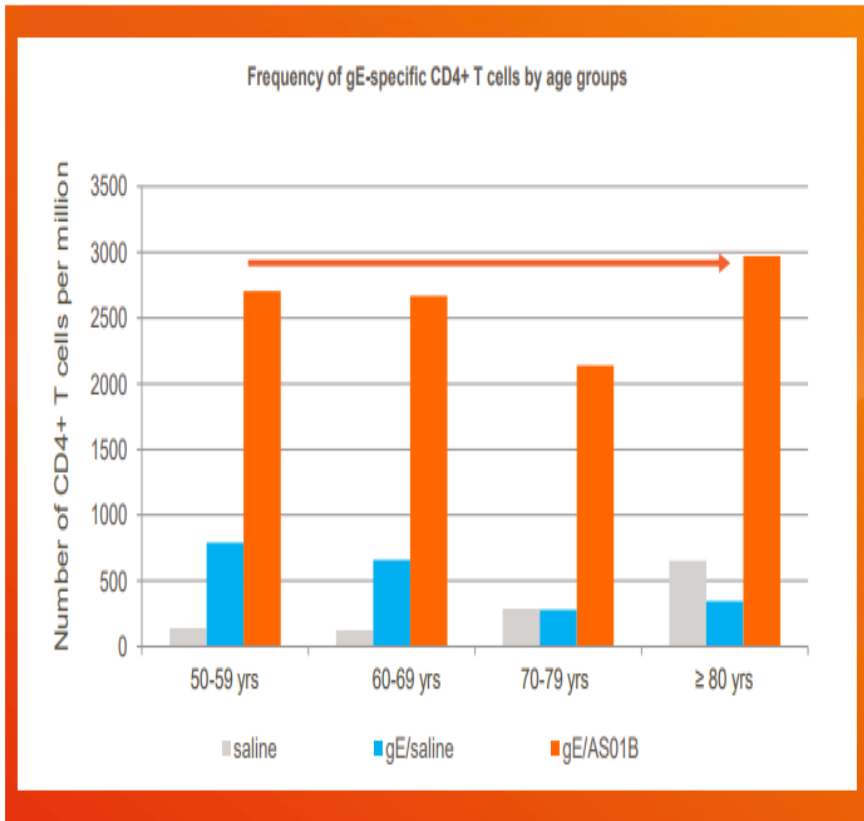
Note: The Shingles Prevention Study, Short-term Persistence Study, and Long-term Persistence Study followed the same study population in a randomized control trial over time.

Cunningham et al. N Engl J Med 2016; 75:1019-1032

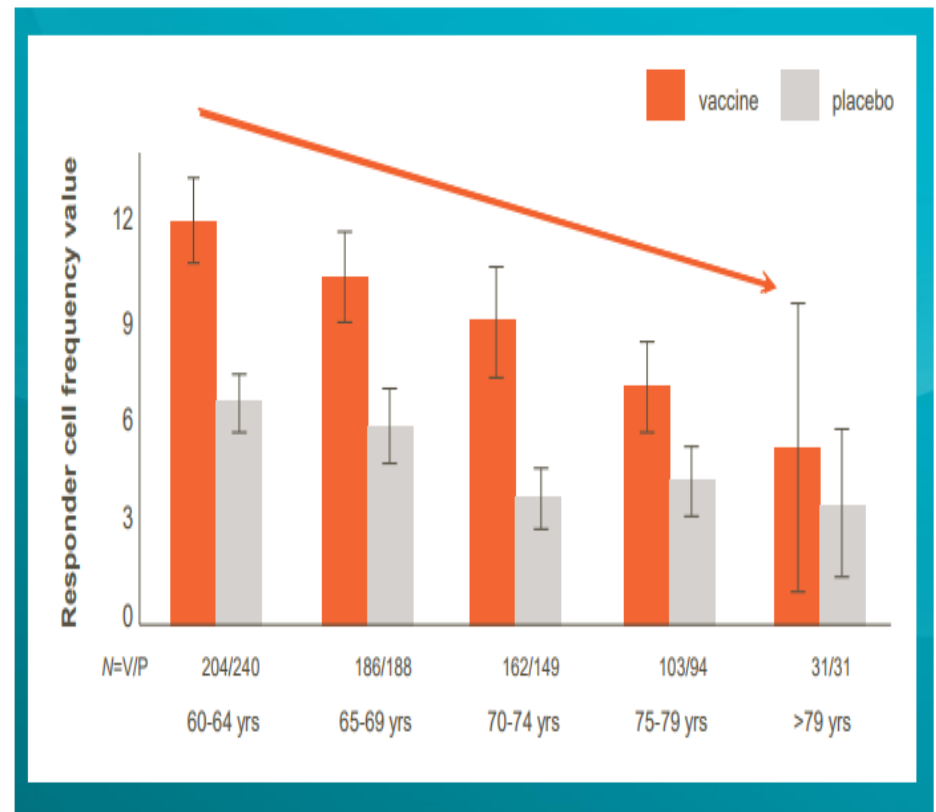
Morrison et al. Clin Infect Dis 2015; 60:900-909

# Immune response across age segments

## HZ/su vaccine



## ZVL vaccine



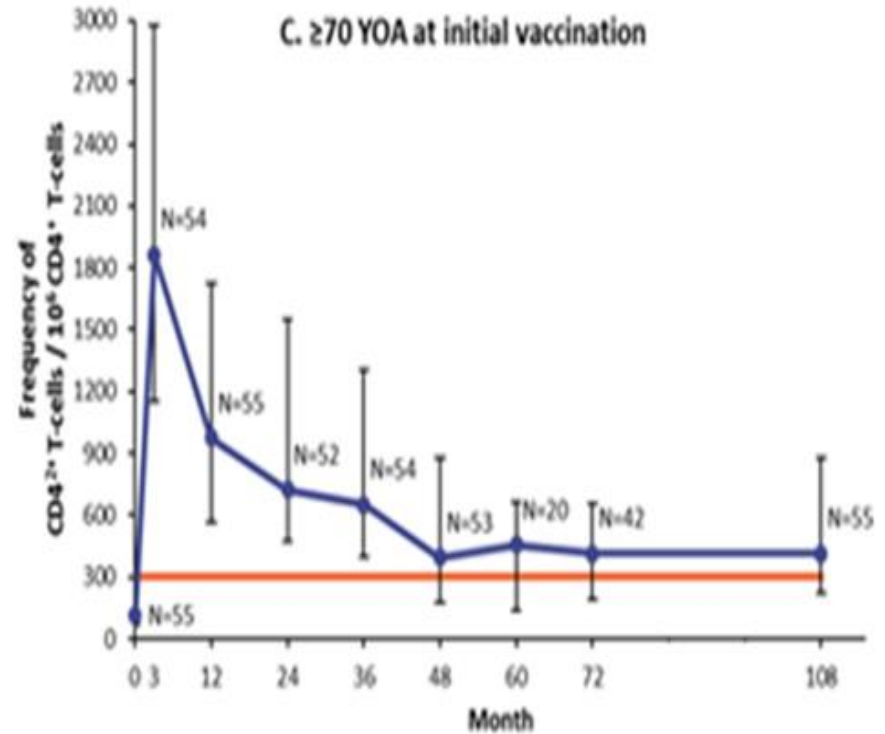
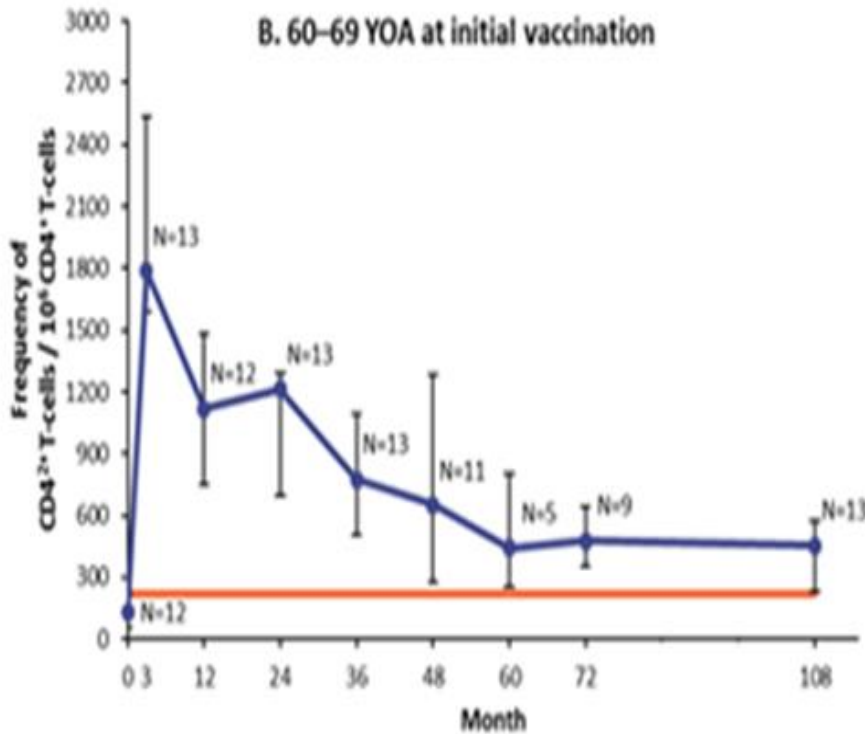
Chlibek et al. J Infect Dis 2013; 208:1953-61

Levin et al. J Infect Dis 2008; 197:825-35



# 9 years follow-up of immune response of HZ/su vaccine

## Predictor of duration of efficacy



**Median frequencies of gE-specific CD4<sup>+</sup> T-cells expressing ≥2 activation markers (ATP cohort for immunogenicity)**

## Brief Overview of Zoster-048

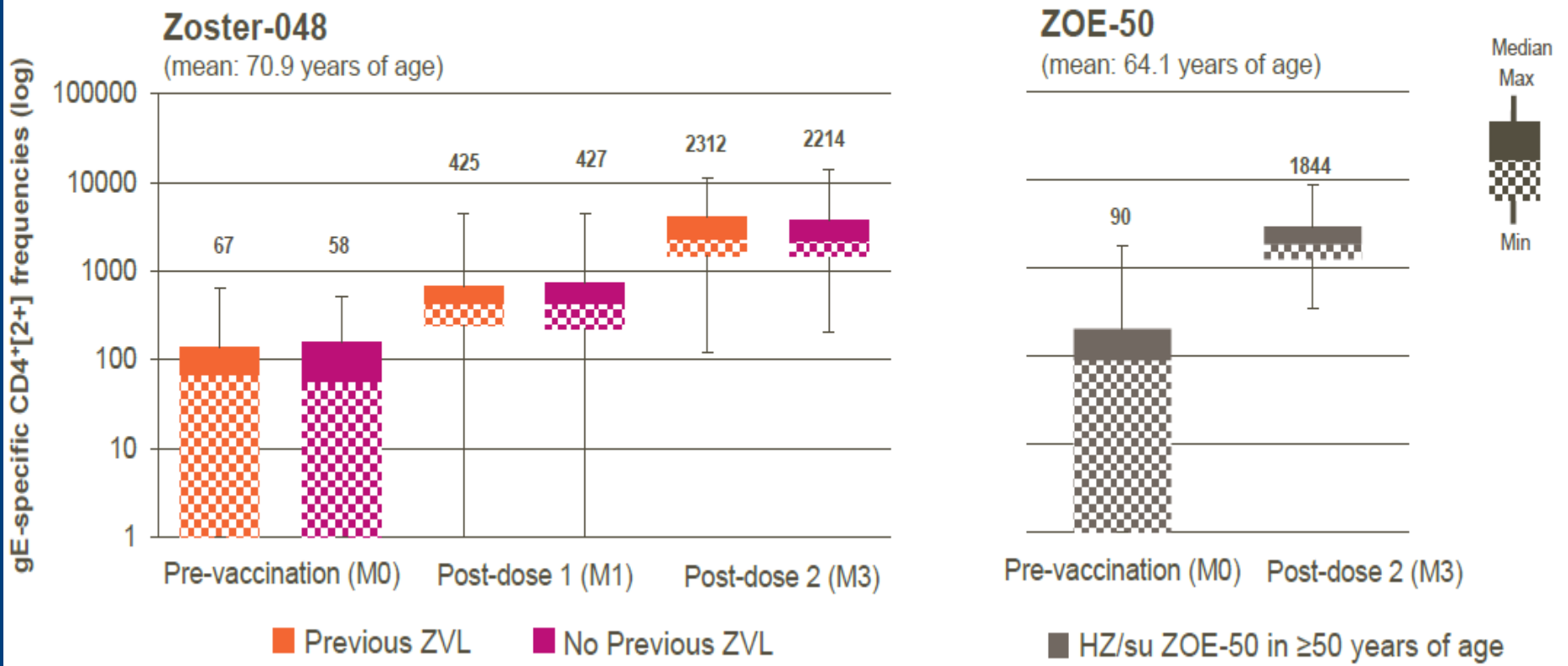
*Prospective, group-matched, non-randomized trial*

	Previous ZVL	No Previous ZVL
Experimental design	Phase III, prospective, group-matched, non-randomized, open label, multicenter study in US	
HZ vaccination history	ZVL $\geq 5$ years prior	No previous HZ vaccine
Age range	$\geq 65$ years of age	
Co-primary objectives	<ul style="list-style-type: none"> <li>• Compare anti-gE antibody concentrations 1 month post-dose 2 (non-inferiority)<sup>a</sup></li> <li>• Safety and reactogenicity up to 1 month post dose 2</li> </ul>	
Secondary objectives	<ul style="list-style-type: none"> <li>• Humoral immune response and cell-mediated immunity at baseline, 1 month post-dose 1, and 1 and 12 months post-dose 2</li> <li>• Safety up to 12 months post-dose 2 (ongoing)</li> </ul>	

<sup>a</sup>Non-inferiority: upper limit of two-sided 95% CI of adjusted geometric mean concentration ratio (No Previous ZVL over Previous ZVL 1 month post-dose 2) is below 1.5 for anti-gE antibodies.

# Month 3 Cellular Immune Responses Similar Between Groups and Consistent With ZOE-50 Trial

*gE-specific CD4+[2+] frequencies*



Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). CD4+[2+], CD4+ T-cells secreting at least two activation markers (IFN-γ, IL-2, TNF-α, CD40L); gE, glycoprotein E; M, month; Q1, Quartile 1=25<sup>th</sup> percentile; Q3, Quartile 3=75<sup>th</sup> percentile; ZOE-50, zoster efficacy trial ≥50 years of age.

October 25, 2017

## ACIP: New Vaccine Recommendations for Shingles Prevention



The Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) voted in favor for the use of Shingrix (zoster vaccine recombinant, adjuvanted; GlaxoSmithKline) for the prevention of shingles (herpes zoster).

The ACIP recommends Shingrix for the prevention of herpes zoster and related complications for immunocompetent adults aged  $\geq 50$  years and adults who previously received [Zostavax](#) (zoster vaccine live; [Merck](#)). The Committee voted that Shingrix is preferred over Zostavax for the prevention of zoster and related complications.




*Shingrix was approved earlier this month by the FDA for use in adults aged  $\geq 50$  years*



# Co-administration

ACCEPTED MANUSCRIPT EDITOR'S CHOICE

## Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine co-administered with seasonal influenza vaccine in adults aged 50 years and older

Tino F Schwarz , Naresh Aggarwal, Beate Moeckesch, Isabelle Schenkenberger, Carine Claeys, Martine Douha, Olivier Godeaux, Katrijn Gruppig, Thomas C Heineman, Marta Lopez Fauqued ... [Show more](#)

*The Journal of Infectious Diseases*, jix481, <https://doi.org/10.1093/infdis/jix481>

**Published:** 26 September 2017 **Article history** ▼

### Conclusions

No interference in the immune responses to either vaccine was observed when co-administered and no safety concerns were identified.

## Conclusion

- HZ/su vaccine is a milestone in the prevention of an infectious disease in an ageing population
- HZ/su vaccine will substantially reduce the burden of disease (HZ and PZN)
- Improve the quality of life in the elderly
- Will reduce costs for the health care system
- Current national zoster vaccine recommendations will have to be adopted