

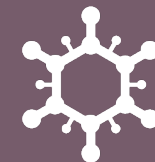
# ADULT IMMUNISATION FORUM

2023

This event will start at 8:30am AWST

22 JUNE 2023

8:30AM–5:00PM AWST



IMMUNISATION  
COALITION

# SESSION 3



Tony Cunningham

Herpes Zoster



Laurens Manning

Adult Strep A Disease and the  
Potential Impact of a Vaccine



Deb Strickland

Immunomodulatory  
Therapies

# Tony Cunningham

Herpes Zoster – Vaccines in the Ageing



Director, Centre for Virus Research,

The Westmead Institute for Medical Research

Professor, School of Medical Sciences, Faculty of Medicine and Health,  
University of Sydney

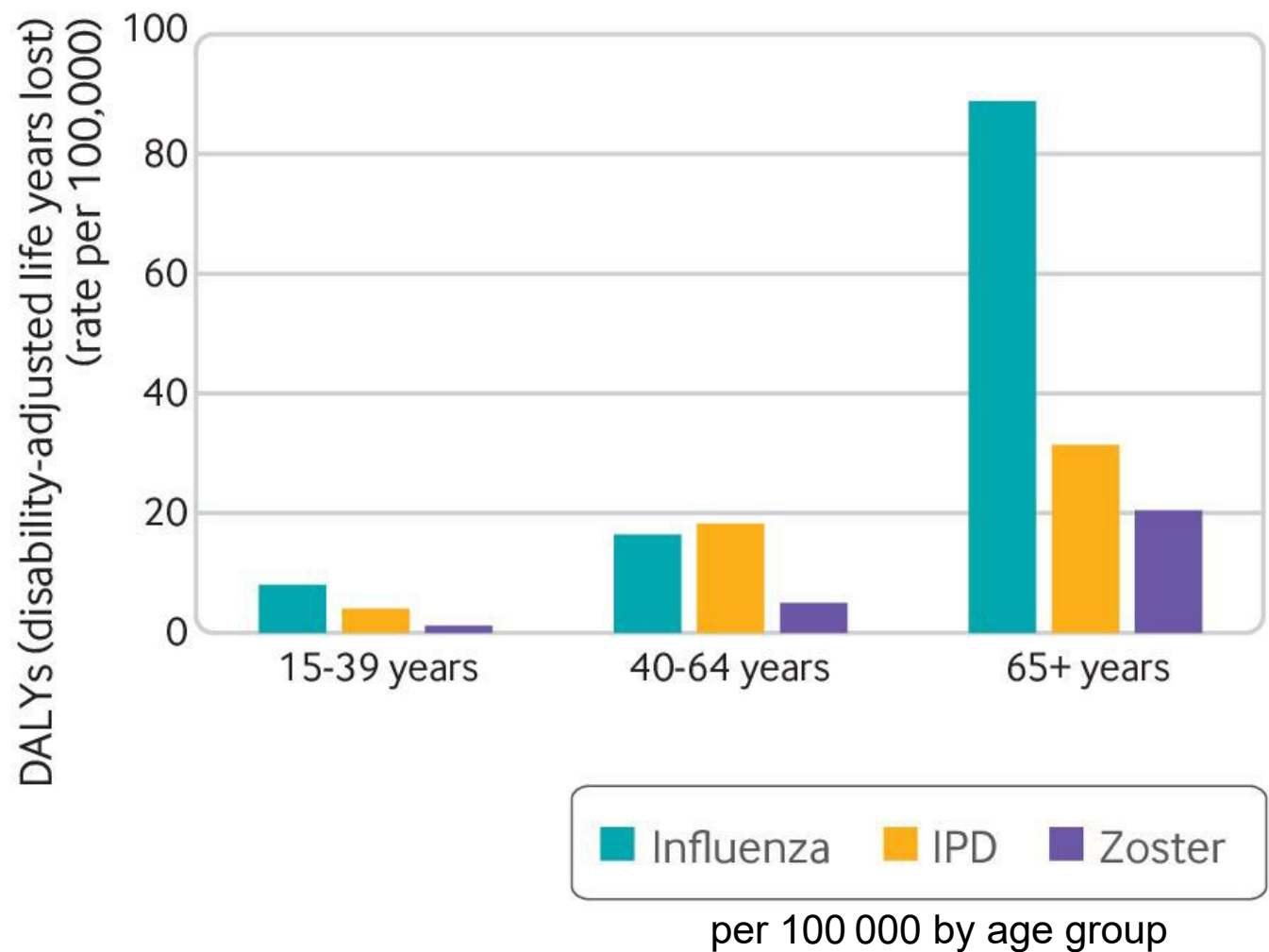
Sydney Institute for Infectious Diseases (Sydney ID)

Director, Australian Centre for HIV and Hepatitis Virology Research (ACH<sup>4</sup>)

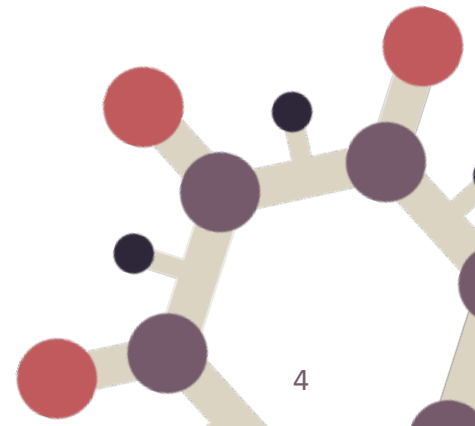
NHMRC Leadership Fellow

Chair, NSW/ACT Branch, Australian Academy of Health and Medical Sciences

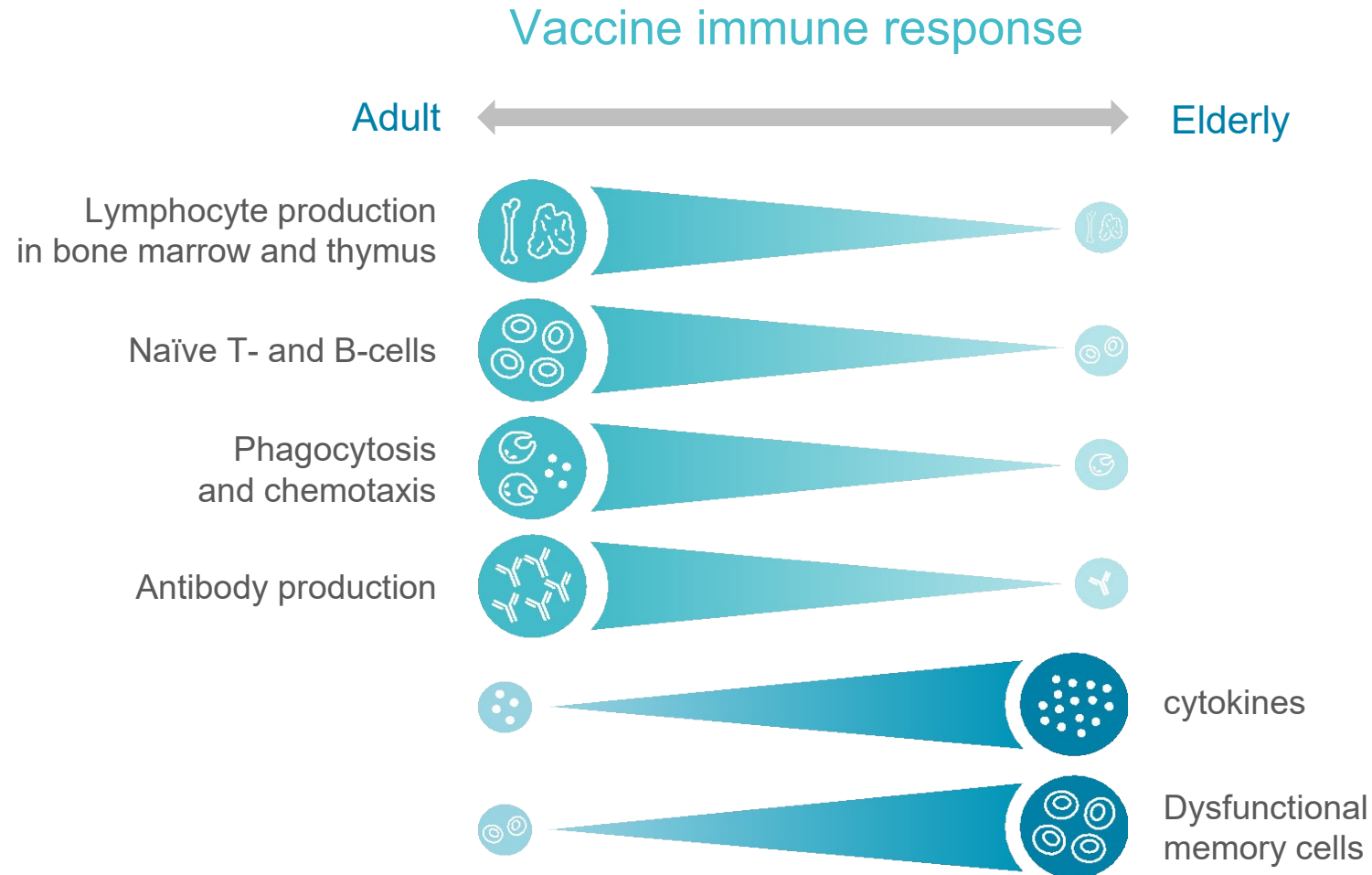
# The effect of influenza, herpes zoster, and invasive pneumococcal disease (IPD) on disability-adjusted life years



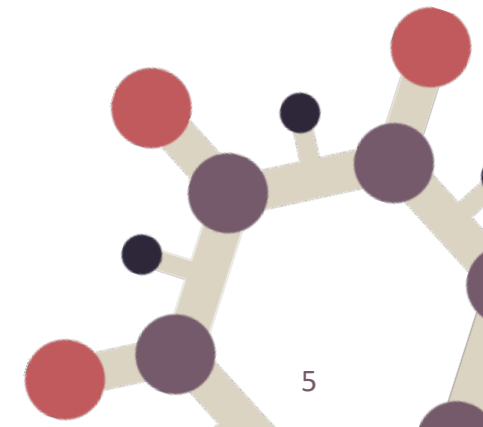
©2021 by British Medical Journal Publishing Group  
Anthony L Cunningham et al. *BMJ* 2021;372:bmj.n188



# Immune response to disease and vaccines decreases with ageing



1. Xu W et al. *Seminars in Immunopathology* 2020;42:559-572.



# Shingles is a painful disease that can have serious and long-lasting complications<sup>1,2</sup>



## Acute HZ presentation

- Unilateral, vesicular rash<sup>1</sup>
- Pain that can be “excruciating”<sup>1</sup>

Severe, worst imaginable pain\* reported in 65% of subjects in ZOE-50 placebo arm<sup>3</sup>



## Complications

### Post-herpetic neuralgia (PHN)

- Neuropathic pain that persists for >3 months after an outbreak of HZ<sup>5</sup>
- Affects up to 30% of patients with shingles<sup>2</sup>

### Herpes zoster ophthalmicus (HZO)

- Affects up to 25% of patients with shingles<sup>1</sup>
- May lead to vision loss in rare cases<sup>1</sup>

### Other complications

- Cardiovascular and cerebrovascular events<sup>4</sup>
- Hearing loss<sup>1</sup>
- Scarring<sup>1</sup>
- Cranial involvement<sup>6</sup>



**HZ symptoms and complications may be more frequent and of longer duration in immunocompromised patients<sup>7,8</sup>**

HZ=herpes zoster.

Picture 1: [ncbi.nlm.nih.gov/pubmed/articles/PMC5389218/figure/F3/](https://pubmed.ncbi.nlm.nih.gov/24811118/), Picture 2, Wim Opstelten, Michel J W Zaal, BMJ VOLUME 331 16 JULY 2005, Picture 3: [bmj.com/content/364/bmj.k5234](https://pubmed.ncbi.nlm.nih.gov/24811118/). \*; Severe Worst Zoster Brief Pain Inventory (ZBPI) score of  $\geq 7/10$  was seen in 65.2% (157/241) subjects.<sup>3</sup>

References: 1. Centers for Disease Control and Prevention. MMWR. 2008 May;57(RR-5):1-30. 2. Kawai K, et al. BMJ Open. 2014 Jun;4(6):e004833. 3. Curran D, et al. J Gerontol A Biol Sci Med Sci 2019;74:1231-1238. 4. Erskine N;PLoS One;2017;12;1-18. 5. Mallick-Searle T, et al. J Mult Healthcare. 2016 Sep;21(1)447-454. 6. Tsau Po-Wei, et al. J Clin Med 2020;8:946.. 7. McKay SL, et al. Clin Infect Dis. 2019 Nov;ciz1090. 8. Kennedy PGE, et al. Viruses. 2018;10(11):609.

# The burden of shingles increases as persons age, with steep increases >50 years<sup>1,2</sup>

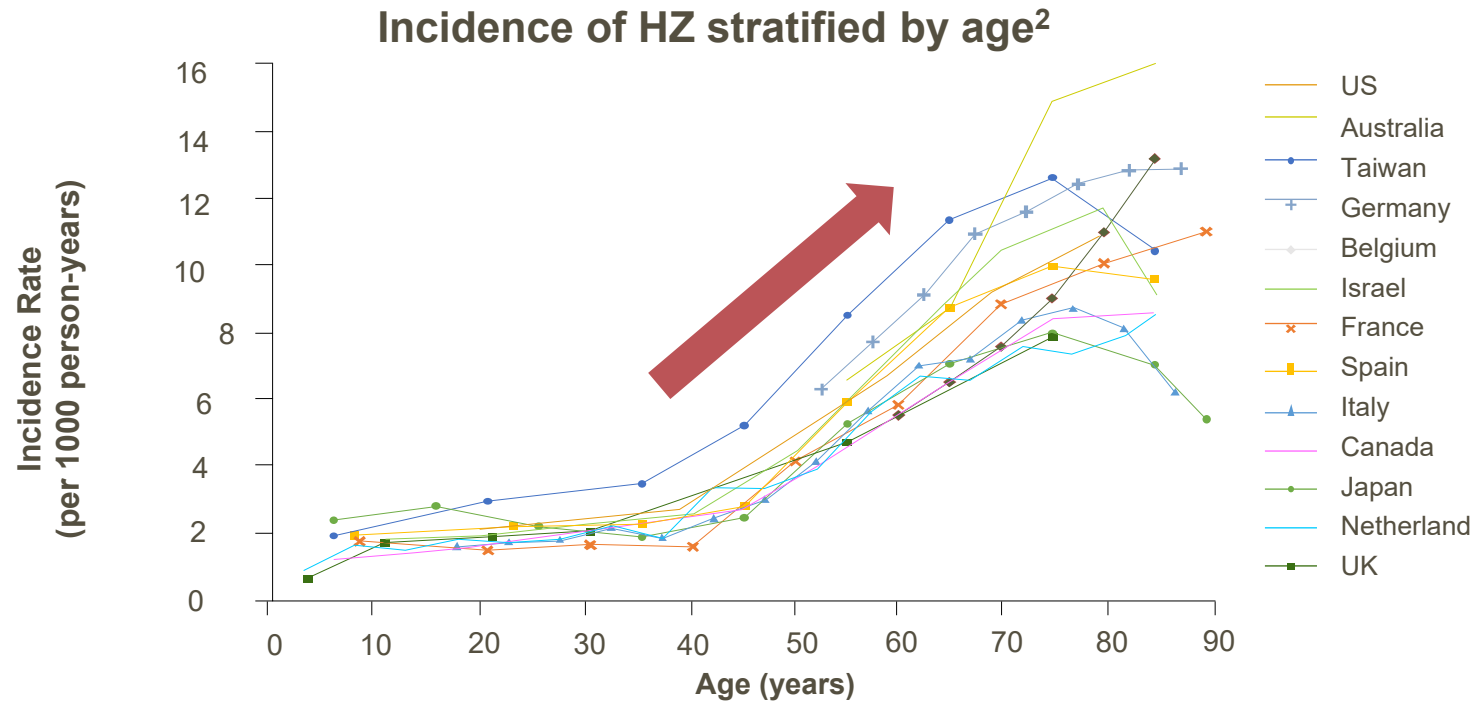


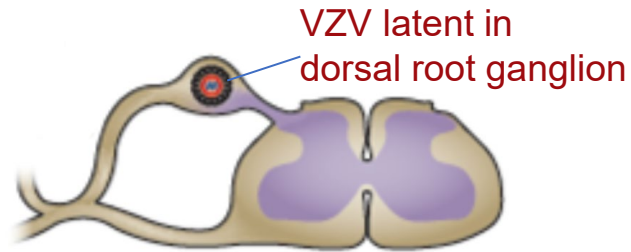
Figure reproduced from Kawai K *et al.* *BMJ Open* 2014;4:e004833 with permission from BMJ Publishing Group Ltd.

# 99.5% of adults $\geq 50$ years of age are infected with VZV and are at risk for shingles<sup>1\*</sup>



Varicella

Control of primary infection



Latency

Failed immune control, virus reactivation



Zoster

- **1 in 3 people** will develop shingles in their lifetime due to VZV reactivation<sup>1</sup>.
- Incidence rates are similar throughout North America, Europe, and Asia Pacific (6-8 cases per 1000 person-years at age 60)<sup>3</sup>. The incidence in New Zealand is similar to the global incidence rates.
- Each year there are an estimated **1 million** new cases of shingles in the United States, **1.7 million** in Europe, and **1.5 million** in China<sup>1,4,5</sup>.

References:1. Harpaz R, et al. MMWR Recomm Rep. 2008 June;57(RR-5):1-30. 2. Zerboni L, et al. Nat Rev Microbiol. 2014 Mar;12 (3):197-210. 3. Kawai K, et al. BMJ Open. 2014 Jun;4(6):e004833. 4. Pinchinat S, et al. BMC Infect Dis. 2013 April;13(170):1471-2334. 5. Li Y, et al. Open Forum Infect Dis. 2016 Mar;3(2):ofw067..



# Shingles causes burning, stabbing, deep aching pain<sup>1</sup>

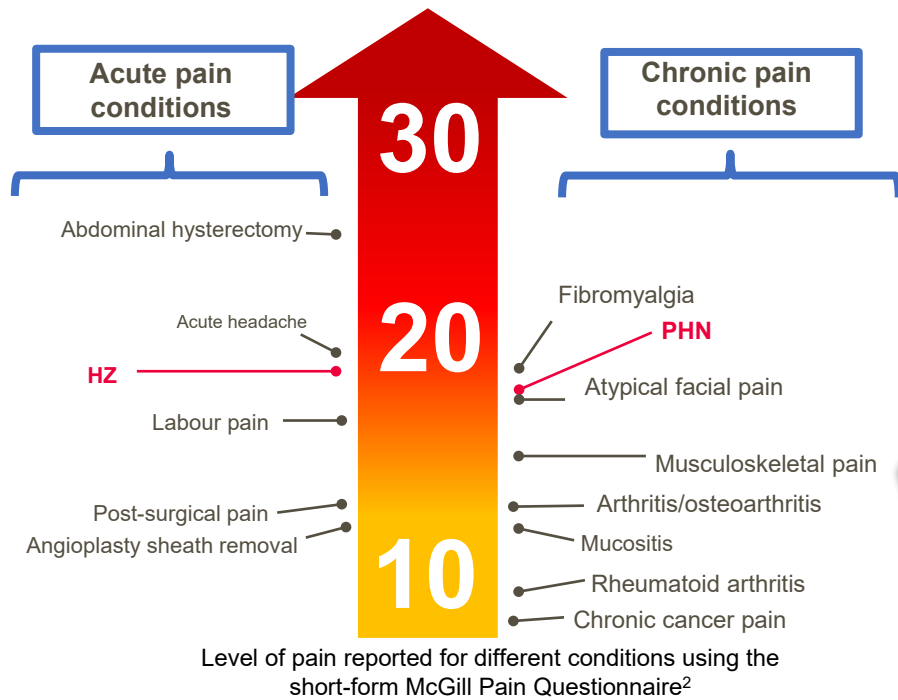
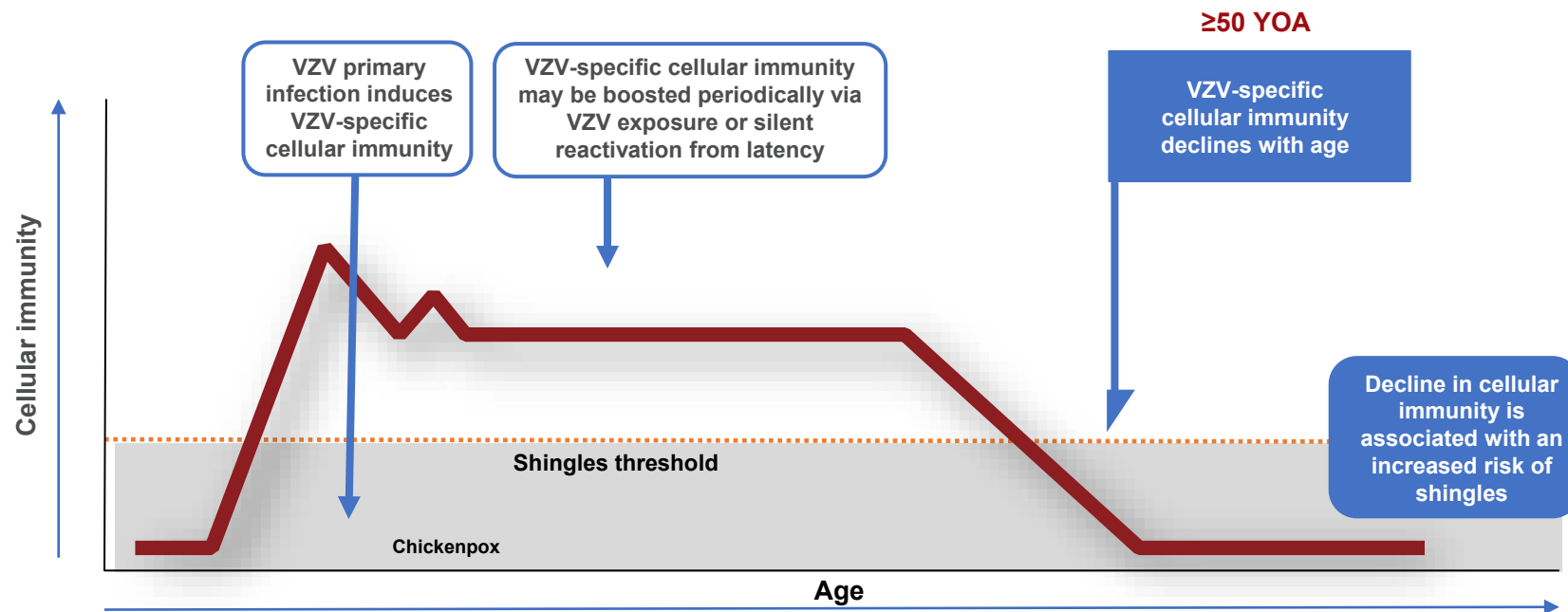


Figure modified from Katz J et al. Surg Clin North Am 1999;79:231-252 with permission from Elsevier



from original data in Drolet, M. 2017. N=261 patients

# Age-related decline in immunity and IMMUNOSUPPRESSION increase shingles risk\*<sup>1-3</sup>



This illustration has been independently created by GSK from information first published in the New England Journal of Medicine.

\*Immunodeficiency caused by medical conditions or immunosuppressive medications may also increase the risk of shingles.<sup>2,4,5</sup>

VZV=varicella zoster virus; YOA=years of age.

**References:** 1. Harpaz R, et al. MMWR Recomm Rep. 2008 June;57(RR-5):1-30. 2. Kimberlin DW, et al. N Engl J Med. 2007 Mar;356(13):1338-43. 3. Dworkin RH, et al. Clin Infect Dis. 2007 Jan;44(suppl 1):S1-26. 4. Tseng HF, et al. J Infect Dis. 2016 Jun;213(12):1872-75. 5. Goodwin K, et al. Vaccine. 2006 Feb;24(8):1159-69.

# Prevention of HZ with live attenuated vaccine

Adults 50 to 59 years of age: Zostavax<sup>®</sup> compared to placebo in the ZEST study

Endpoint	Vaccine efficacy	95% CI
Incidence of Herpes Zoster		
50-59 years	69.8%	54.1, 80.6

ZEST: Zostavax<sup>®</sup> Efficacy and Safety Trial

N= 22,439, randomized 1:1

Table recreated from Zostavax<sup>®</sup> Approved Australian Product Information<sup>4</sup>

Vaccine efficacy against PHN was not assessed in the ZEST study<sup>1</sup>

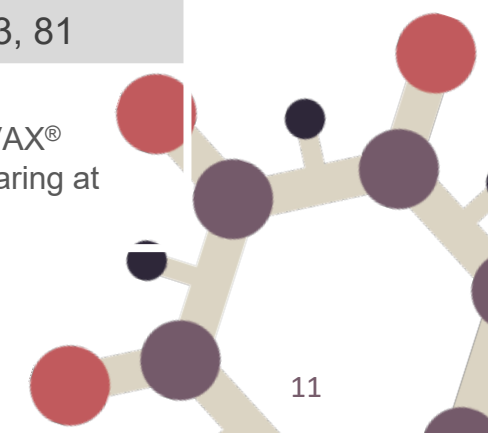
Adults ≥60 years of age: Zostavax<sup>®</sup> compared to placebo in the shingles prevention study (SPS)\*

Endpoint	Vaccine efficacy	95% CI
Incidence of Herpes Zoster		
Overall	51%	44, 58
60-69 years	64%	56, 71
≥70 years	38%	25, 48
Incidence of Post-Herpetic Neuralgia <sup>^</sup>		
Overall	67%	48, 79
60-69 years	66%	20, 87
≥70 years	67%	43, 81

N= 38,546, randomized 1:1. Conducted in the United States.<sup>5</sup>

\*Study was conducted using the frozen formulation of ZOSTAVAX<sup>®</sup>

<sup>^</sup>Clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash.



**References:** 1. Australian Register of Therapeutic Goods (ARTG) Zostavax<sup>®</sup> listing 130229 <https://www.tga.gov.au/australian-register-therapeutic-goods> 2. NCIRS history of immunisation fact sheet: Zoster <https://www.ncirs.org.au/sites/default/files/2020-12/Zoster-history-Dec-2020.pdf> 3. Lin J, et al. Vaccine 2021;39:1493-1498 4. Zostavax<sup>®</sup> New Zealand Data Sheet.

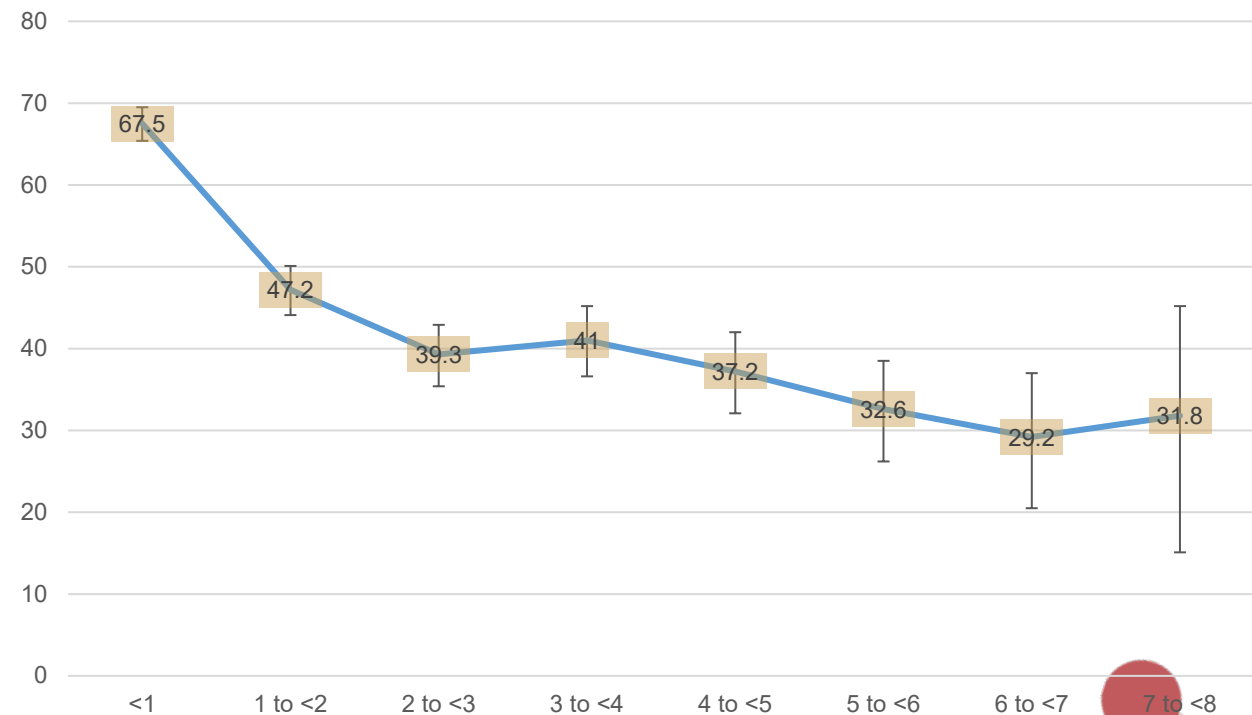
5. <https://clinicaltrials.gov/ct2/show/NCT00007501>

Zostavax<sup>®</sup> (Zoster virus vaccine live) is a registered trademark of Merck Sharp & Dohme Pty Ltd

# Prevention of HZ with live attenuated vaccines

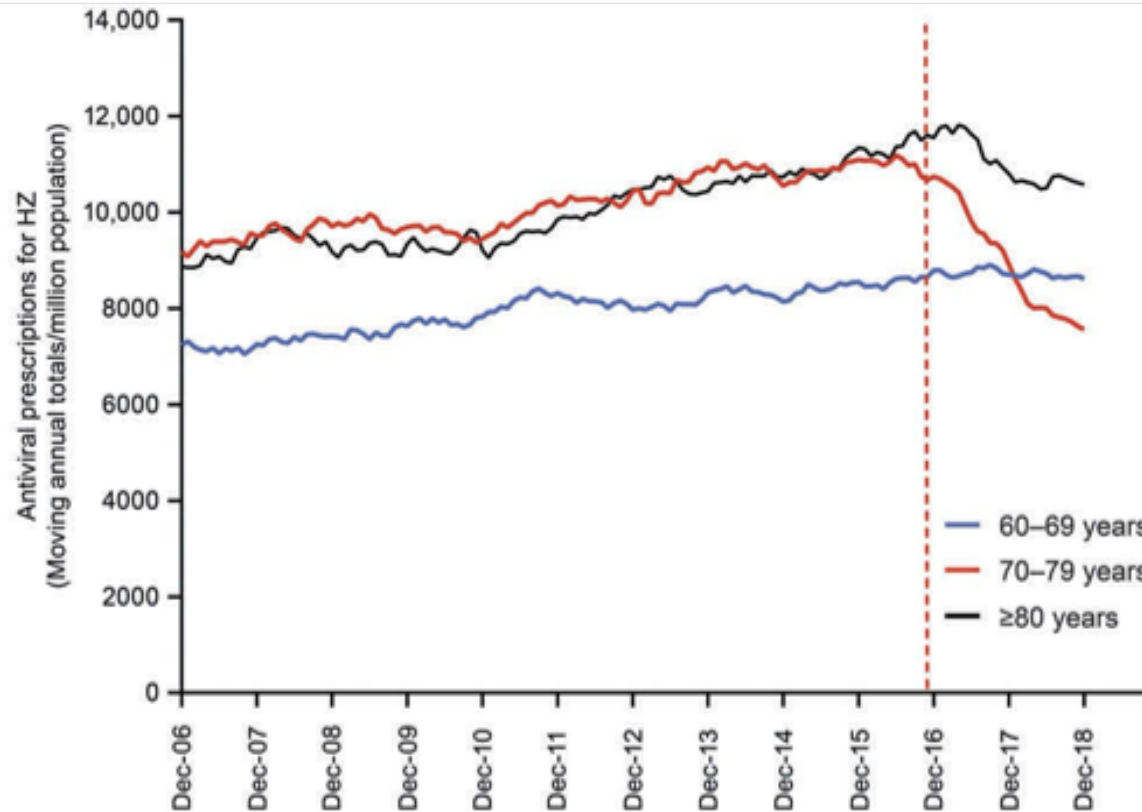
- Live attenuated HZ vaccines are still available in some countries and included in national recommendations<sup>1-3†</sup>

- Live attenuated HZ vaccine may cause VZV-related disease in immunocompromised hosts Limited use in patients with immunosuppression or immunodeficiency



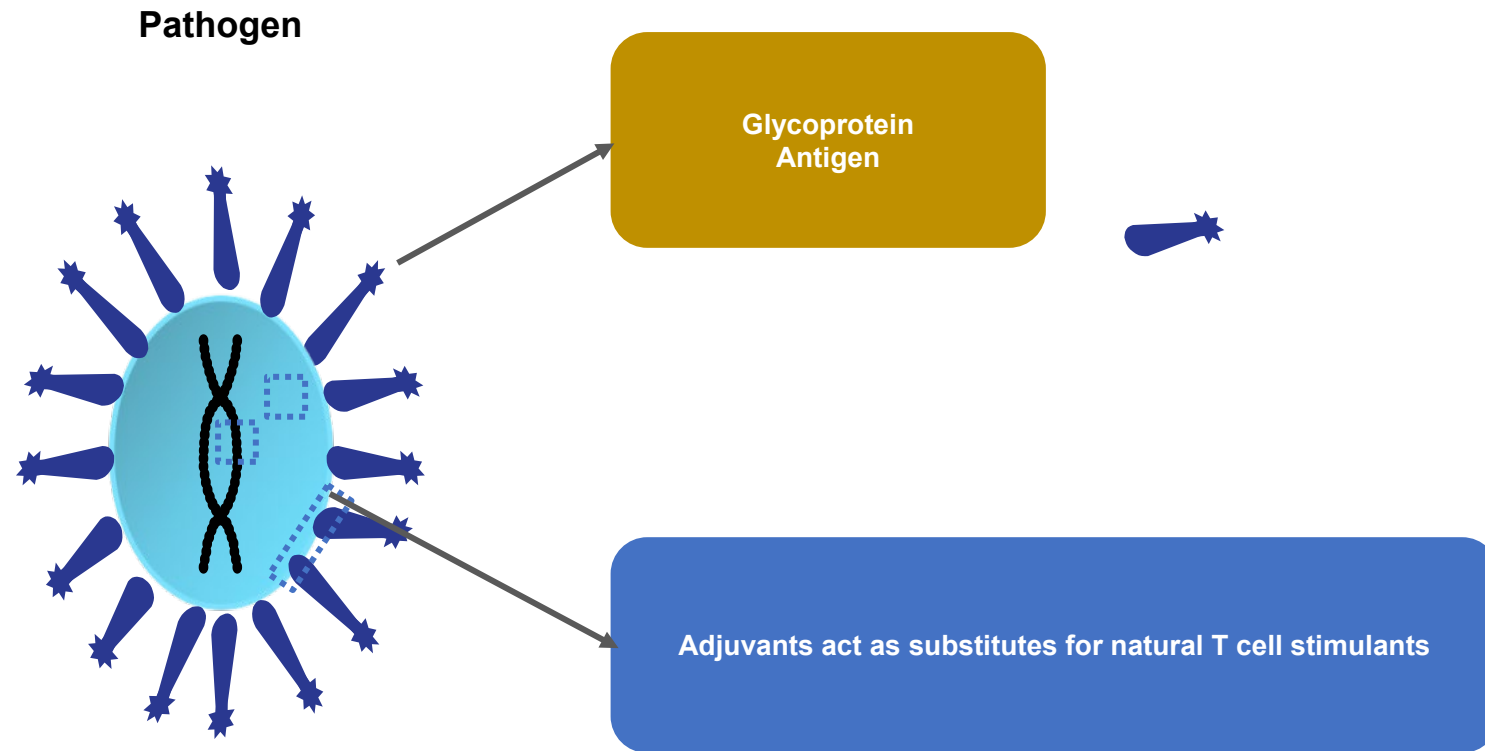
# Effect of Zostavax on antiviral prescriptions

(a)



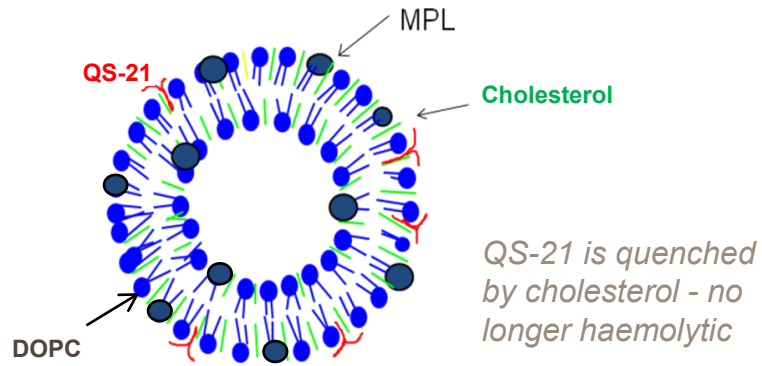
Litt J..Cunningham AL Hum Vaccine Immunother 2020

# Recombinant VZV glycoprotein E + T cell adjuvant



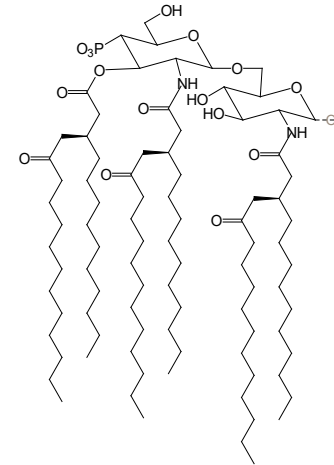
- Viral proteins alone may be insufficiently immunogenic
- Adjuvants act as substitutes for viral immune stimulants enhancing and directing the immune response

# AS01 formulation

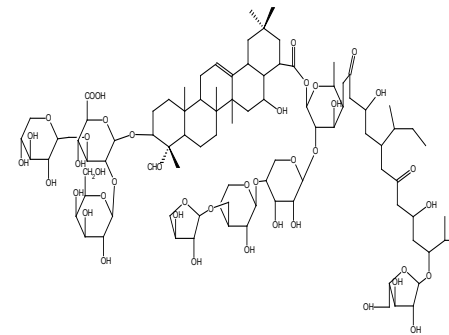


## Immuno-Enhancers

MPL

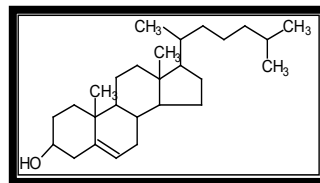


QS-21

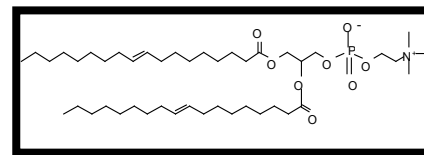


## Vehicle

Cholesterol

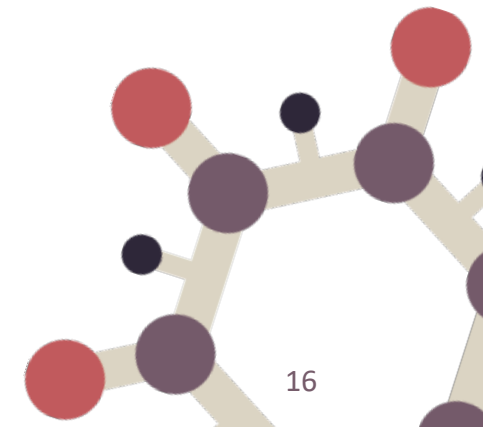
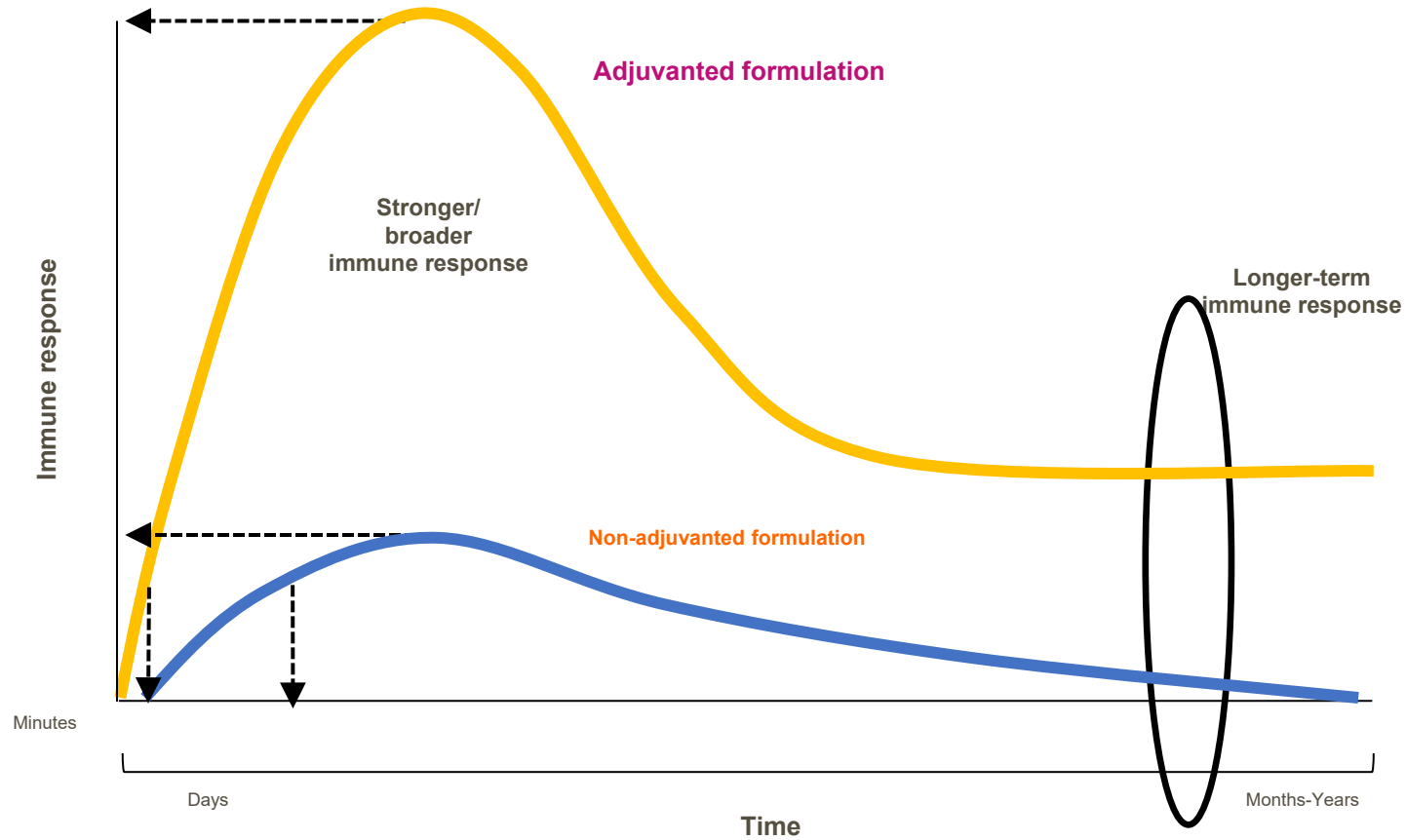


DOPC



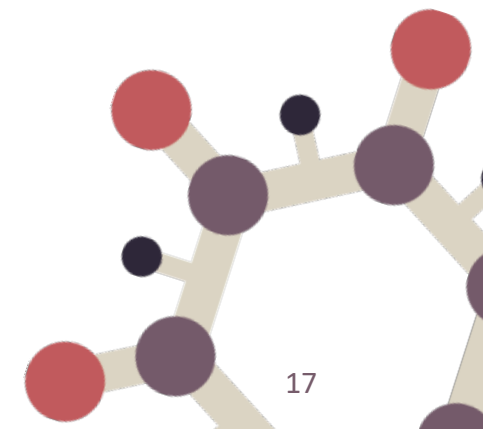
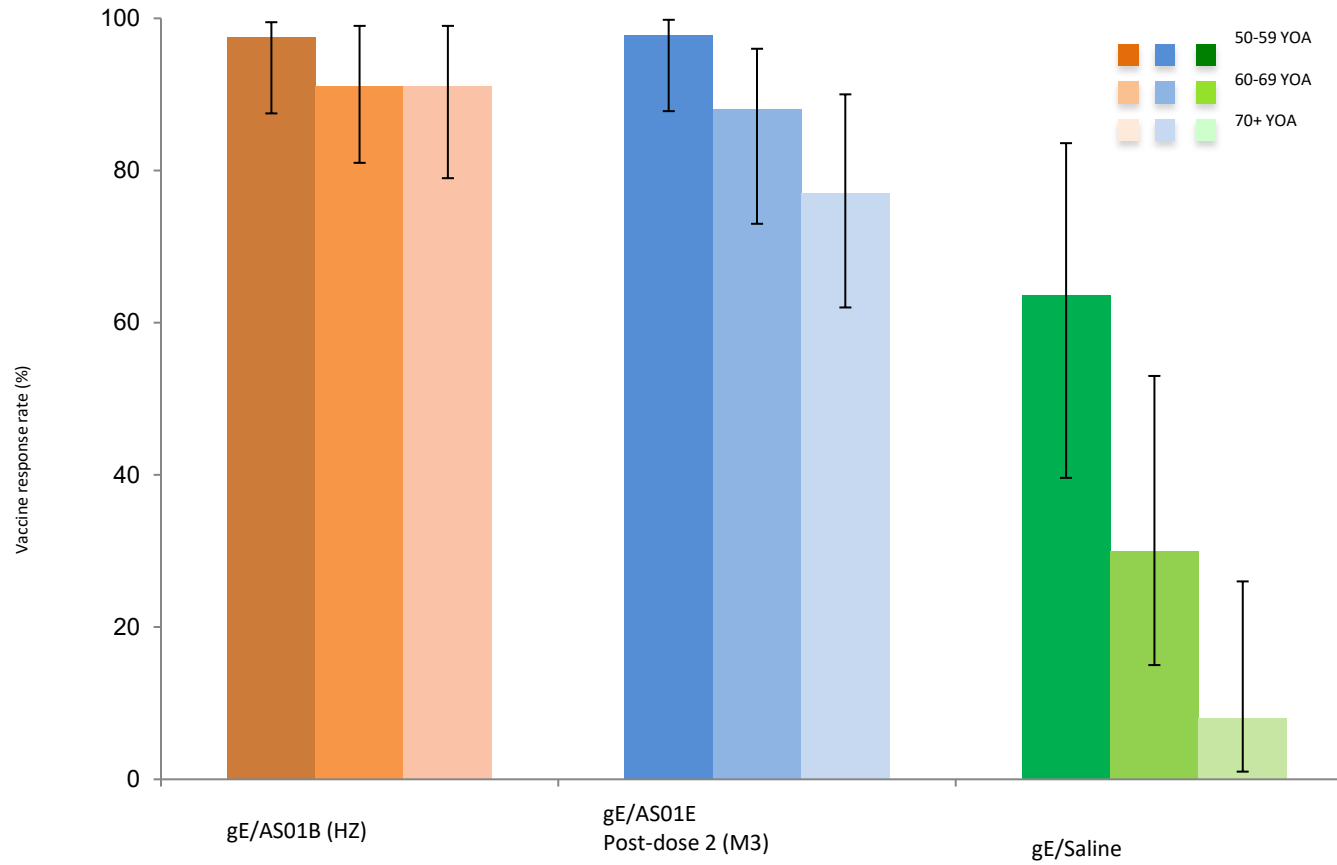
Confidential

# AS01 adjuvant increases peak immune response to vaccine and its durability





# Phase I/II: T cell responses to RZV (gE/AS01<sub>B</sub>) but not gE alone diminish little with advancing age



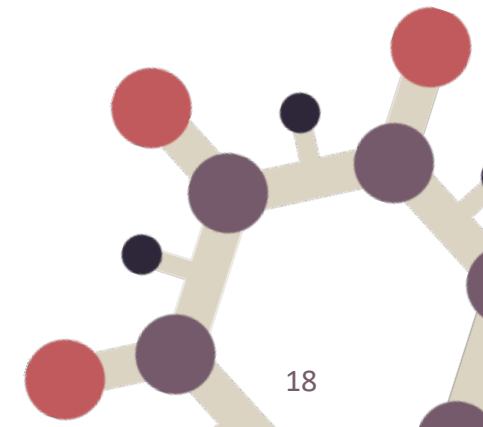
# Shingrix was thoroughly investigated in 2 large pivotal phase III clinical trials<sup>1-3</sup>

Study Design and Objectives	ZOE-50 (Zoster-006)	ZOE-70 (Zoster-022)
Experimental design	Randomized, observer-blind, placebo-controlled, multicenter, multinational (North America, Europe, Latin America, Asia, Australia)	
Primary objectives	<b>HZ efficacy in persons ≥50 YOA</b>	<b>HZ efficacy in persons ≥70 YOA</b>
Primary objectives in pooled analysis	PHN efficacy in 70+ HZ efficacy in 70+	
Actual enrollment	<b>16,160 enrolled</b>	<b>14,816 enrolled</b>

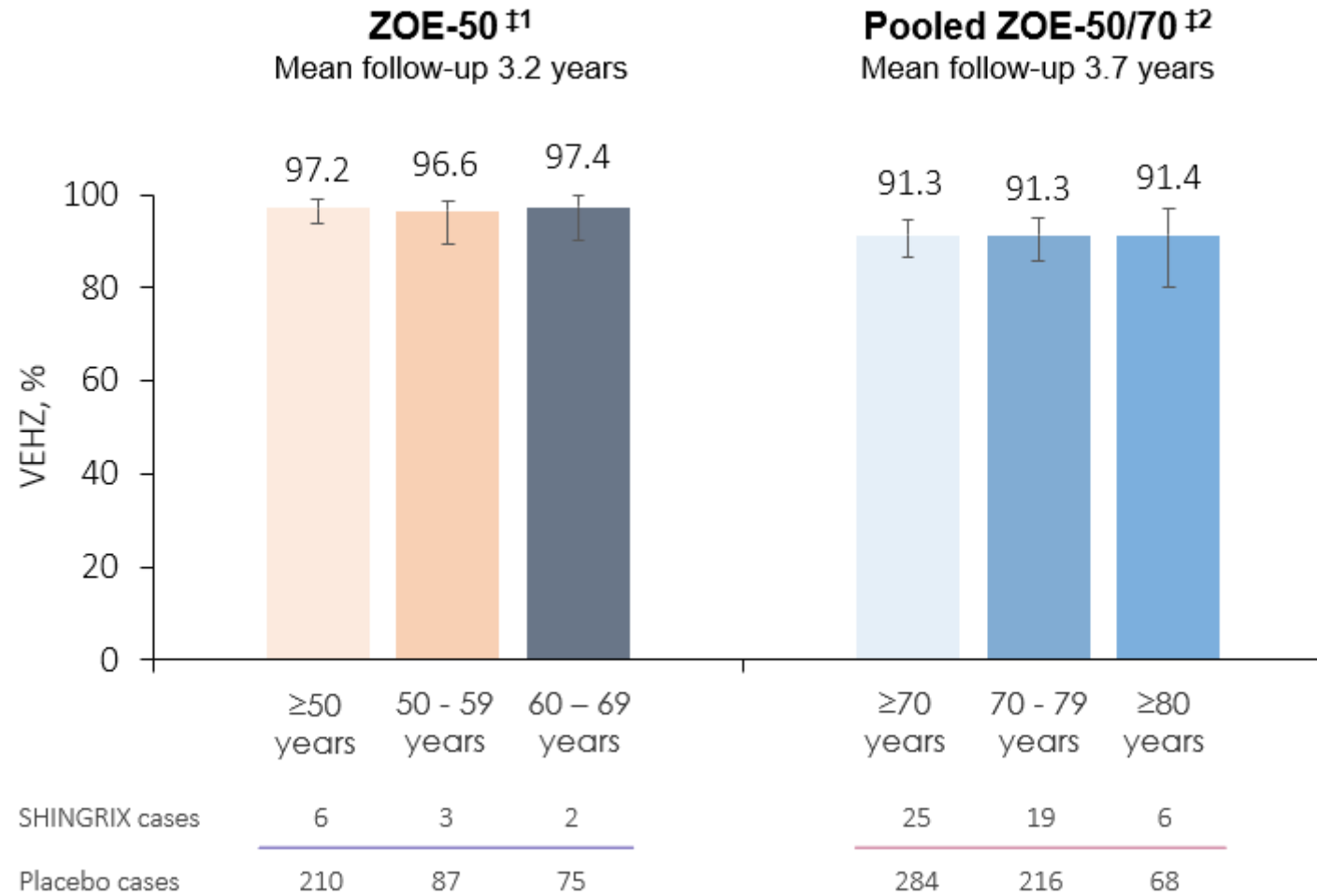
**ZOE 50/70 efficacy studies conducted at the same sites.  
Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70.**

HZ=herpes zoster; PHN=post-herpetic neuralgia; YOA=years of age.

**References:** 1. Lal H, Cunningham AL et al. N Engl J Med. 2015 May;372(22):2087-96. October 2021]. 3. Cunningham AL, et al. N Engl J Med. 2016 Sep;375(11):1019-32.

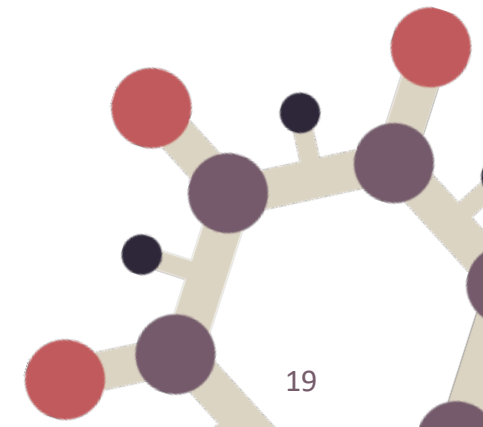


# Shingrix delivered >90% efficacy AGAINST herpes zoster in patients $\geq 50$ years of age<sup>1-3\*</sup>



\*Shingles case = a new unilateral rash with pain that had no other diagnosis and confirmed by PCR.<sup>2</sup>

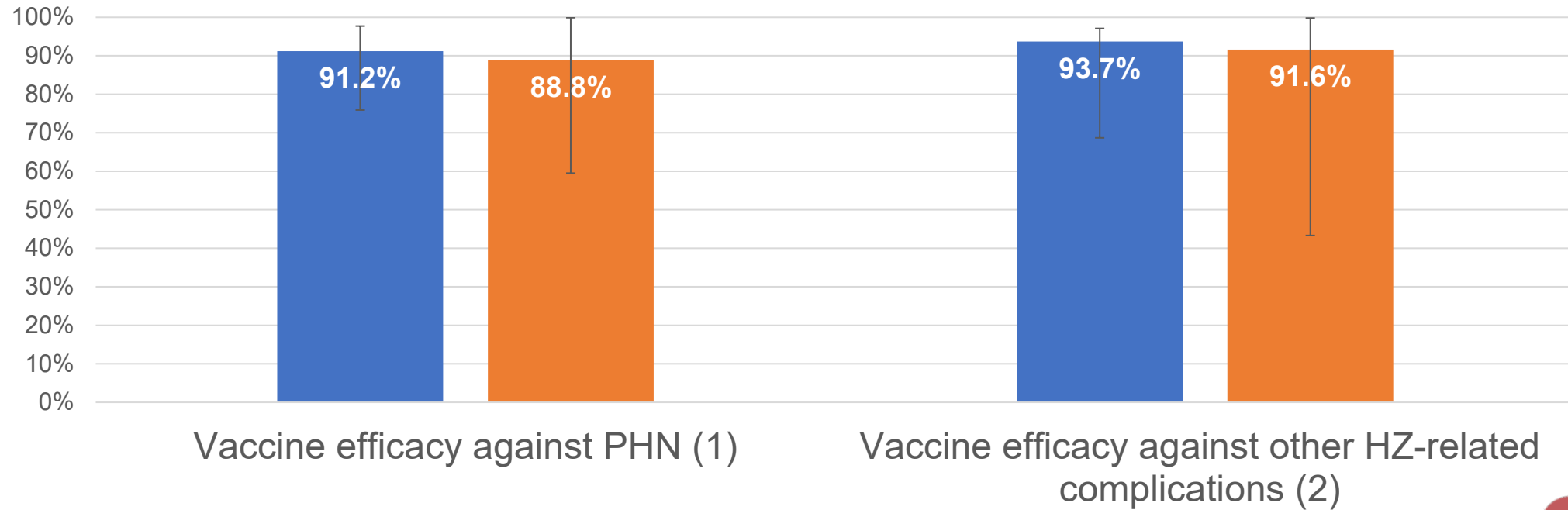
References: 1. Lal H, Cunningham AL et al. N Engl J Med. 2015 May;372(22):2087-96. 2. Cunningham AL; N Engl J Med;2016;375;1019-32



# By preventing shingles, Shingrix significantly reduced risk of PHN and other complications<sup>1,2</sup>

## Vaccine efficacy (95% CI)

■ ≥50 ■ ≥70

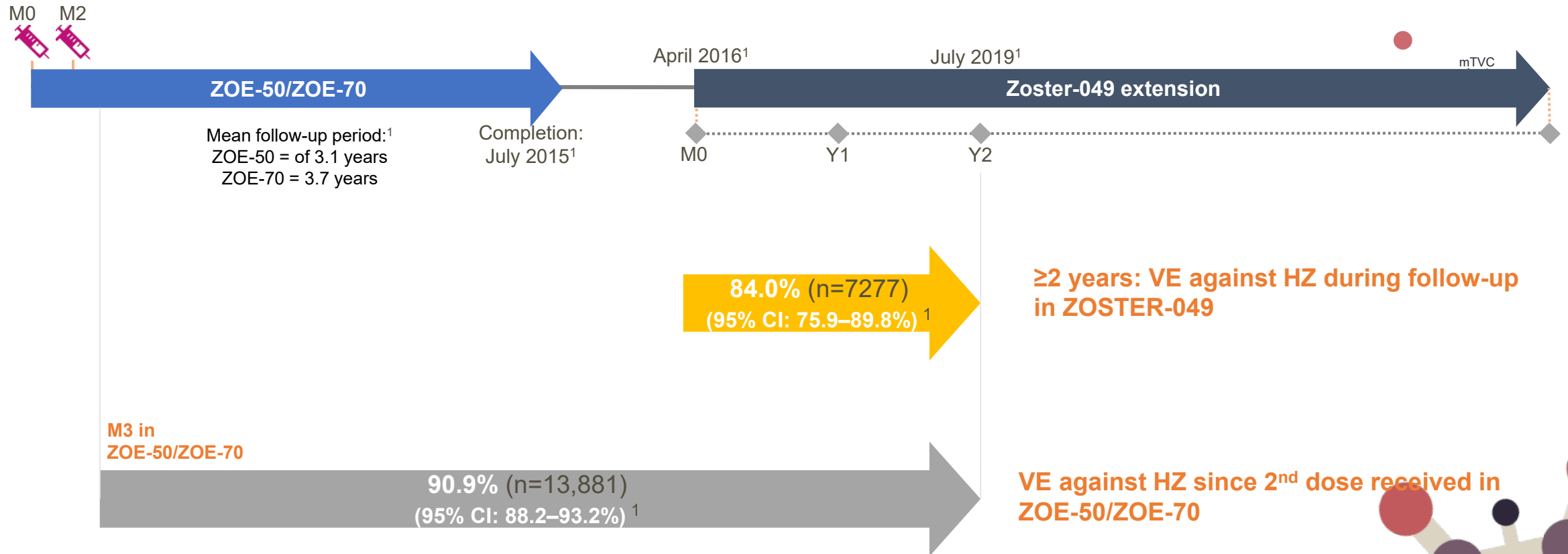


PHN is defined as HZ-associated pain rated as  $\geq 3$  on a 0-10 scale, occurring or persisting for at least 90 days<sup>1</sup>

Other complications included HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke<sup>1</sup>

Reference: 1. Cunningham AL, et al. N Engl J Med. 2016 Sep;375(11):1019-32; 2. Kovac M et al. Vaccine;2018;36;1537-1541

# Long term follow up against HZ sustained >7 years<sup>1</sup>

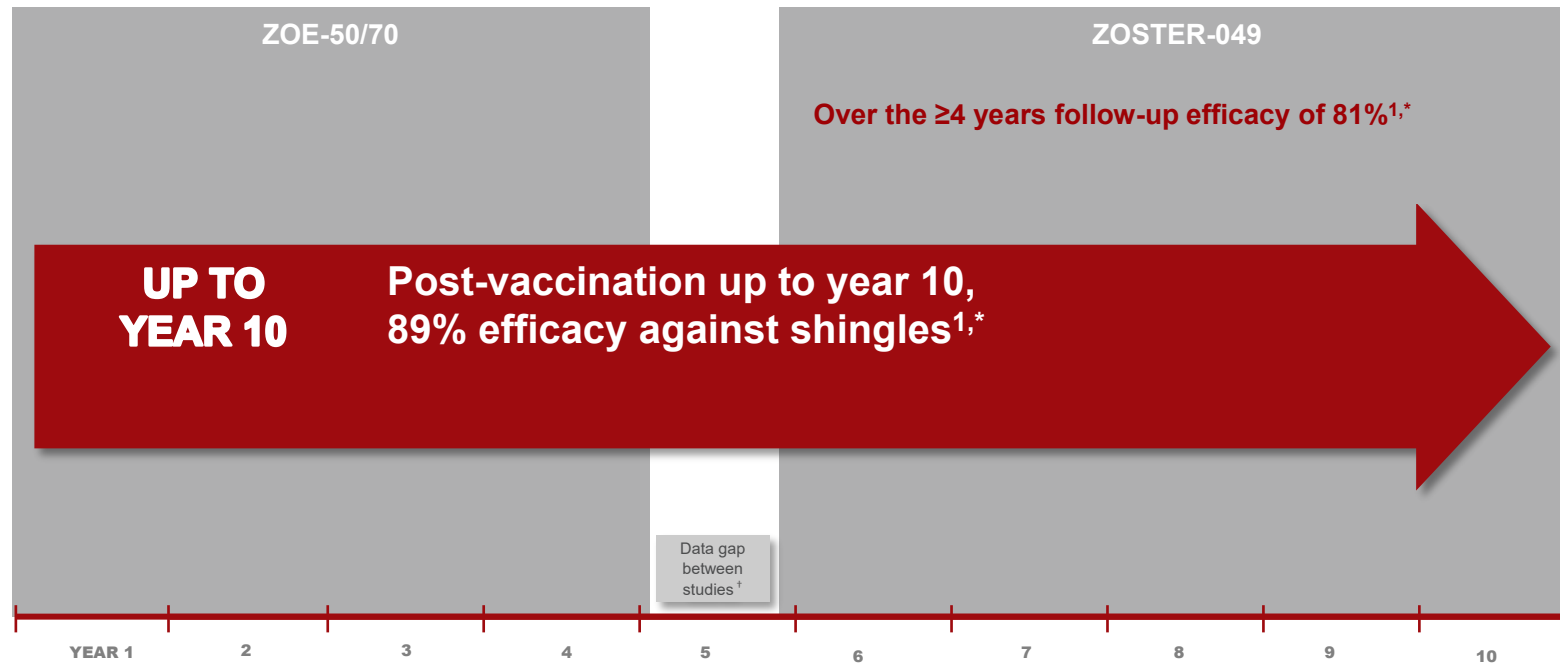


Boutry C et al. Cunningham AL CID 2021

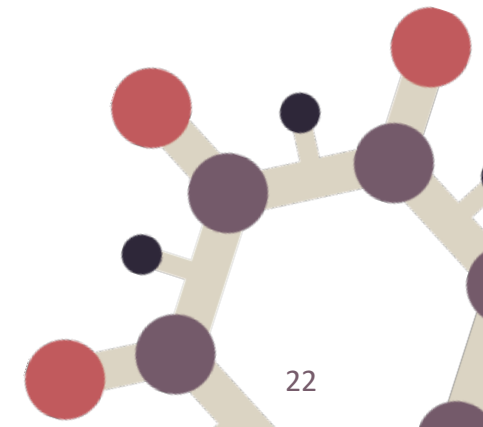
CI, confidence interval; HZ, herpes zoster; M, month; mTVC, modified total vaccinated cohort; RZV, recombinant zoster vaccine; VE, vaccine efficacy; Y, year.

1. Boutry C, et al. Clinical Infectious Diseases;2021;1-30

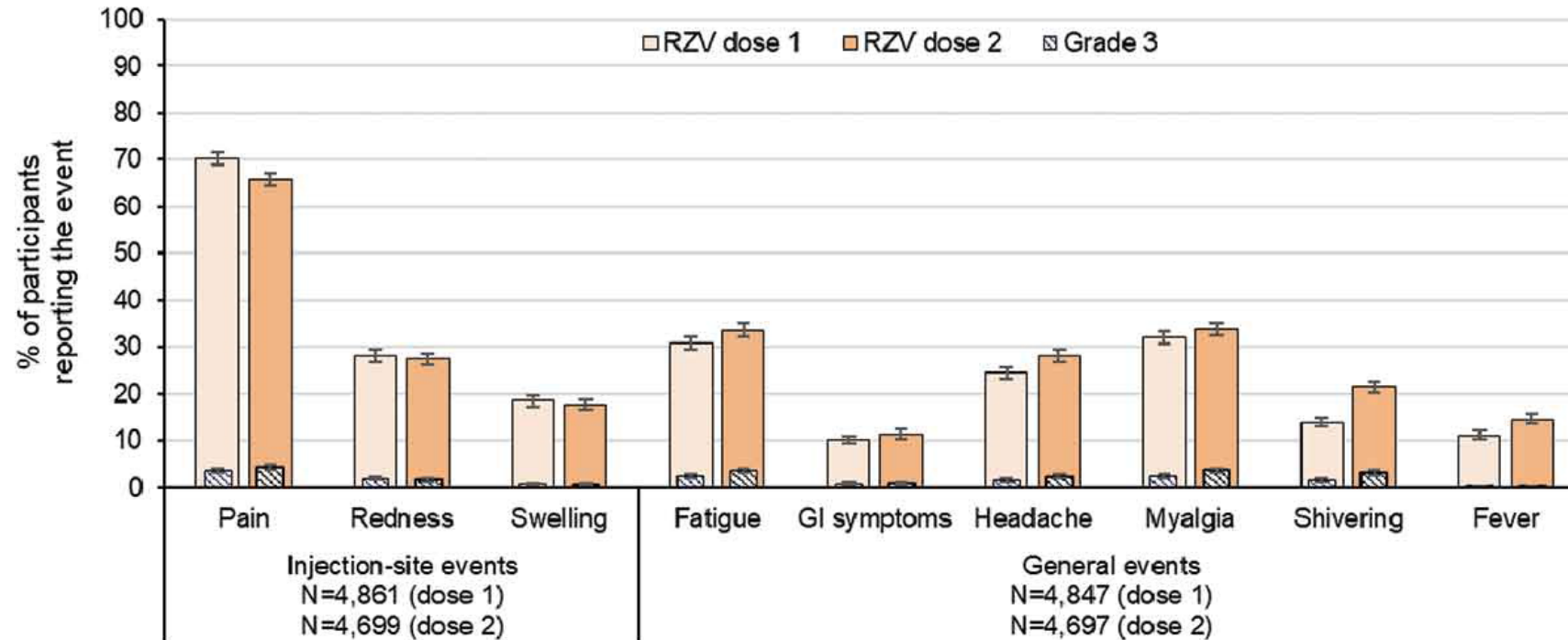
# RZV efficacy lasts >10 years



Boutry C et al Cunningham AL Clin Infect Dis 74:1459, 2022; Open Forum Infect Dis 9:485, 2022



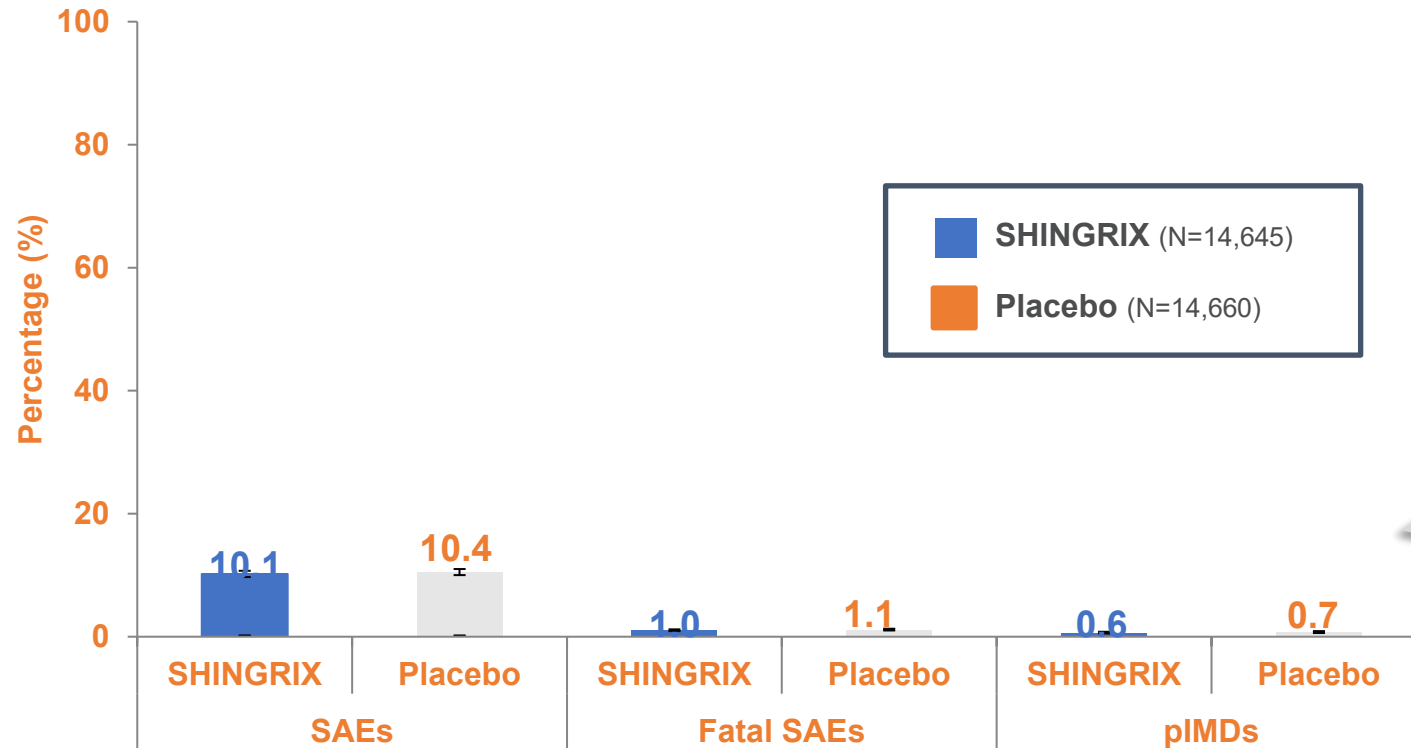
# Local and general reactogenicity to RZV



Reactogenicity to RZV generally lasts only 2-3 days after immunisation, mostly mild to moderate  
Grade 3 systemic and local reactogenicity: 11.5%; 9.5% respectively

Colindres R...Cunningham AL Human Vacc Immunother 2020

# Safety results support the favourable benefit-risk profile of RZV in subjects $\geq 50$ years of age



SHINGRIX was comparable with placebo in overall incidence of SAEs, fatal SAEs, and pIMDs at 1 year post-vaccination



# RZV as a booster following Zostavax and after previous Herpes zoster

- Zostavax: Important where high ZV coverage: equally immunogenic and safe
- RZV after natural herpes zoster (physician documented):
  - safe but high reactogenicity as for ZOE-50/70
  - antibody to vaccine in patients >50: 90.2%

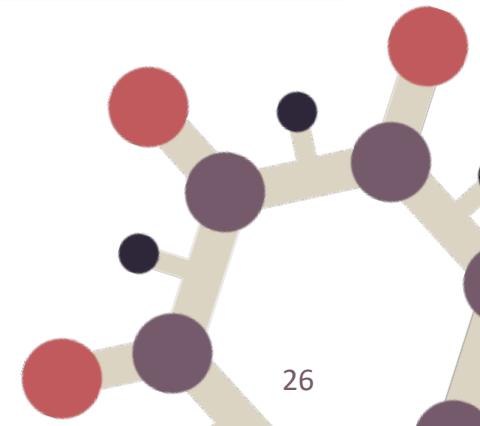
# RZV can be co-administered with the following vaccines

- ✓ **Influenza** (unadjuvanted inactivated seasonal)<sup>1,2</sup>
- ✓ **Pneumococcal** (PPV23)<sup>1,3</sup>
- ✓ **Diphtheria-Tetanus-Pertussis** (DTaP)<sup>1,4</sup>

Co-administration generally well tolerated<sup>1-3</sup>

No safety issue raised<sup>1-3</sup>

No immunologic interference observed<sup>1-3</sup>



# RZV, Shingrix: summary and issues

- ~90% efficacy against herpes zoster and complications (including PHN)
- Unaffected by age (e.g. <80 years of age) and frailty
- Two doses required 2-6 months apart: compliance in real world setting seems high
- High reactogenicity: severe, impairing everyday activity: local, 9%; systemic 11%; but lasts only ~2 days, only one-third are severe with second dose
- Duration of efficacy: 89% >10 years (longer term trials in progress)
- Risk of auto immunity (and gout) with new adjuvants: none seen in trials but needs long term post marketing surveillance.

# Recombinant Zoster Vaccine: recent advances

- High Vaccine efficacy unaffected by presence of multiple comorbidities or frailty (cf influenza and pneumococcal vaccines)
- RZV ameliorates pain in the acute stages of breakthrough HZ
- Retrospective community effectiveness studies show a single dose is ~15% less effective than the standard double dose.
- Good RZV immunogenicity does not require marked reactogenicity i.e. there is only a weak association between the two

Curran D et al JAGS 2021; Izurieta H et al CID 2021; Kim JH Pain In press; Callegero A JID 2021

# RZV in immunocompromised populations

Adults ≥18 years of age



**HUMAN IMMUNODEFICIENCY VIRUS<sup>1</sup>**  
Living with HIV



**AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANT<sup>2</sup>**  
Post transplant



**HAEMATOLOGIC MALIGNANCIES<sup>3</sup>**  
Receiving immunosuppressive chemotherapy\*



**RENAL TRANSPLANTS<sup>4</sup>**  
Post-renal transplant



**SOLID TUMOUR<sup>5</sup>**  
Receiving immunosuppressive chemotherapy

Trial	Zoster-015	Zoster-002	Zoster-039	Zoster-041	Zoster-028
Phases	Phase 1/2a (N=123)	Phase 3 (N=1846)	Phase 3 (N=562)	Phase 3 (N=264)	Phase 2/3 (N=232)
Trial Type	Placebo controlled, ≥18 years of age				
Endpoints	Immuno/Safety	Efficacy/Immunogenicity/Safety		Immunogenicity/Safety	
Dose Timeline	Month 0, 2, 6 (3 doses)	Month 0, 1-2	Month 0, 1-2	Month 0, 1-2	Month 0, 1-2

Two doses of vaccine-induced humoral and cell-mediated immune responses that persisted at 1-year post-vaccination.<sup>1-5</sup>

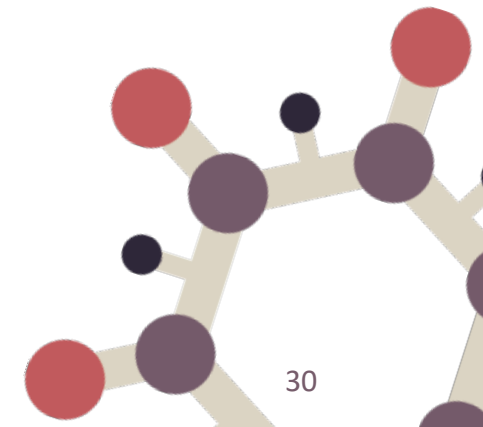
**References:** 1. Berkowitz EM, et al. J Infect Dis. 2015 Apr;211(8):1279-87. 2. Bastidas A, et al. Open Forum Infect Dis. 2019 Oct;6(Suppl 2):S84-S85. 3. Dagnev AF, Lancet Infect Dis. 2019 Jan;19(9):988-1000. 4. Vink P, et al. Clin Infect Dis. 2020 Jan;70(2):181-190. 5. Vink P, et al. Cancer. 2019 Apr;125(8):1301-12.

# Immunogenicity and efficacy of RZV in immunocompromised patients aged 50+ years\*<sup>1-4</sup>

Condition	Vaccine response rate (gE antibody)	Vaccine response rate (CD4-2 <sup>+</sup> count)	VE <sub>HZ</sub>
Autologous HSC transplantation <sup>1,2</sup> (N=1296)	<b>71%</b> (58, 83)	<b>89%</b> (72, 98)	<b>67%</b> (53, 78)
Renal transplant <sup>3,4</sup> (N=166)	<b>74%</b> (63, 83)	<b>64%</b> (38, 86)	not reported
Haematological malignancy <sup>5,6</sup> (N=407)	<b>60%</b> (53, 67)	<b>84%</b> (69, 93)	87%
Solid tumours with chemotherapy <sup>7,8</sup> (N=171)	<b>92%</b> (82, 98)	<b>46%</b> (19, 75)	not reported

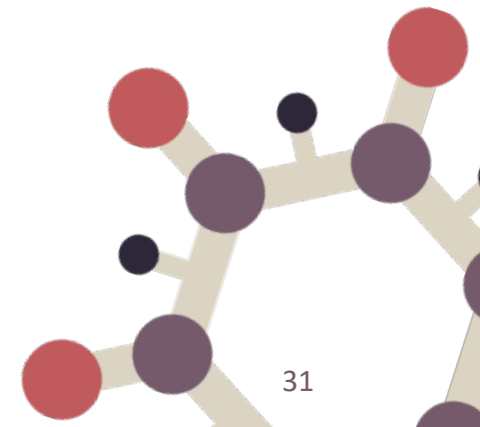
**Phase I/II studies have also demonstrated that RZV was immunogenic and well tolerated in patients with HIV.<sup>4</sup>**

1. Bastidas A, et al. JAMA 2019;132(2):123-133; 2. Stadtmauer EA, et al. Blood 2014;124(19):2921-2929;. 3. Vink P, et al. Clin Infect Dis 2020;70(2):181-190;. 4. Vink P, et al. Cancer 2019;125(8):1301-1312..



# RZV in the immune-compromised: reactogenicity

- Local: similar to immunocompetent
- Systemic: markedly increased (66-82%) but mainly due to underlying disease as not much more than placebo recipients



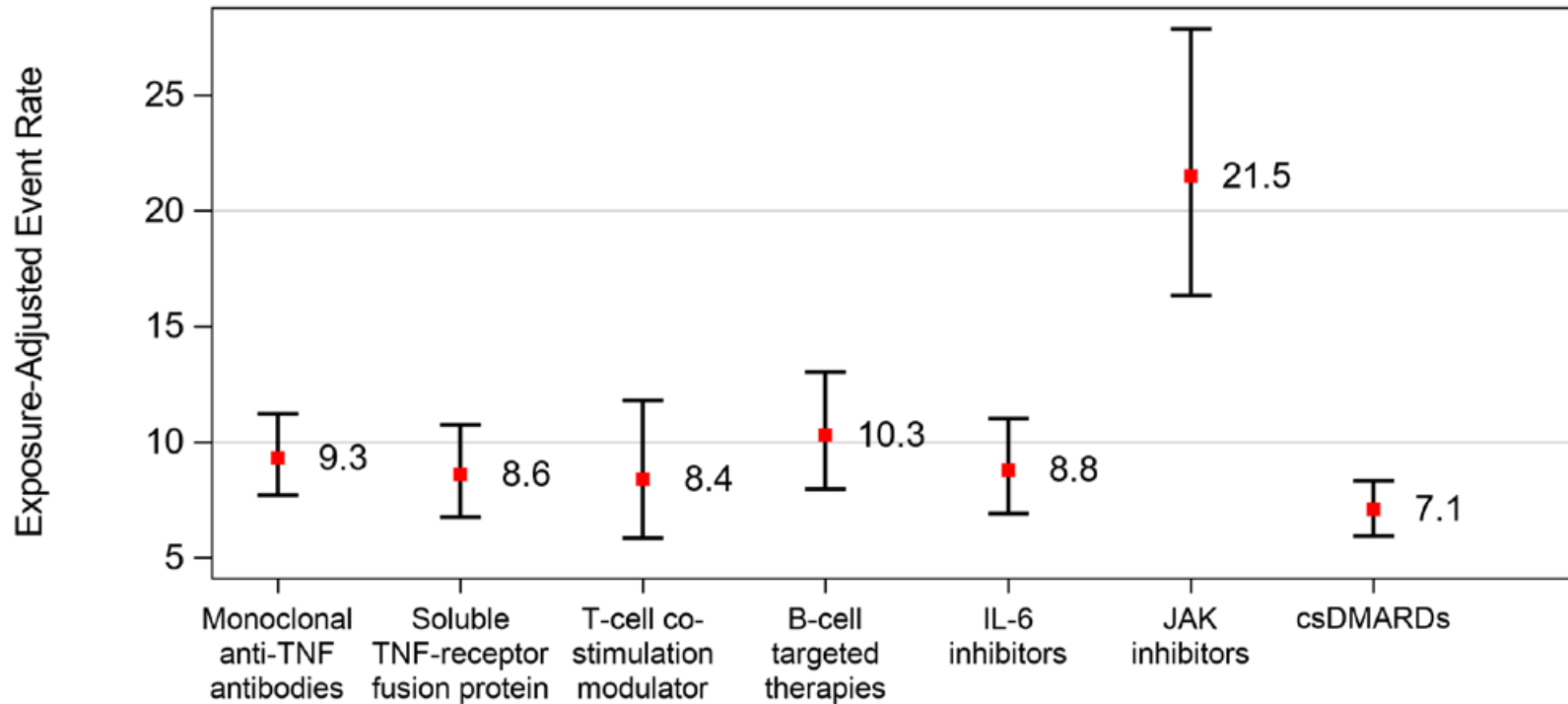
# RZV in the immune-compromised: questions and future research

- Phase III trials in subjects with solid organ transplants and malignancies to be completed to determine efficacy
- Duration of efficacy (>1-2 years) in immune-compromised patients
- Real life effectiveness studies (as for immune competent patients)
- RZV efficacy, immunogenicity and safety in subjects receiving immunosuppressive agents (DMARDs) for auto-immune diseases





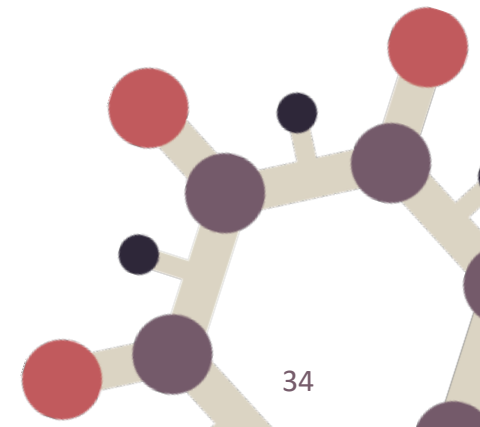
# Risk of herpes zoster with DMARDs

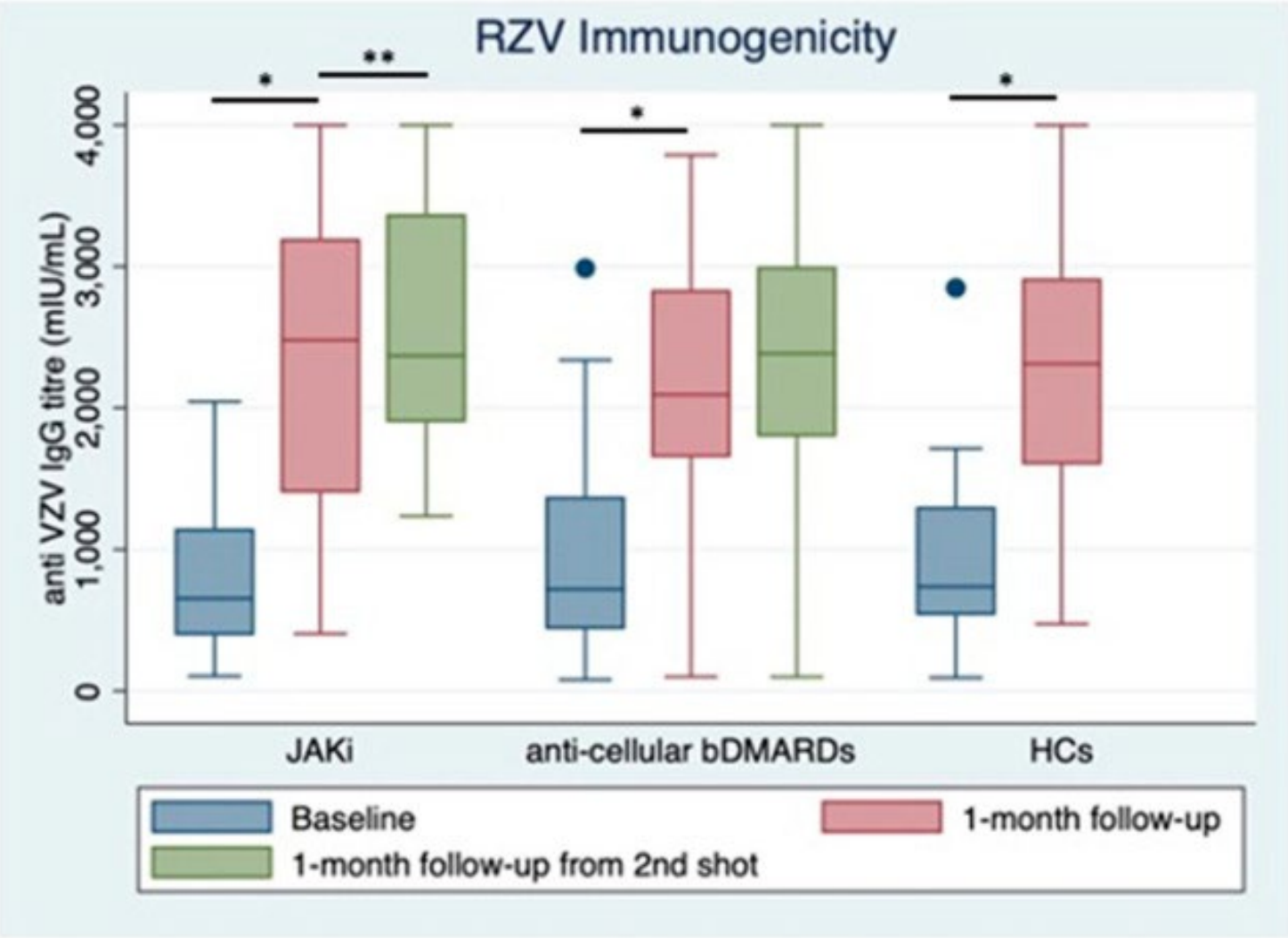


Patient-years	12207	8850	4027.6	6522.9	8543.9	2691.5	20114
No. events	114	76	34	67	75	58	142
95% CI	7.7-11.2	6.8-10.8	5.9-11.8	8.0-13.0	6.9-11.0	16.4-27.9	6.0-8.3

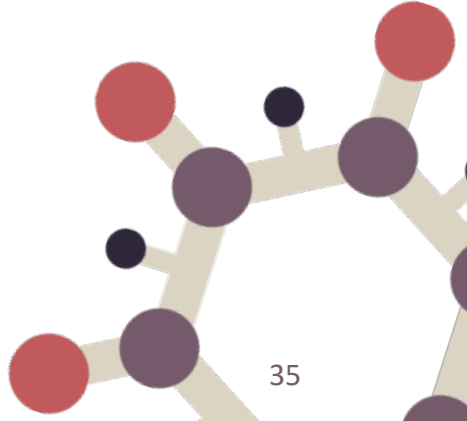
# RZV in patients treated with DMARDs

- 4 phase III trials in progress
- Early trials how reduced slightly immunogenicity of immunocompetent
- Rheumatoid flares ?increase in  $\ll 10\%$





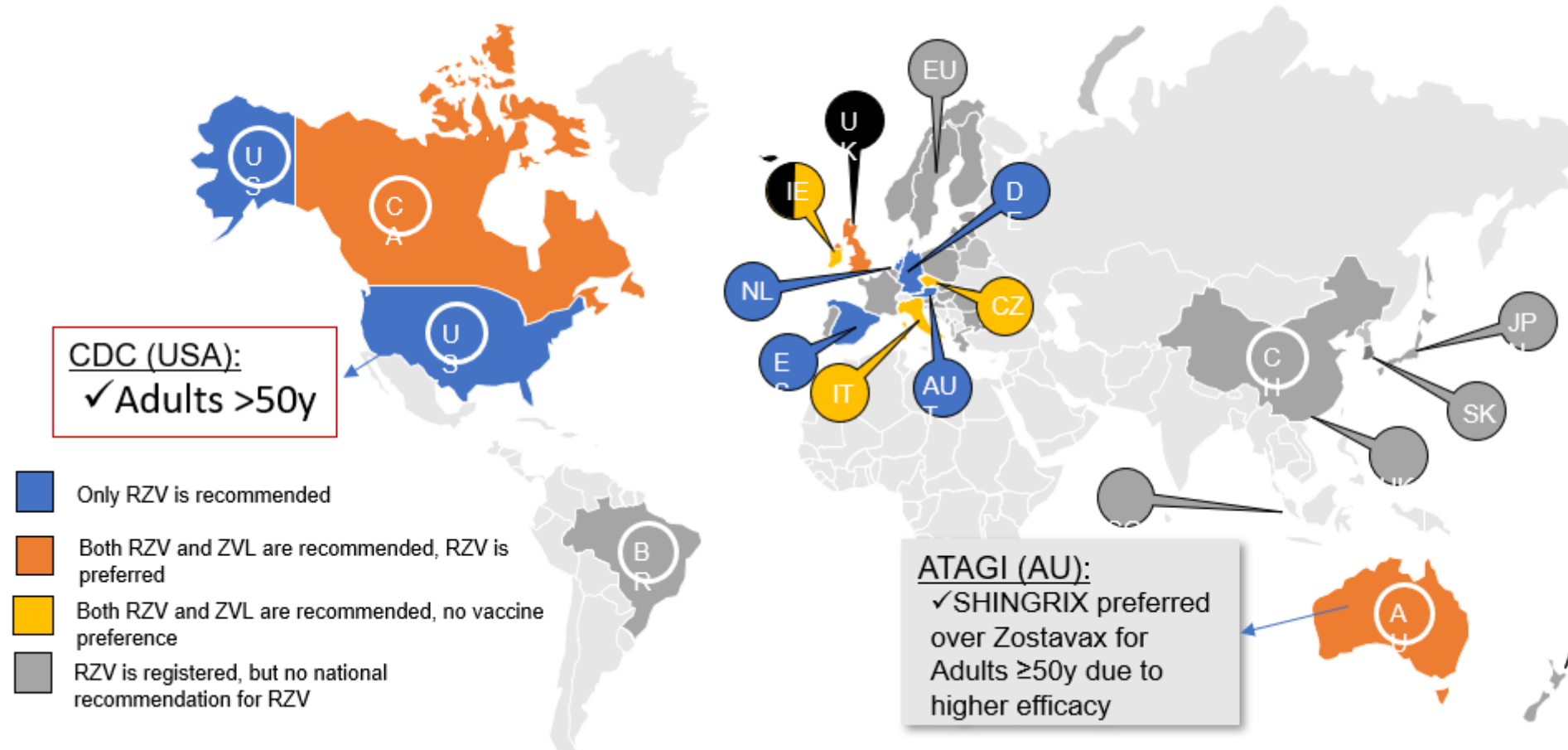
\* p<0.001  
 \*\* p=0.03



# National Centre for Immunisation Research and Surveillance (NCIRS) recommendations

- Both immunocompromised and immunocompetent people aged  $\geq 50$  years should have RZV to prevent herpes zoster and its complications.
- In immunocompetent people aged  $\geq 50$  years, Shingrix is preferred over Zostavax for prevention of herpes zoster and its complications.
- In people  $\geq 50$  years who are immunocompromised, Zostavax is contraindicated and so Shingrix should be used.
- Use Zostavax for immunocompetent people  $\geq 50$  years if Shingrix is not available or affordable. Zostavax is NIP-funded for people aged 70 years.

# Shingrix is registered in >35 countries with local recommendations of varying degrees of preference



# Recombinant Zoster Vaccine (RZV): National Immunisation Program (NIP) Recommendations

- The Pharmaceutical Benefits Advisory Committee (PBAC) recommended NIP listing for:
  - non-Indigenous individuals at 70 years of age
  - Aboriginal and Torres Strait Islander individuals aged  $\geq 50$  years
  - individuals aged  $\geq 18$  years with haemopoietic stem cell transplant, solid organ transplant, haematological malignancy, or advanced or untreated HIV
- The start date for the RZV NIP has not been officially announced
- The PBAC also deferred a decision for the broader population of immunocompromised individuals aged  $\geq 18$  years at increased risk of herpes zoster, to seek further ATAGI advice on the appropriate definition of this population.

WE WOULD LIKE TO THANK THE FOLLOWING COMPANIES  
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