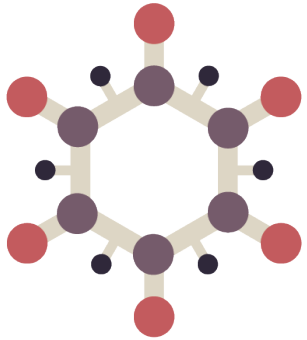
Herpes Zoster



IMMUNISATION
COALITION

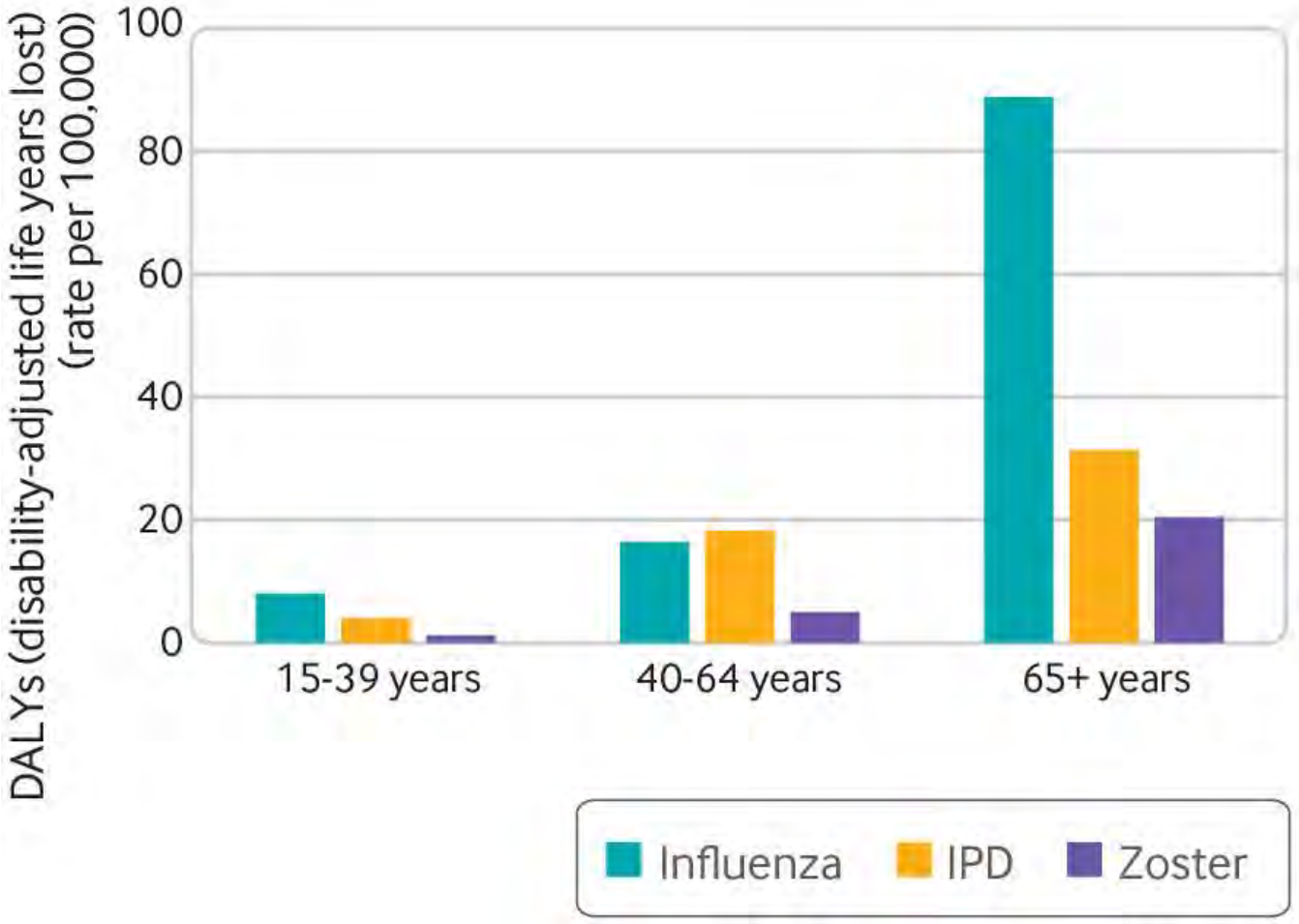
Herpes zoster

Professor Tony Cunningham
Centre for Virus Research, The Westmead Institute for Medical Research
and University of Sydney

Declarations

- Chair, Publications Committee, GSK Shingrix ZoE50 and ZoE70 trials
- Past Member, Global Adult Vaccine Advisory Board, Merck
- Chair, Zostaxax Advisory Board, Seqirus/BioCSL

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



per 100 000 by age group

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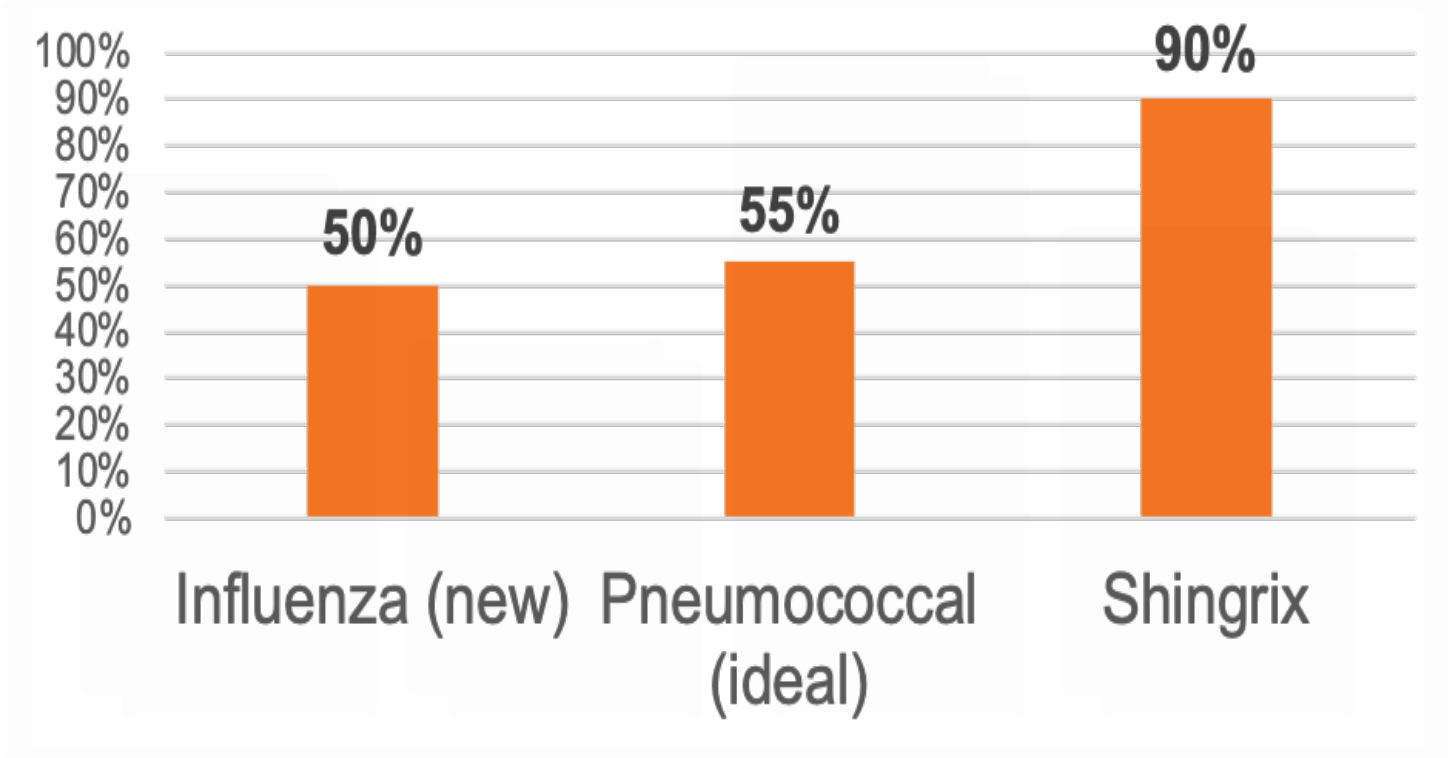
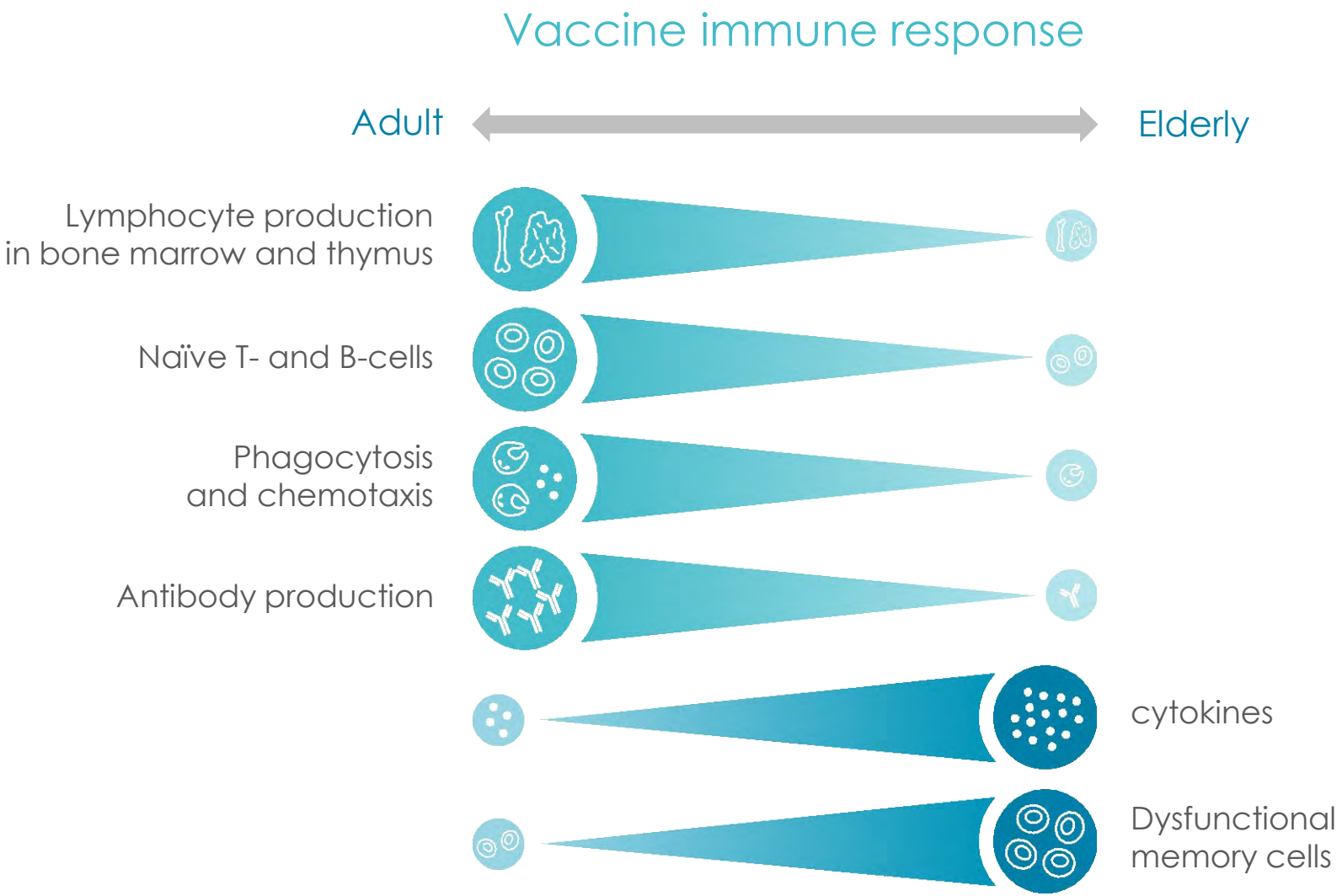
Cunningham AL et al. BMJ 2021;372:bmj.n188

Vaccine efficacy for ageing people (>65 years)



Vaccine response decreases with ageing



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

Zoster: latency and reactivation

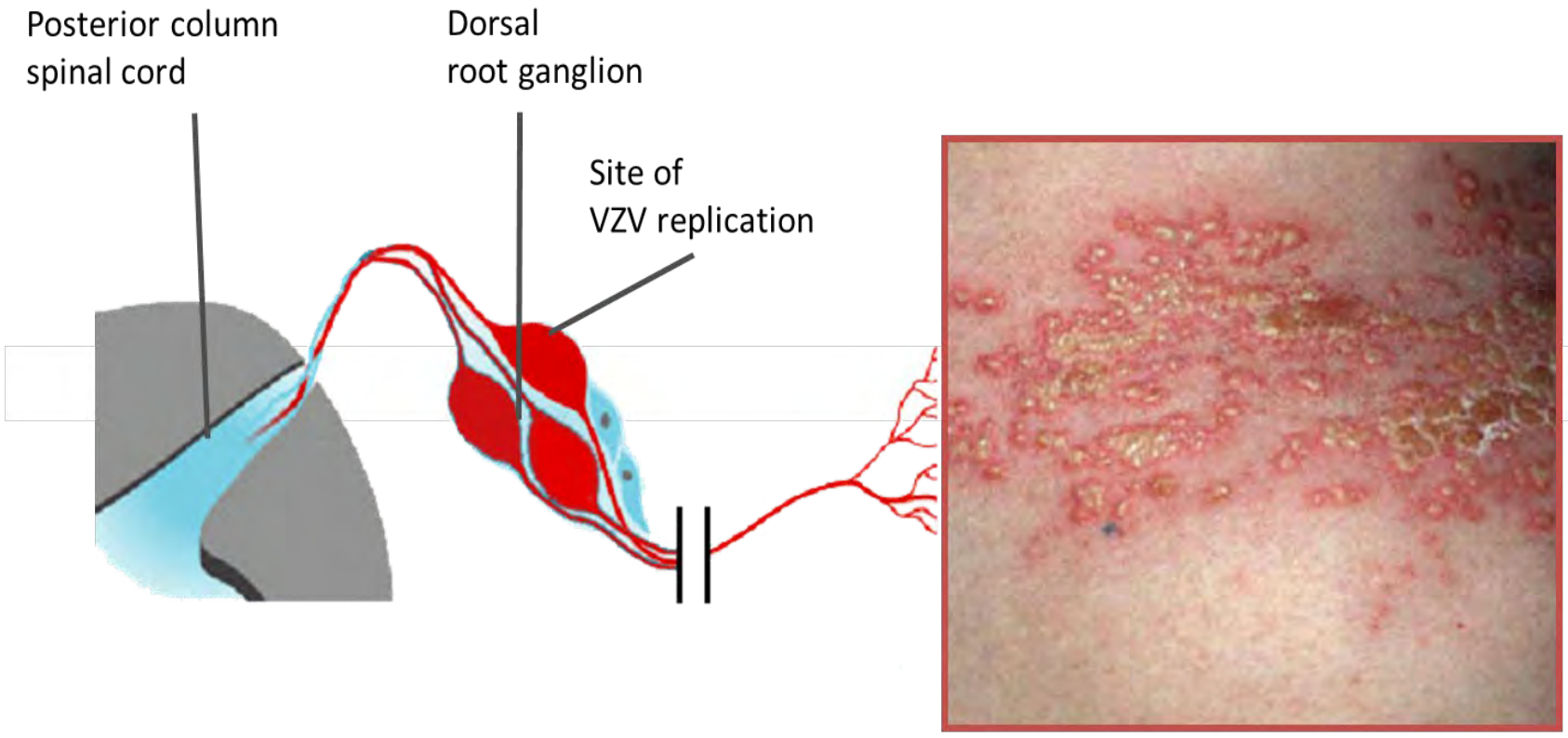
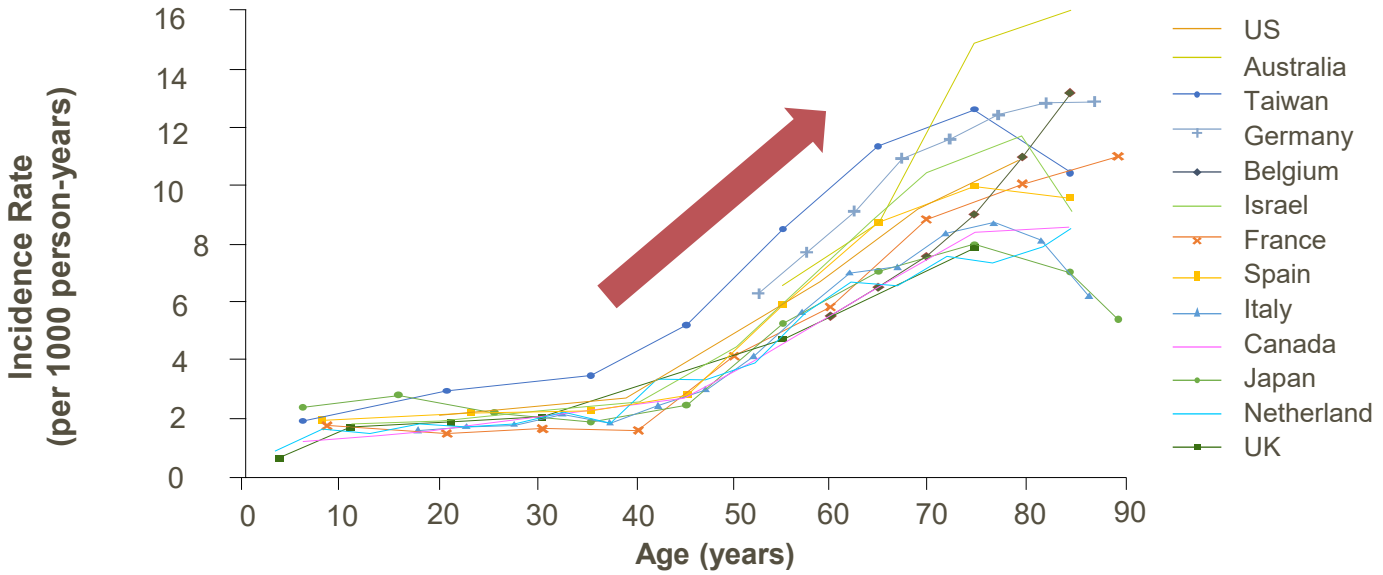


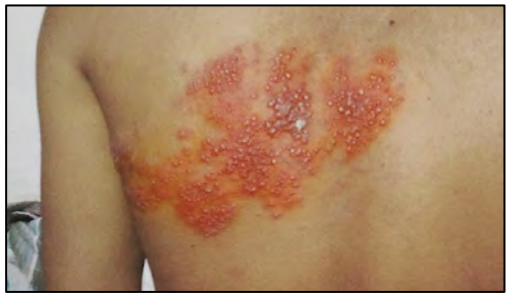
Image courtesy of Thomas P. Habif, MD.

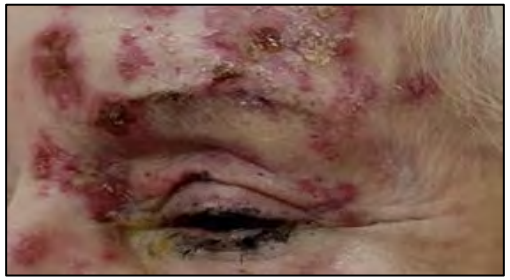
Incidence of HZ stratified by age



https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6333a3.htm

Clinical importance of herpes zoster





Picture 1: ncbi.nlm.nih.gov/pmc/articles/PMC5389218/figure/F3/, Picture 2, Wim Opstelten, Michel J W Zaal, BMJ VOLUME 331 16 JULY 2005, Picture 3: bmj.com/content/364/bmj.k5234

Acute Herpes Zoster (HZ) presentation

- Unilateral, vesicular rash[1]
- Pain can be “excruciating” and is often described as aching, burning, stabbing or shock-like[1]
- Other symptoms of shingles can include: headache, photophobia, malaise and fever[1]

Complications

Post-Herpetic Neuralgia (PHN)

- Neuropathic pain that persists for >3 months after an outbreak of HZ[3]
- Can affect up to 30% of patients with shingles[2]

Herpes Zoster Ophthalmicus (HZO)

- Can affect 10-25% of patients with shingles[1]
- May lead to vision loss in rare cases[1]

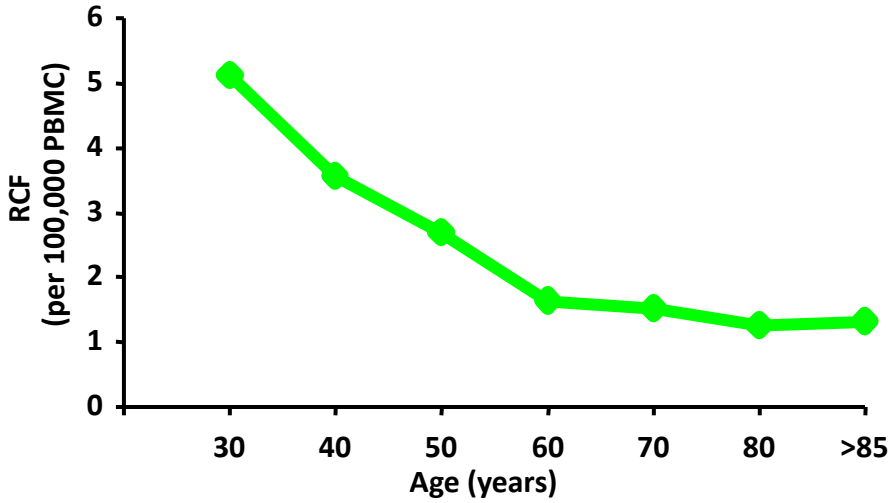
Other complications

- Disseminated disease[3]
- Hearing loss[1]
- Scarring[3]
- Neurological complications[3]
- Cardiovascular and cerebrovascular events[4]

HZ symptoms and complications may be more frequent and of longer duration in immunocompromised patients[5,6]

Rationale for a HZ Vaccine

- *The frequency <u>and</u>* severity *of zoster increase with age*
- *T cell responses to VZV decline with aging, while <u>antibody does not</u>*

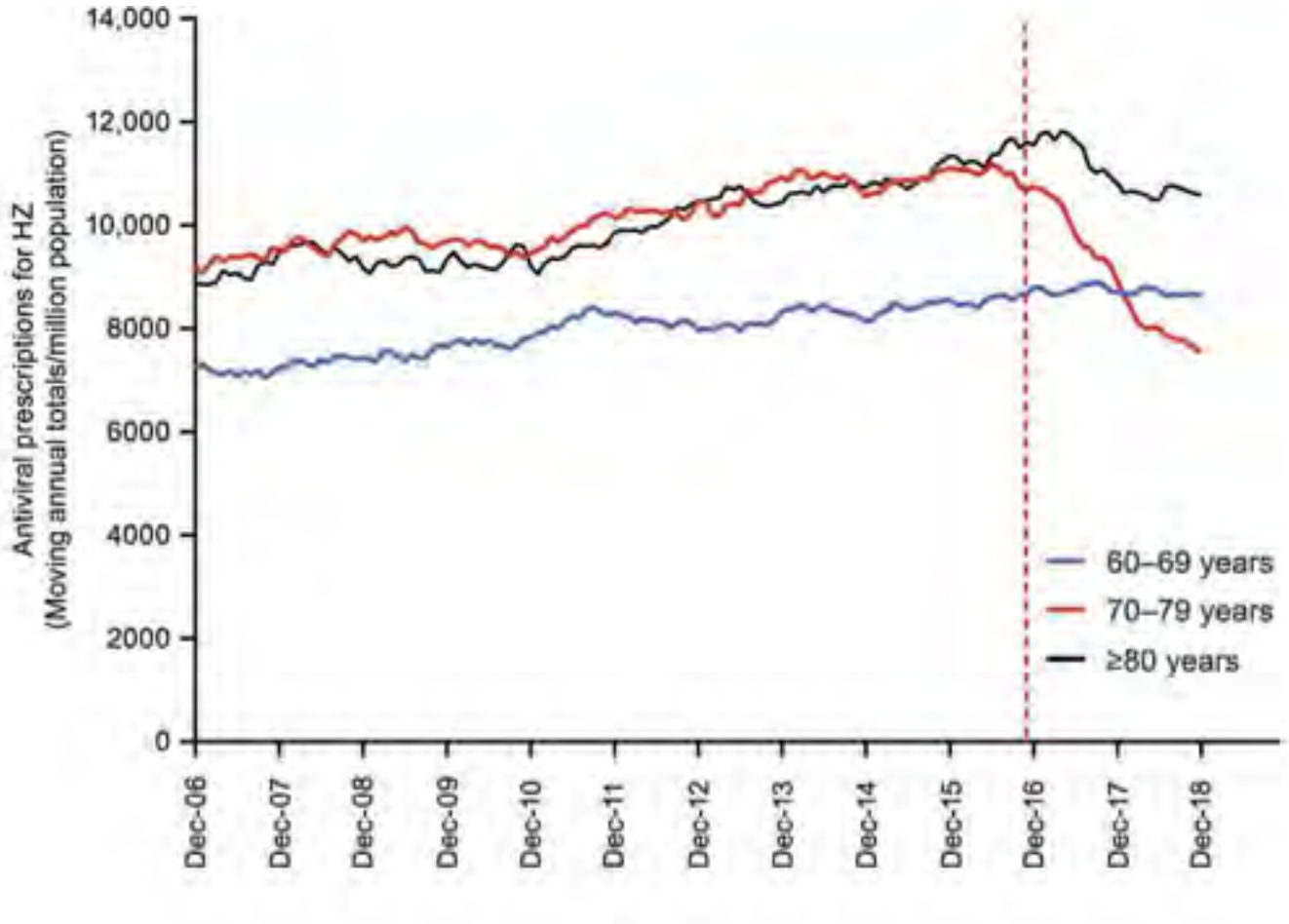


The basis for two hypotheses:

1. the fall in T cell responses to VZV with age to below a threshold permits clinical reactivation of latent VZV

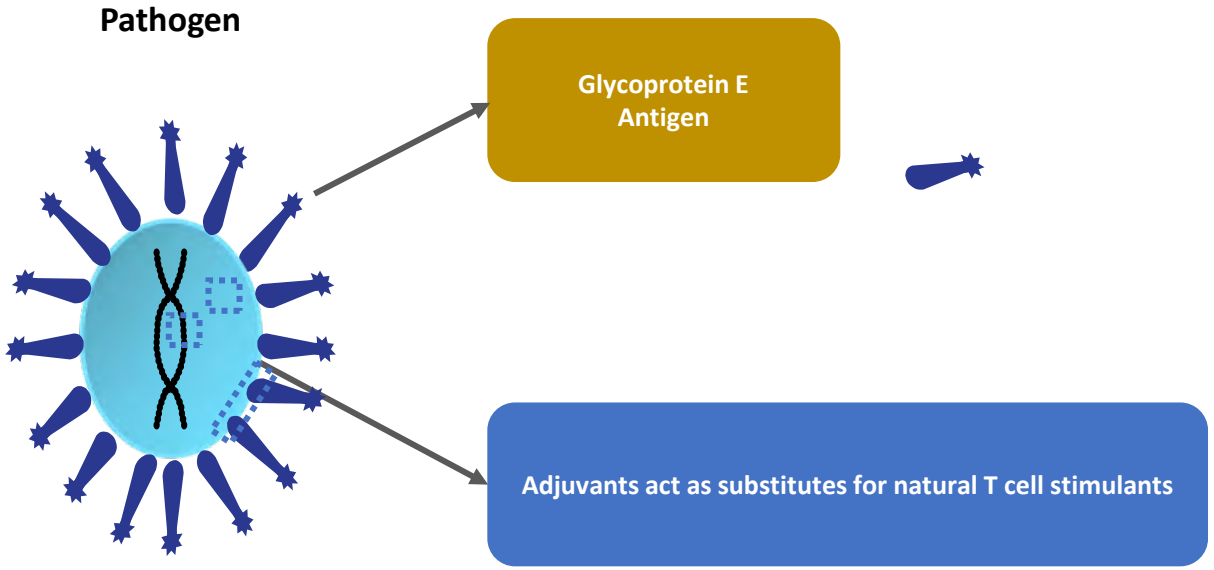
2. increasing the T cell responses to VZV in older people will prevent OR attenuate herpes zoster

Incidence of herpes zoster in Australia has declined after Zostavax introduction



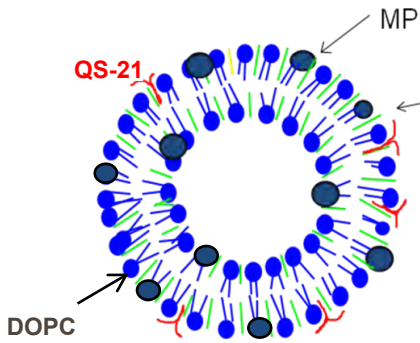
Litt J et al Hum Vacc Immunother 2020

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

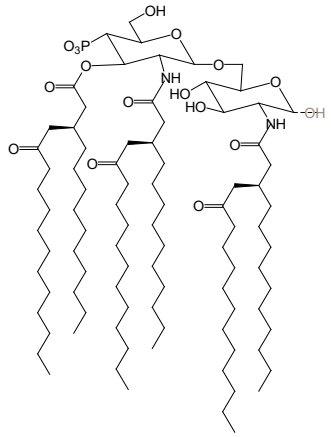
AS01 Formulation



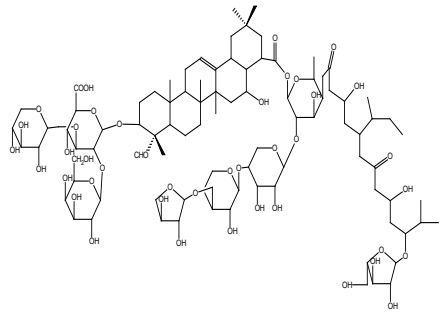
QS-21 is quenched by cholesterol - no longer haemolytic

Immuno-Enhancers

MPL

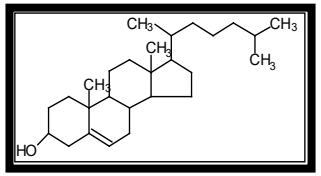


QS-21

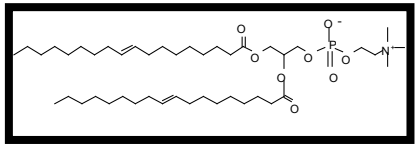


Vehicle

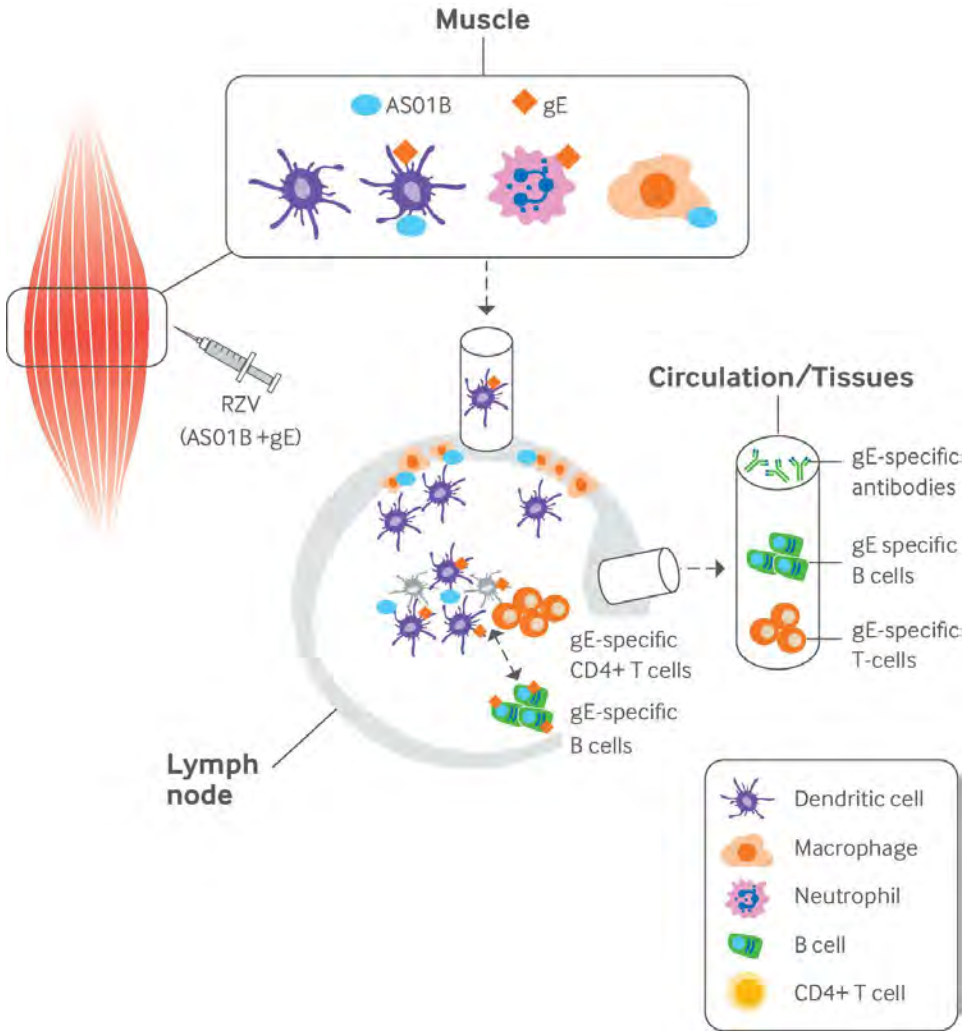
Cholesterol



DOPC



Mechanism of AS01B action in mouse lymph node



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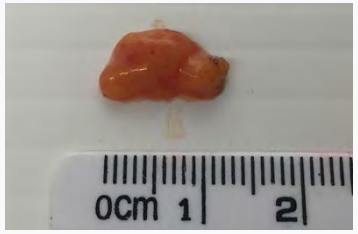
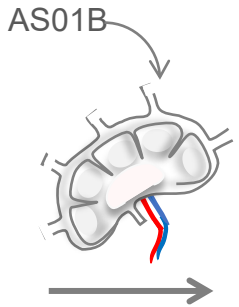
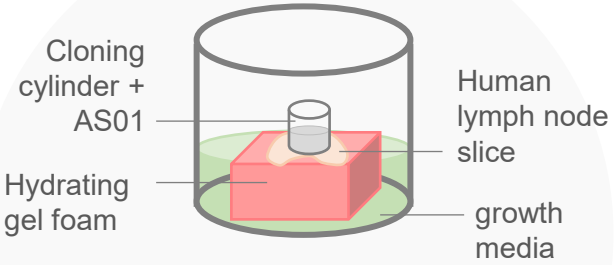
Cunningham AL et al. BMJ 2021;372:bmj.n188

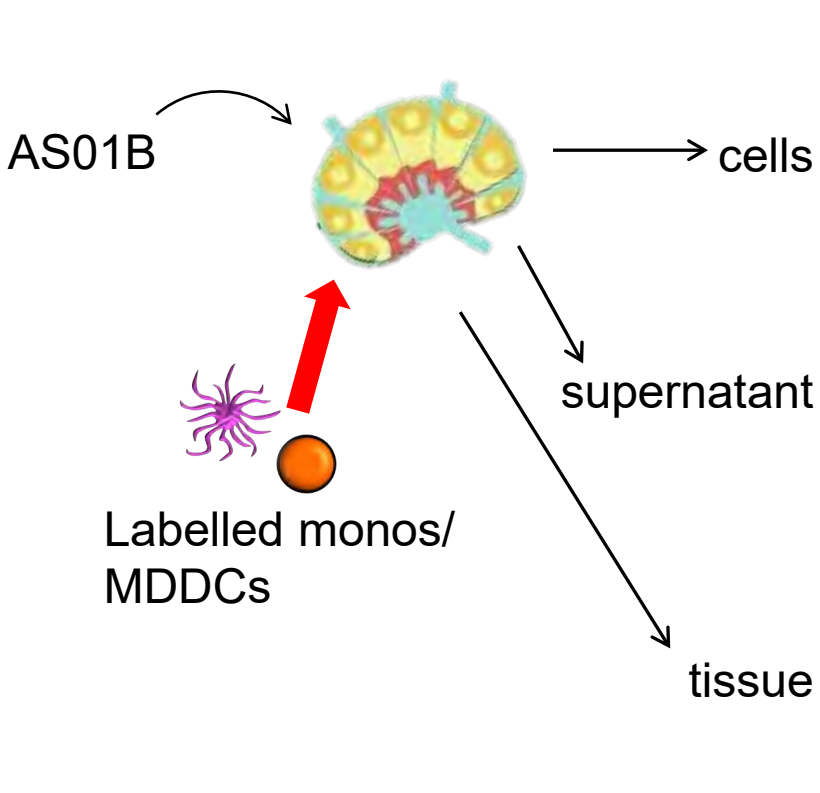
Mechanism of Action of vaccines/adjuvants in human lymph node explant model

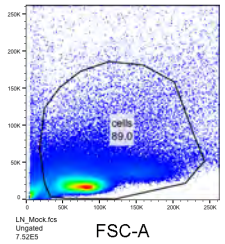




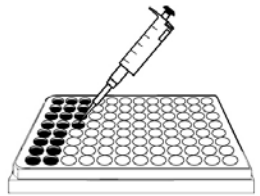


Overview of experimental approach

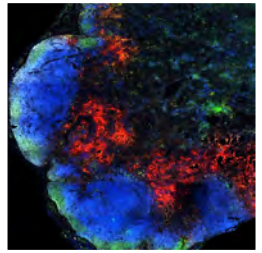




Quantitative analysis of cells

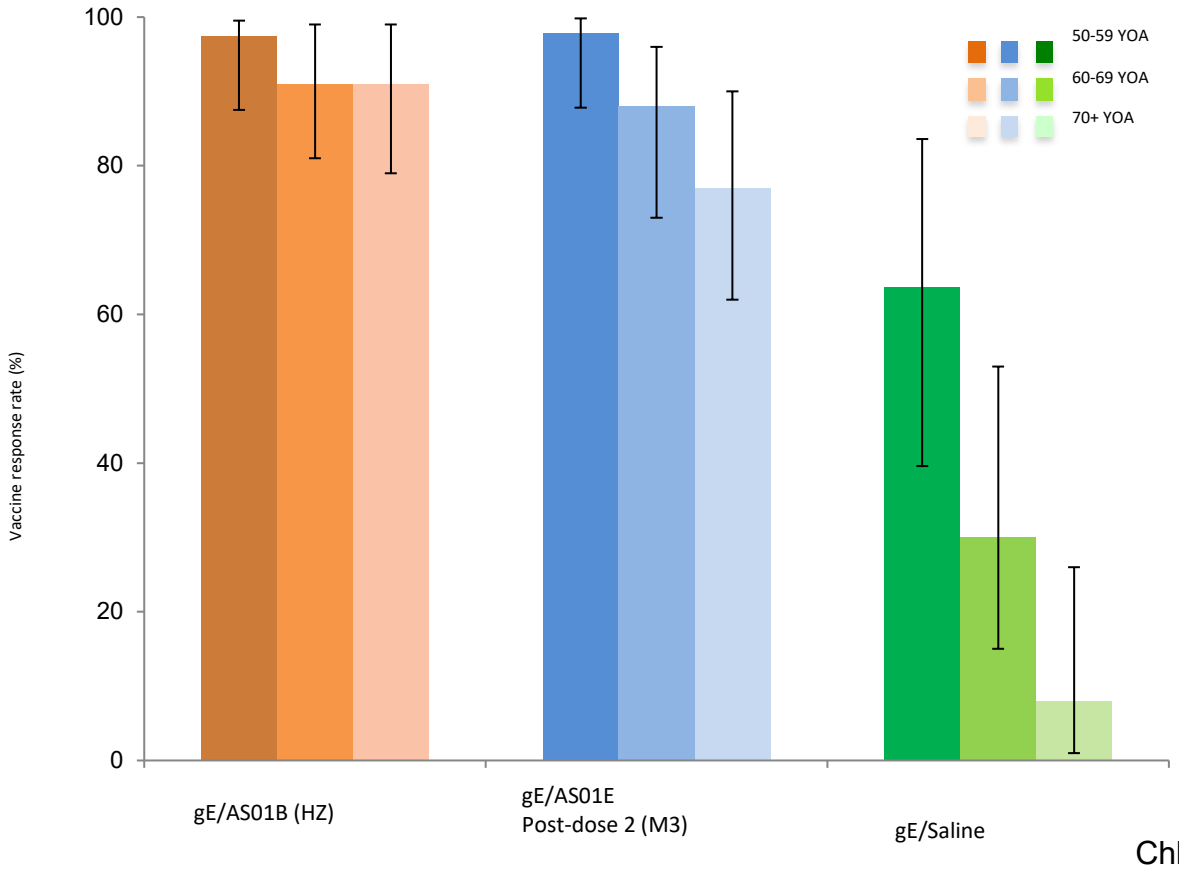


Cell function



Imaging of whole lymph nodes – immune cells interacting with AS01

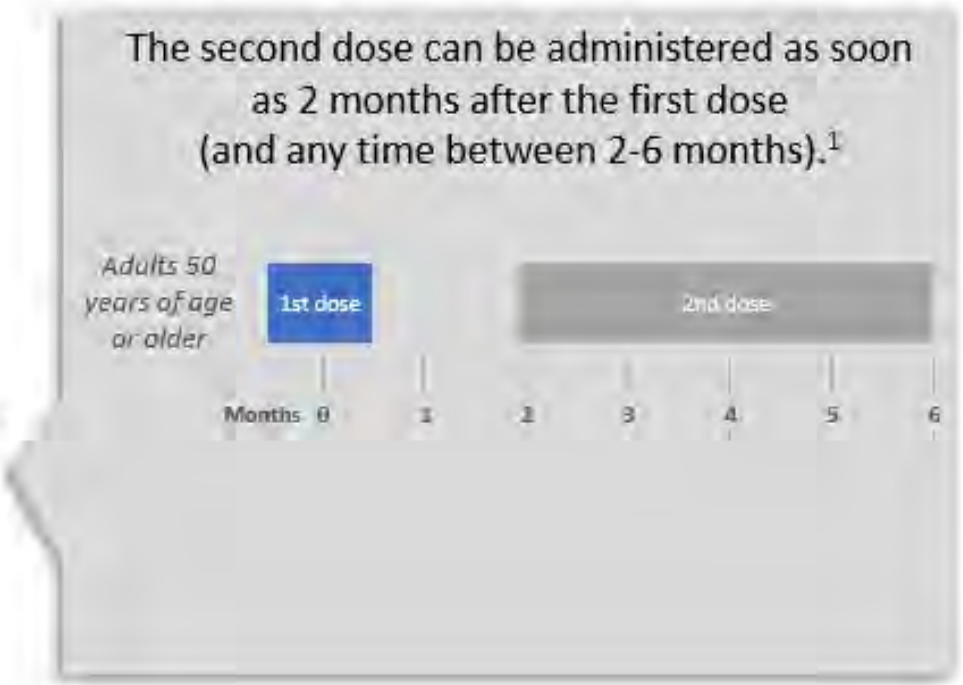
Phase I/II: T cell responses to RZV (gE/AS01$_B$) but not gE alone diminish little with advancing age



Chlibek et al 2015

SHINGRIX efficacy is only confirmed in a 2-dose series

The same results were first published in Vaccine.*
*The graph has been independently created by GSK from the original data.
gE=glycoprotein E.



Chlibek R, et al. Vaccine. 2014; Chlibek R, et al. 2014 Schwarz TF, et al. Hum Vaccin Immunother. 2018

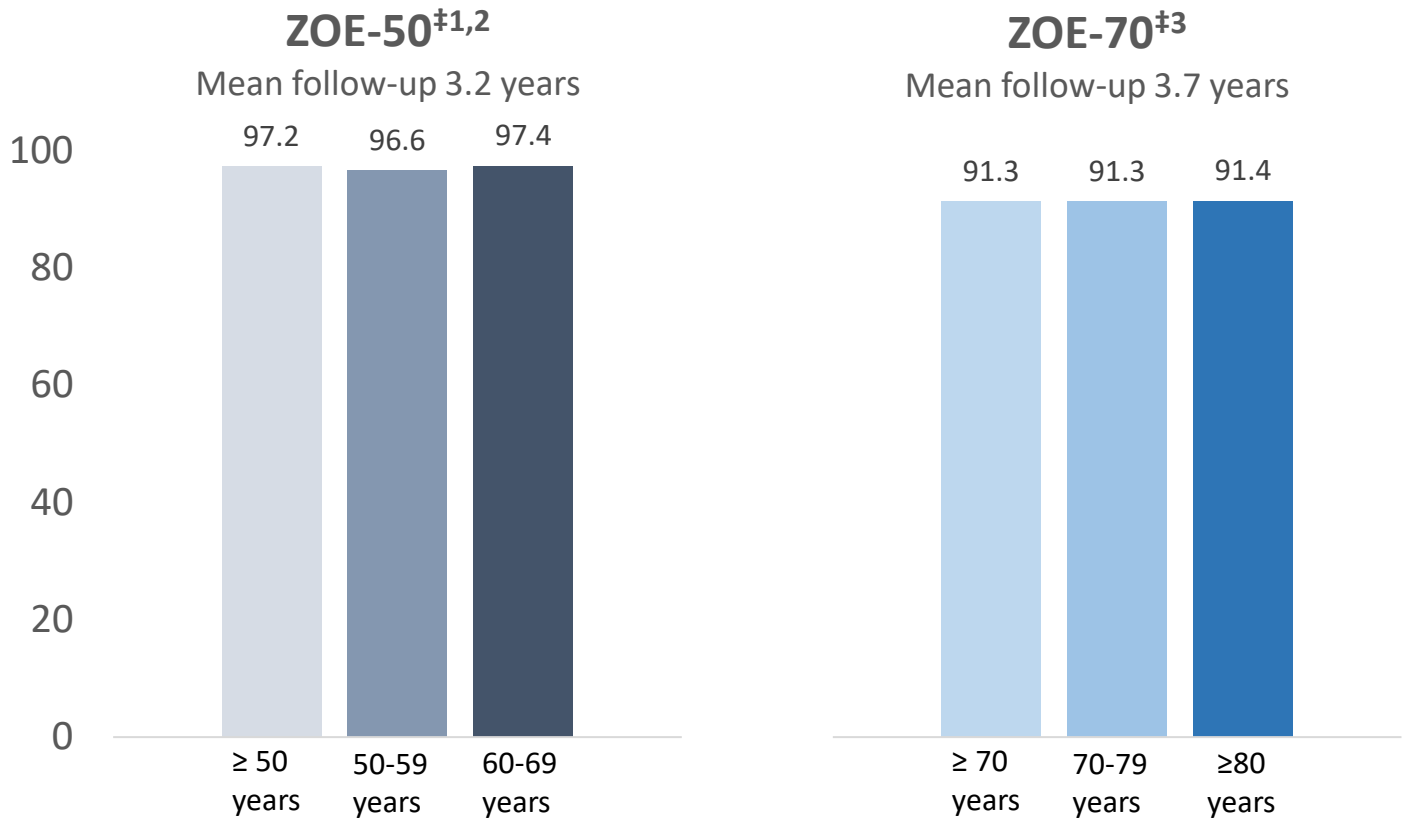
The Pivotal Phase 3 Shingrix Trial Program: ZOE-50 and ZOE-70

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	HZ efficacy in persons ≥50 YOA	HZ efficacy in persons ≥70 YOA
Primary objectives in pooled analysis	PHN efficacy in 70+ HZ efficacy in 70+	
Actual enrollment	16,160 enrolled	14,816 enrolled

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

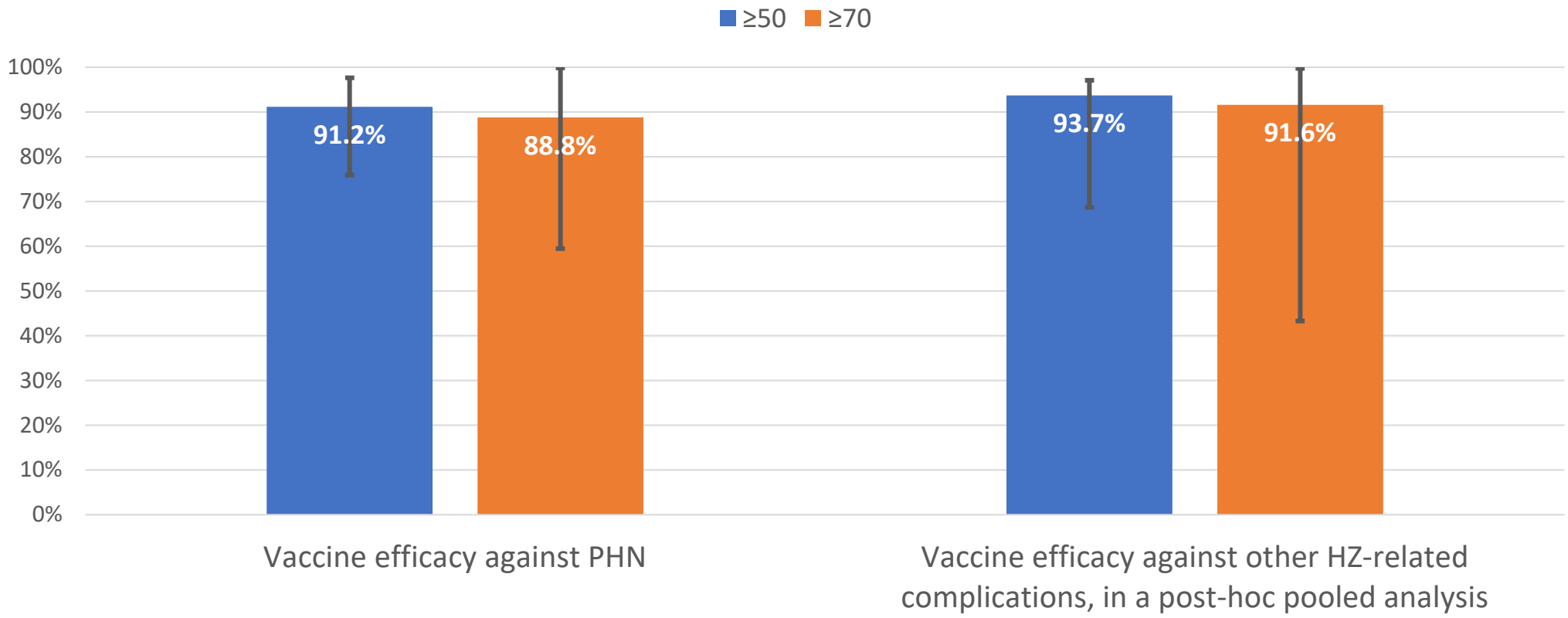
HZ, herpes zoster; PHN, postherpetic neuralgia; YOA, years of age.

Efficacy of RZV against Herpes Zoster in Subjects >50 and >70YOA



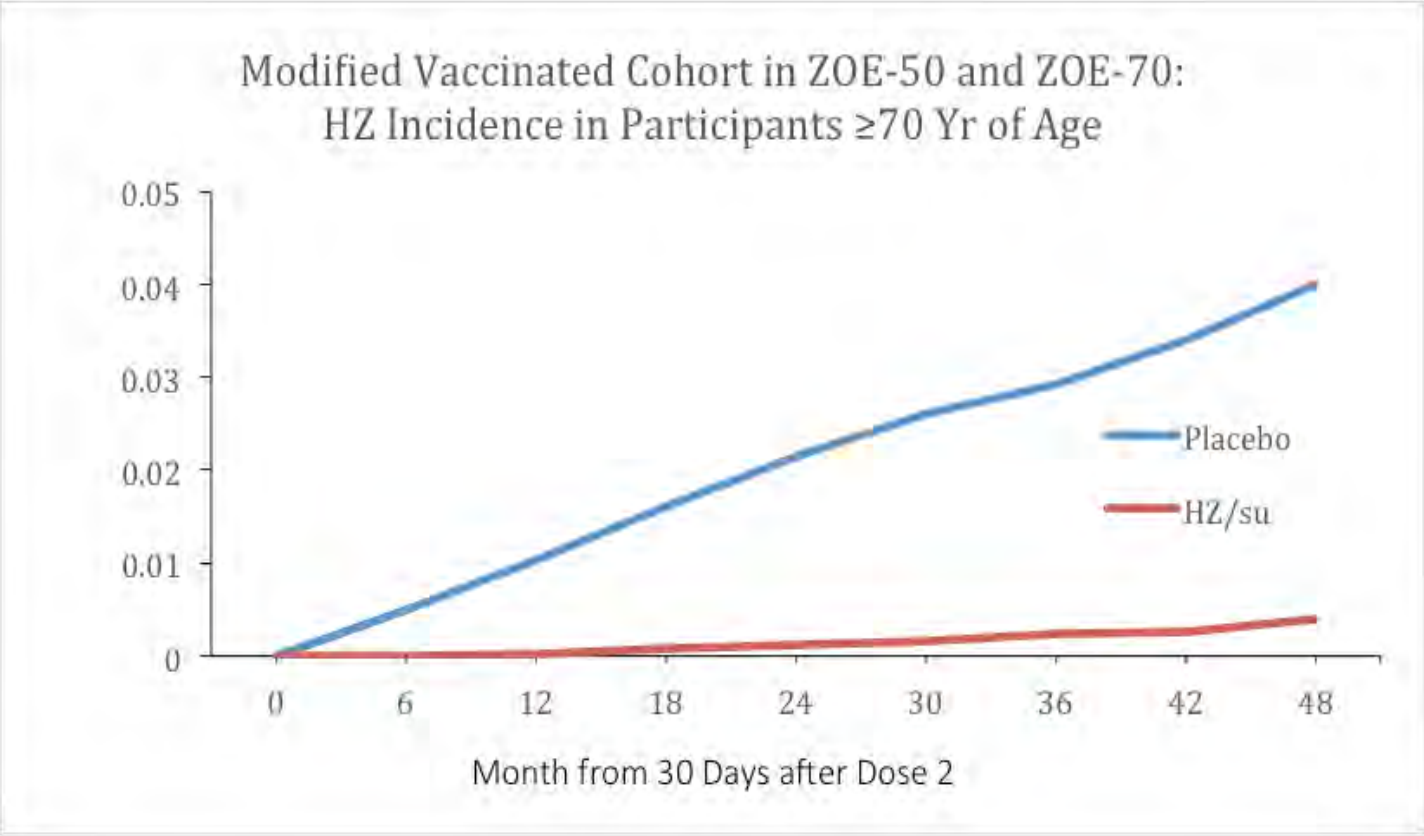
1. Lal H, Cunningham AL et al, N Engl J Med, 2015
2. Cunningham AL et al, HeinemanT N Engl J Med, 2016

RZV efficacy against PHN and other complications



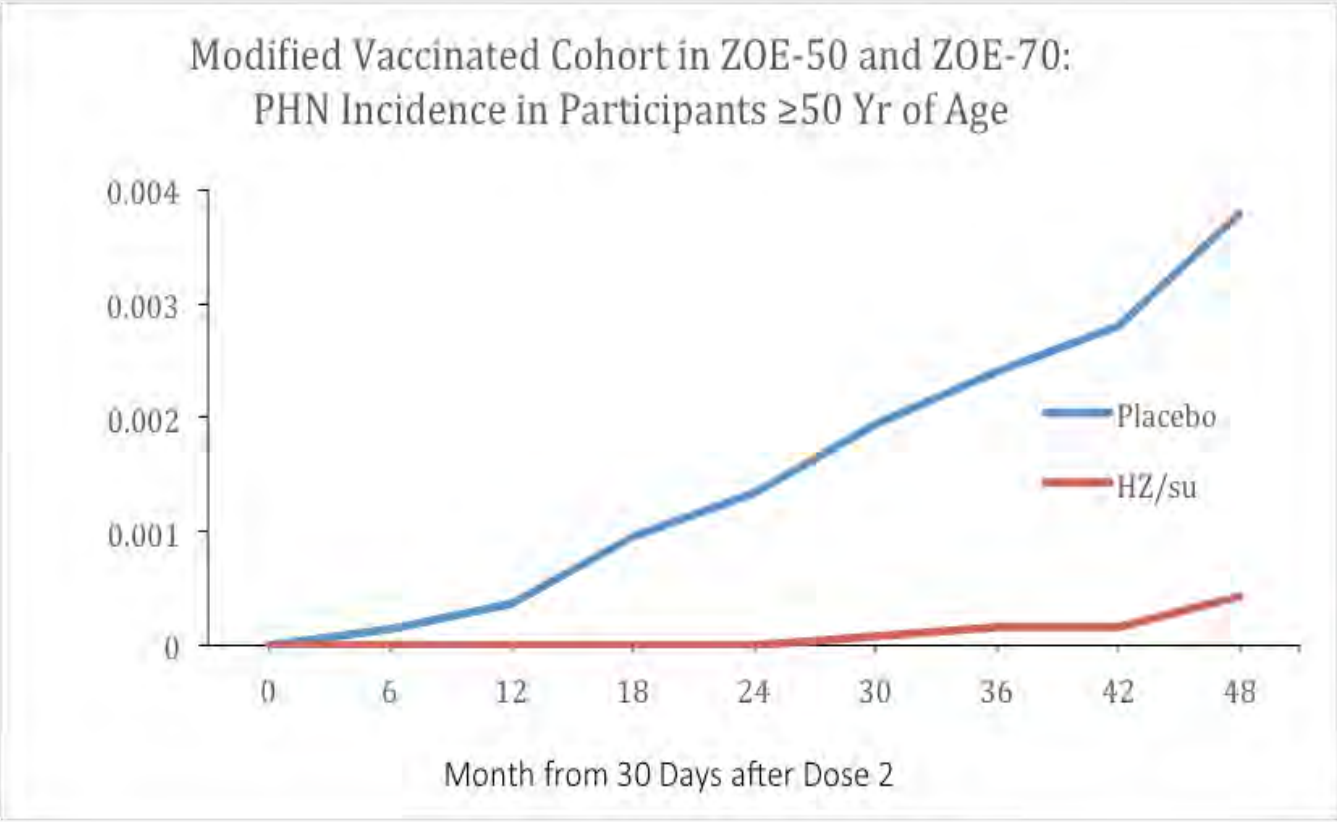
Cunningham AL, et al. N Engl J Med. 2016; 2. Kovac M et al. Vaccine 2018

ZOE-70: Risk of development of herpes zoster after vaccination



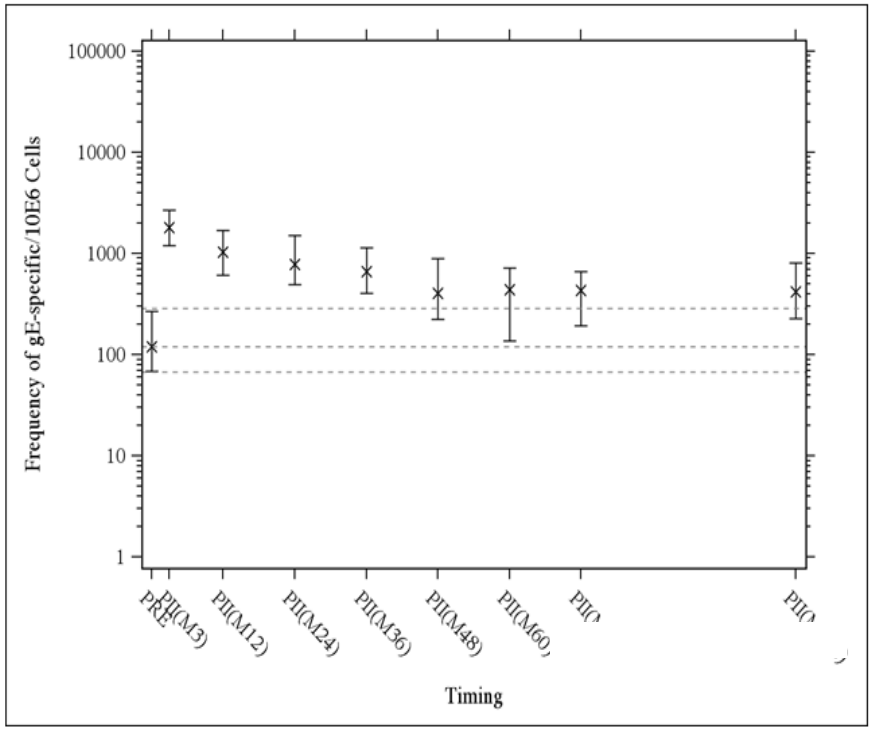
Cunningham AL et al N Engl J Med 2016

ZOE-70: Risk of development of post-herpetic neuralgia after vaccination



Cunningham AL et al.N Engl J Med 2016

Durable cellular immune response to RZV over 9 years



Q3 (75th percentile

Median (50th percentile)

Q1 (25th percentile)

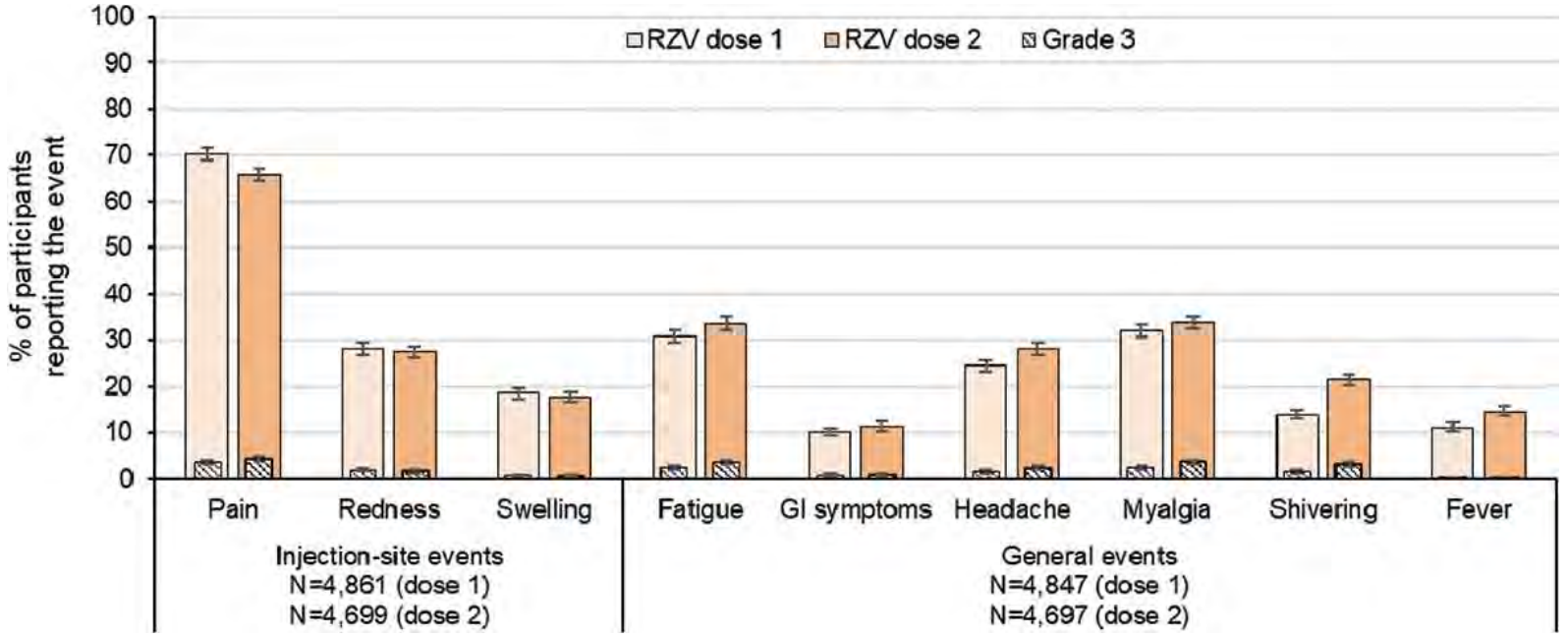
Interim analysis at 7.1 years:
Last two years: VE = 84%
Overall: 90.9%

RZV in subjects with multiple morbidities and frailty

- Conditions with an increased risk of HZ:
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - inflammatory bowel disease
  - chronic obstructive pulmonary disease/asthma
  - chronic kidney disease/renal failure
  - hypertension, diabetes mellitus (type I)
  - spinal disc herniation/osteoarthritis
- No difference in vaccine efficacy in any of these conditions and even in multiple conditions, up to 6 (~frailty)
- Efficacy and reactogenicity not affected by frailty

(Oostvogels L et al Hum Vacc Immunother 2019, Curran et al, Submitted)

Local and general reactogenicity to RZV



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

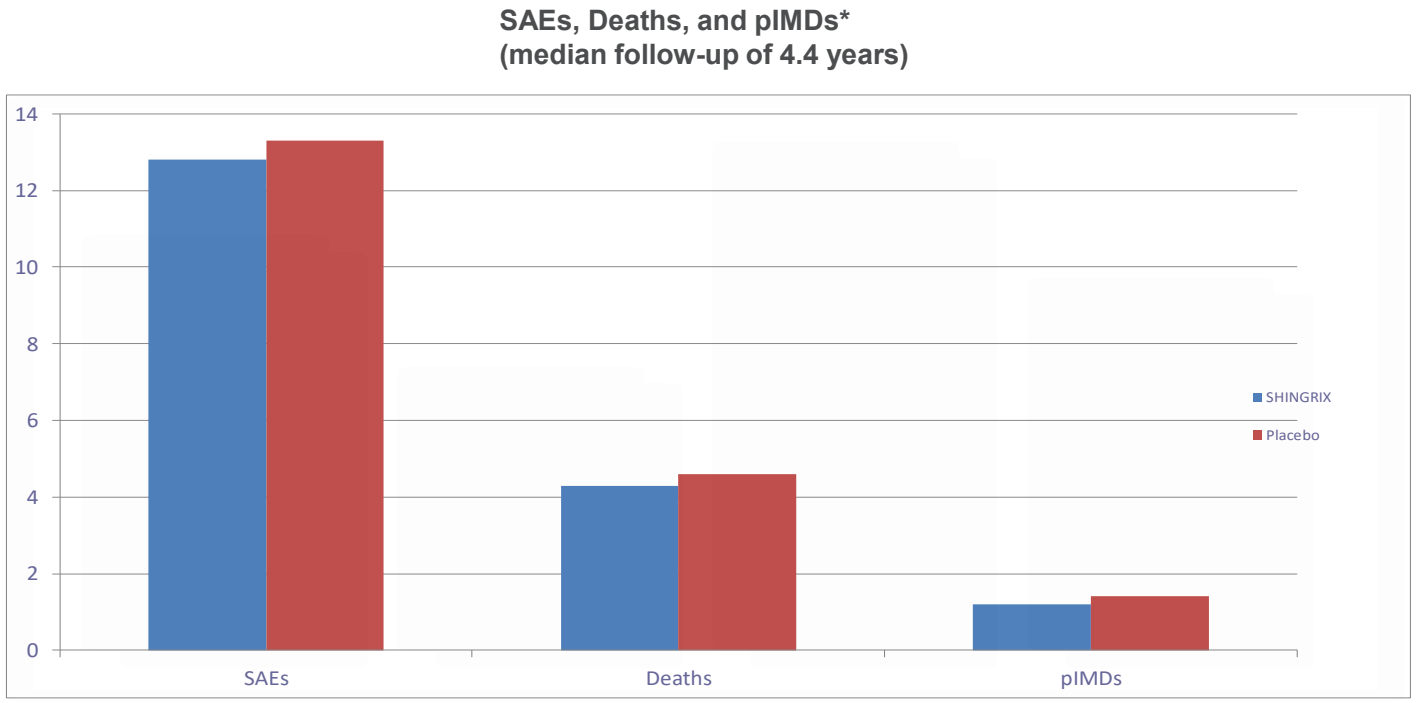
Colindres R…Cunningham AL Human Vacc Immunother 2020

Reactogenicity after first and second doses of RZV

- Similar incidence of grade 3 reactogenicity after first and second doses
- 95% returned for second dose
- 34% of those with grade 3 injection site reacto after first dose had grade 3 after second dose
- Less reactogenicity with advancing age
- HZ in previous 5 years did not influence safety or reactogenicity

Colindres R…Cunningham AL Human Vacc Immunother 2020

No increase in serious adverse events vs placebo[1]



Cunningham AL, et al. N Engl J Med. 2016; Lal H, et al. N Engl J Med. 2015.

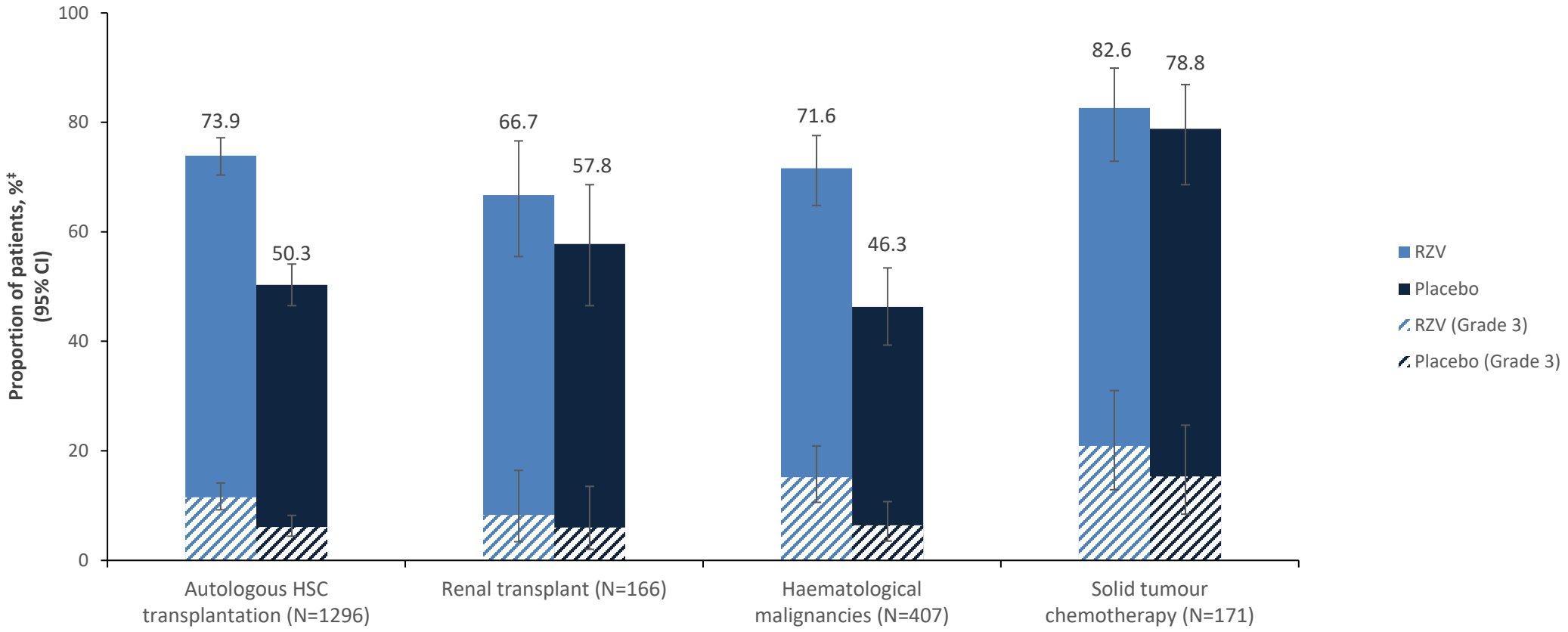
RZV in immune compromised patients III

Condition	Number	Antibody to gE (response rate)	gE T cell (response rate)	Efficacy
Autologous Stem Cell Transplantation[1]	1846	67%	93%	**68% vs. HZ 90% vs PHN**
Hematologic malignancies	561	80%[2]	80%	**87% vs HZ**
HIV CD4 (CD4 = 200-500/µl)	124	96%	86%	**Not reported**
Renal transplantation	240	80%	71%	**Not reported**
Solid malignancy with chemotherapy	185	94%	50%[3]	**Not reported**

Need also to examine HZ/su in moderately immuncompromised patients; Rx with DMARDs (for autoimmune diseases)

Bastidas A, et al. JAMA 2019; Stadtmauer EA, et al. Blood 2014; Vink P, et al. Clin Infect Dis 2020; Vink P, et al. Cancer 2019;

RZV Reactogenicity in Immunecompromised patients



RZV as a booster following Zostavax?

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

Co administration:

- HZ/su equally immunogenic and safe when co administered with influenza and pneumococcal vaccines

Godeaux O et al Hum Vacc Immunother 2017,
Schwartz TF et al Jinfect Dis 2017
Marechal C et al, Vaccine 2018

RZV, Shingrix: summary and issues

- In immunocompetent: ~90% efficacy against Herpes zoster and complications including prolonged pain (PHN)
- Unaffected by age (eg >80 YOA) and frailty

- Two doses required 2-6 months apart: compliance in real world setting 75-85%

  (Efficacy after a single dose will be lower but degree unknown)

- 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: 84% > 7 years (long term follow up trials still in progress)

- Risk of auto-immunity (and gout) with new adjuvants: none seen in trials but needs long term post marketing surveillance

RZV: Implications

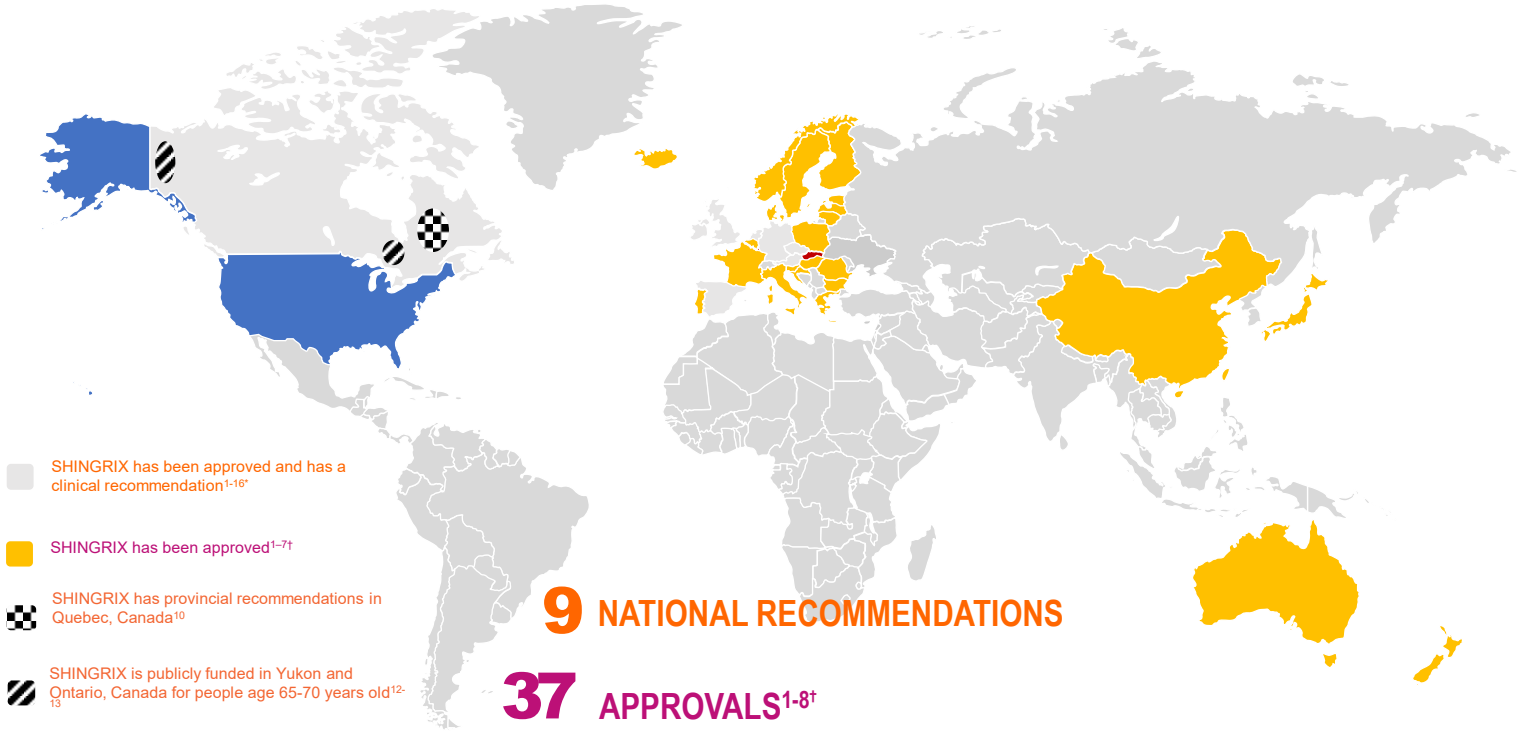
- Shingrix development and trialling confirms several scientific hypotheses:
  - vaccines consisting of a single pathogen protein and adjuvant(s) can be efficacious -and more than a live attenuated vaccine

  - such a combination may cut through immunosenescence = hope for other vaccines in older subjects

  - Elucidation of pathogen/vaccine/adjuvant immunology and MoA is important for (rational) vaccine development

RZV (SHINGRIX) has been approved in 37 countries

Summary – last updated November 2020



*National clinical recommendation, not necessarily linked to funding (in countries where SHINGRIX has been approved)
†SHINGRIX approved across EU countries under a centralised procedure[1]

National Recommendations for RZV

Country	USA	Canada		Germany	UK	Ireland	Netherlands	Spain	Czech	Austria
Recommending Body	CDC[1]	NACI[2]	CIQ*[3] (Quebec)	STIKO[4]	JCVI[5]	NIAC[6]	Health Council[7]	CISNS[8]	Vaccinology Society[9]	National Vaccination Comittee[10]
Immuno-competent Populations	• ≥50 years • Previously received ZVL • Preferred over ZVL	• ≥50 years • Previously received ZVL • Previous episode of HZ	• ≥50 years • Preferred over ZVL • Previously received ZVL (12mo) • Previous episode of HZ (12mo)	≥60 years	≥60 years	≥50 years (RZV, ZVL)	≥60 years	N/A	≥50 years	• ≥50 years • Preferred over ZVL • Previously received ZVL (1 year, min 2mo) • Previous episode of HZ (1-4 years, min 2mo)
IC Populations	• ≥50 years • Limited to those on low-dose immuno-suppressive therapy	• ≥50 years RZV may be considered	≥50 years	≥50 years	≥50 years	≥50 years (cancer, organ transplant)	• ≥60 years • ≥18 years: ❖ In presence of professional guidelines or individual case basis	≥18 years, at risk: ❖ Previous transplant recipient or on waiting-list ❖ HIV	Not specified	• ≥50 years at high risk • <50 years at high risk based on individual case basis

National Centre For Immunisation Research and surveillance (NCIRS) recommendations

- Unless contraindicated, all people aged ≥50 years, both immunocompromised and immunocompetent, are recommended to receive vaccination to prevent herpes zoster and its complications.
- In immunocompetent/healthy people aged ≥50 years Shingrix is preferred over Zostavax for prevention of herpes zoster and its complications.
- In people aged ≥50 years who are immunocompromised, Zostavax is generally contraindicated and so Shingrix should be used*.
- Zostavax is a readily available and effective alternative for immunocompetent people aged ≥50 years if Shingrix is not available or affordable. Zostavax is NIP-funded for people aged 70 years (with catch-up available for those aged 71–79 years until October 2021). People should be encouraged to receive Zostavax if Shingrix is not accessible.

Acknowledgements

Vaccines

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Martina Kovac, GSK Vaccines, Wavre, Belgium

Roman Chlibek, Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic

Timo Vesikari, Vaccine Research Centre, University of Tampere, Finland

Janet E. McElhaney, Health Sciences North Research Institute, Sudbury, Canada

Robert Johnson, University of Bristol

Adjuvant Immunology

Arnaud Didierlaurent, Margherita Coccia GSK Vaccines, Wavre, Belgium

Kerrie Sandgren, Vicki Stylianou, Elizabeth Elder, James French: WIMR, WH

HZ MoA in human lymph nodes

Naomi Truong, Kirstie Bertram, Hafsa Rana, Andrew Harman, WIMR