IMMUNISATION COALITION

Epidemiology of Zoster in the vaccine age (and immunological advances)

10:45 am

Prof Tony Cunningham

Director, Centre for Virus Research,

Westmead Institute, Professor and vaccine theme co-leader, Sydney ID, University of

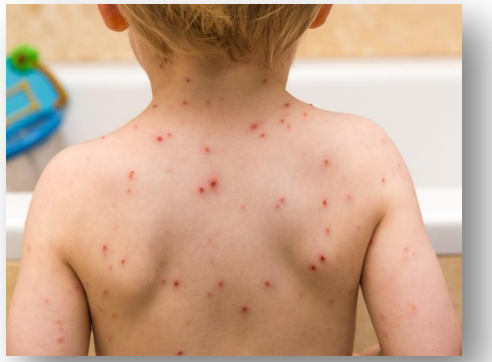
Sydney

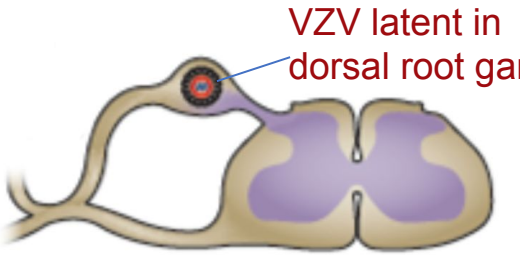
Declarations

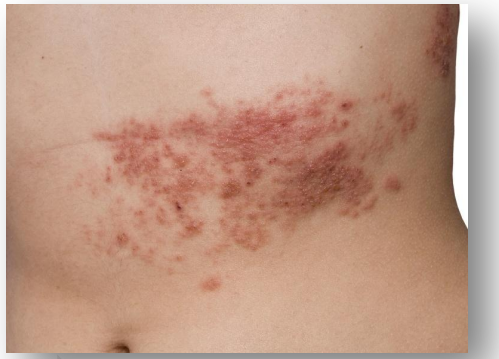
IMMUNISATION COALITION

- Past Chair, Publications Committee, GSK Shingrix ZOE50 and ZOE70 trials
- Past: Member, Global Adult Vaccine Advisory Board, Merck; Chair Zostavax Advisory Board, Seqirus
- COVID Vaccine Advisory Board, Seqirus/BioCSL
- Advisory Board Curevo, USA
- Advisor to Moderna (Australia and USA)

Up to 99.5% of adults ≥50 years of age are infected with VZV and are at risk for shingles[1]*







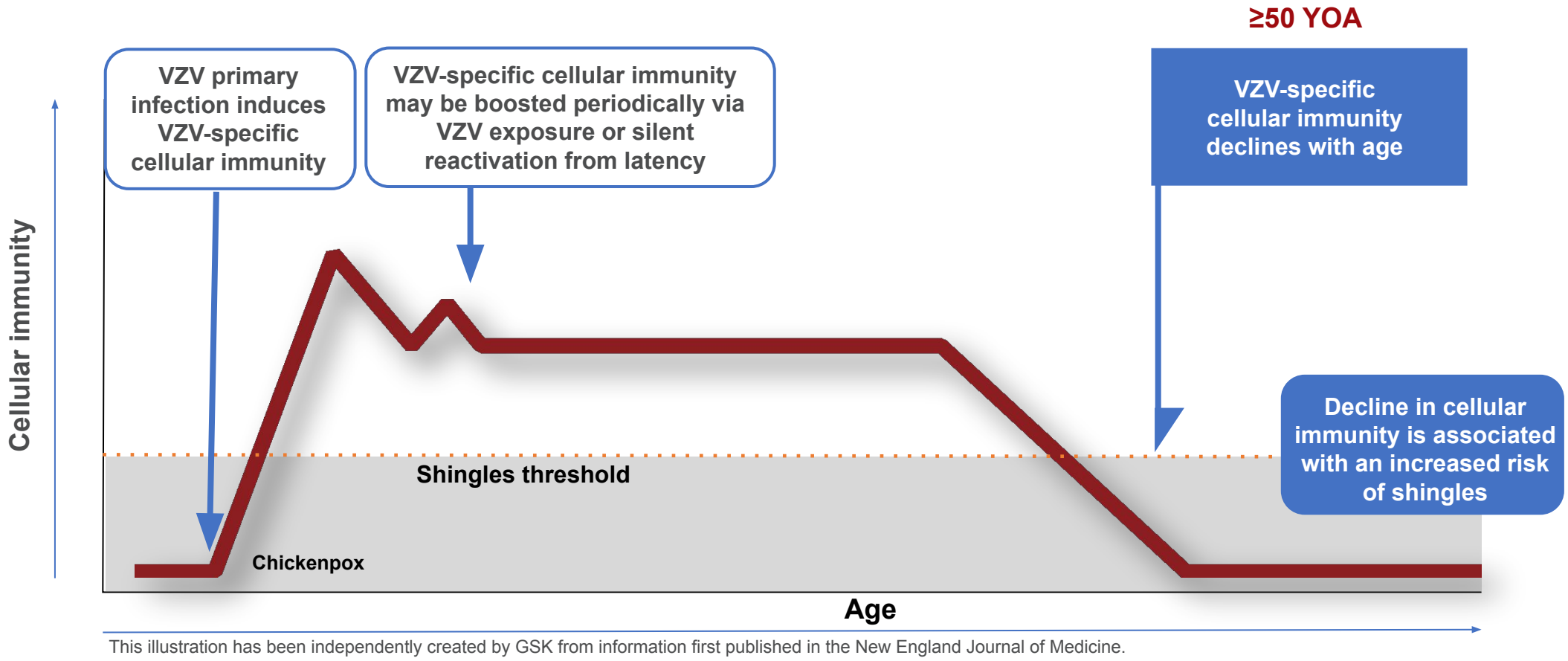
Varicella → **Control of primary infection** → **Latency** → **Reduced immune control, virus reactivation** → **Zoster**

- Up to **1 in 3 people** will develop shingles in their lifetime due to VZV reactivation[1]

- **In Australia**, there are about 560 cases of herpes zoster per 100,000 population per year in all age groups[3]
  - Increasing to 1174 cases per 100,000 in people aged ≥50 years[2]

1. Centers for Disease Control and Prevention. MMWR. 2008 June;57(RR-5):1-30. .. MacIntyre R. et al PLoS One 2015;10(4):e0125025. 4. Zerboni L, et al. Nat Rev Microbiol. 2014 Mar;12 (3):197-210.

Age-related decline in immunity and IMMUNOSUPPRESSION increase shingles risk[1-3,*]



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

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.

The burden of shingles increases as persons age, with steep increases >50 years[1,2]

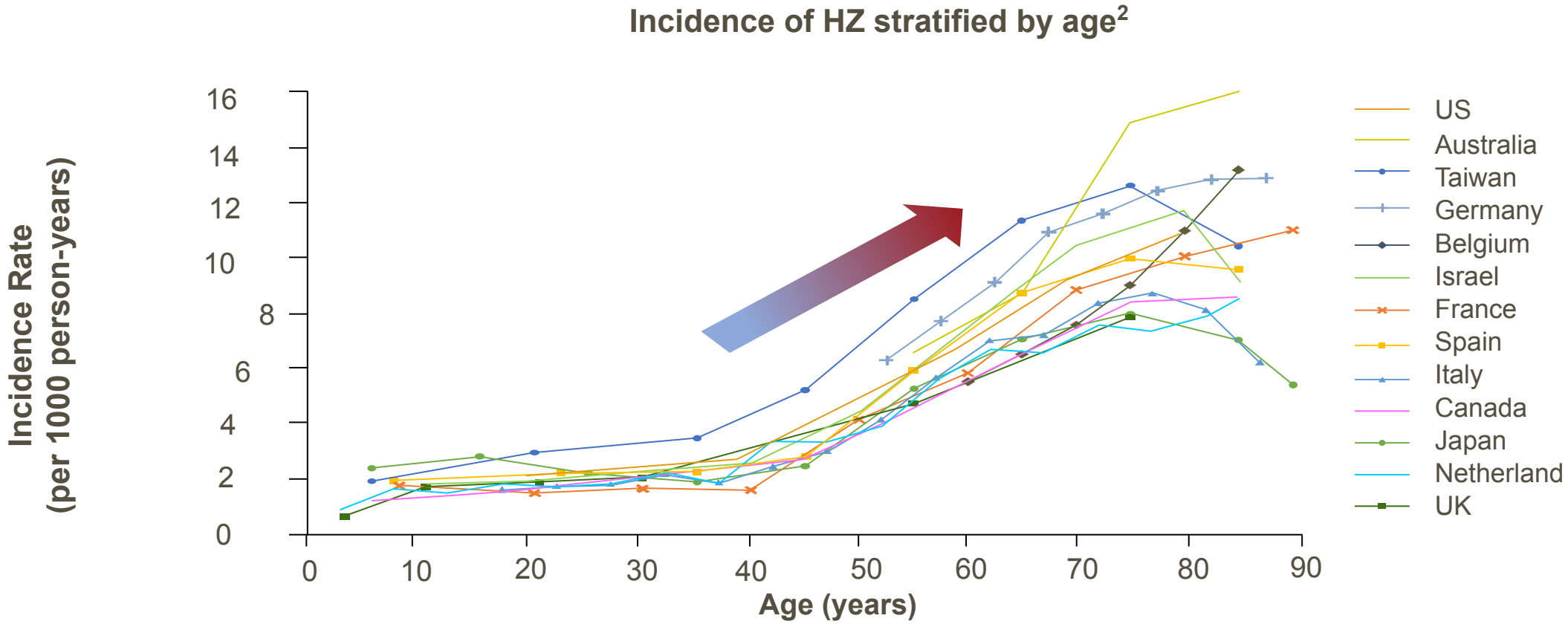
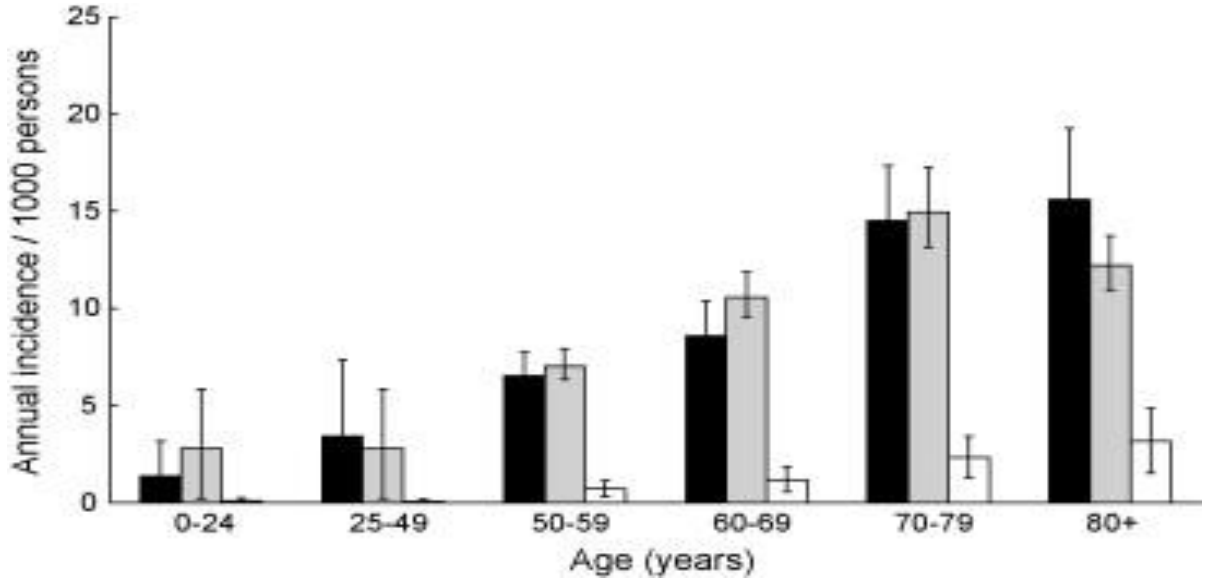
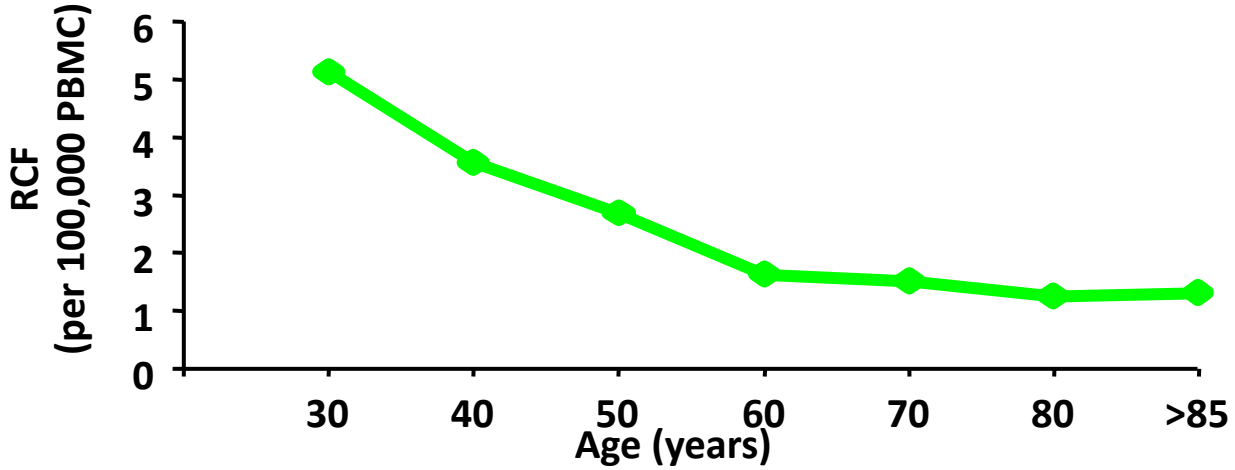


Figure reproduced from Kawai K *et al. BMJ* Open 2014;4:e004833 with permission from BMJ Publishing Group Ltd.

1. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6333a3.htm;. 2. Kawai K, et al. BMP Open 2014;4:e004833

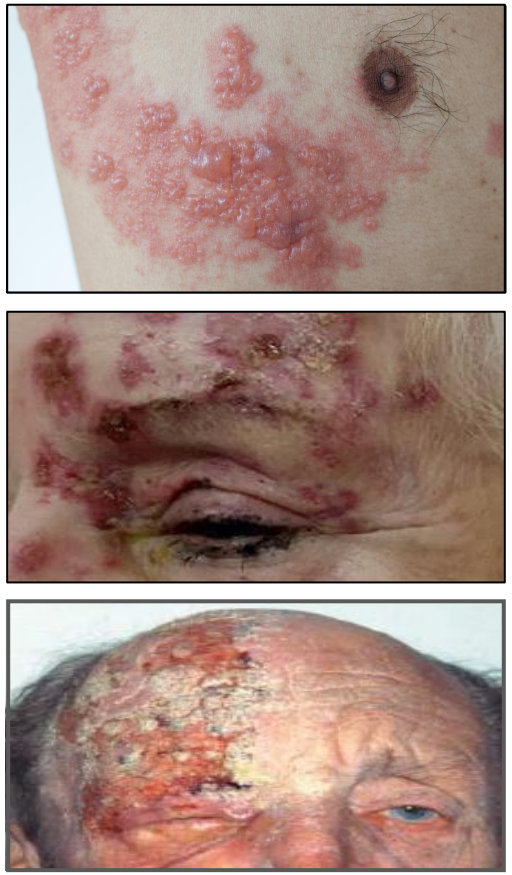
Herpes zoster and PHN increase with age in Australia





Stein A et al Vaccine 2009

Shingles can be a painful disease and can have serious and long-lasting complications[1,2]



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]

Complications

- Other symptoms of shingles can include: headache, photophobia, malaise and fever[1]

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

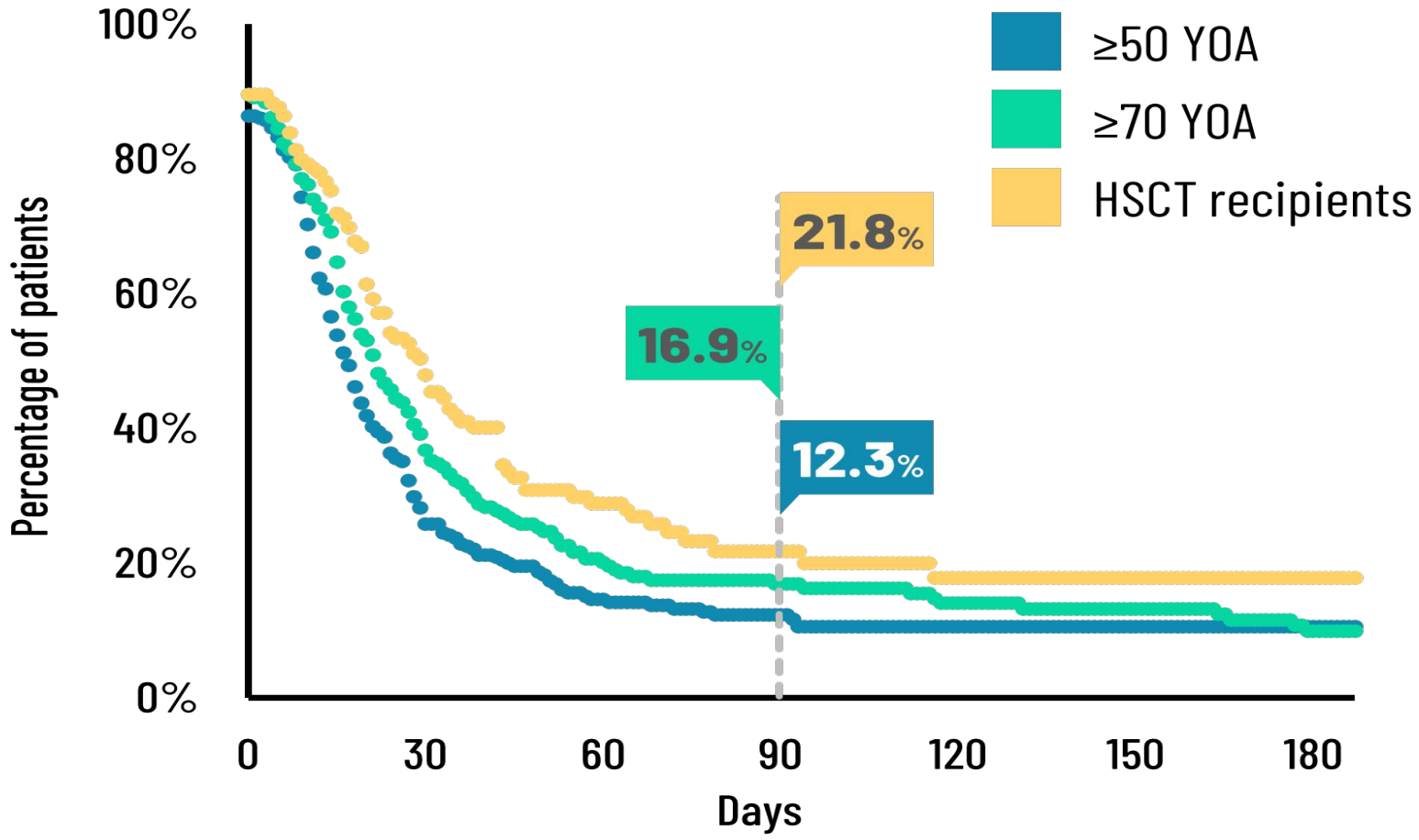
HZ symptoms and complications may be more frequent and of longer duration in immunocompromised patients[5,]

Other complications

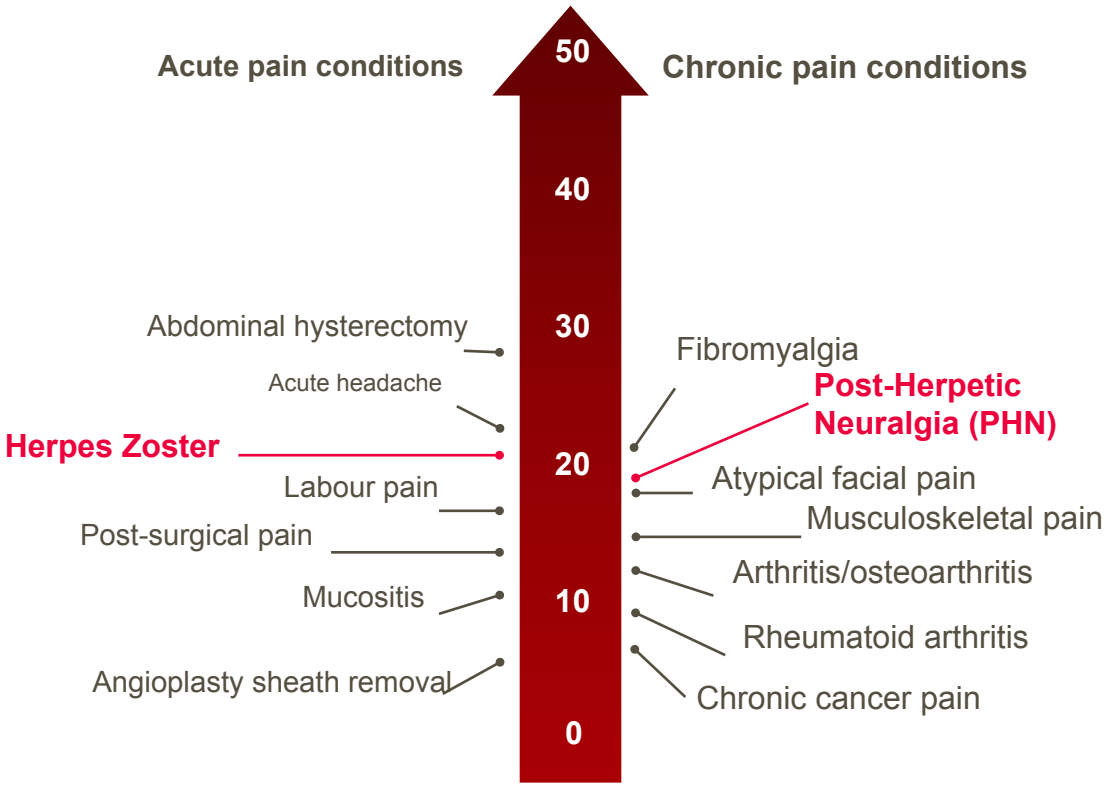
- Disseminated disease (1.3%)[4]

1. Centers for Disease Control and Prevention. MMWR 2008 Jan 4;57(RR-5):1-30. 2. Kawai K, et al. BMJ Open. 2014 Jun;4(6):e004833.
3. Erskine, N; PLoS One; 2017; 12:1-18; Kovac M Vaccine 2018. 4. McKay SL, et al. Clin Infect Dis. 2019 Nov;ciz1090. 5. Kennedy PGE, et al. Viruses. 2018;10(11):609.

Does incidence and duration of HZ pain differ between immunocompetent and severely immune compromised subjects (HSCT recipients)?



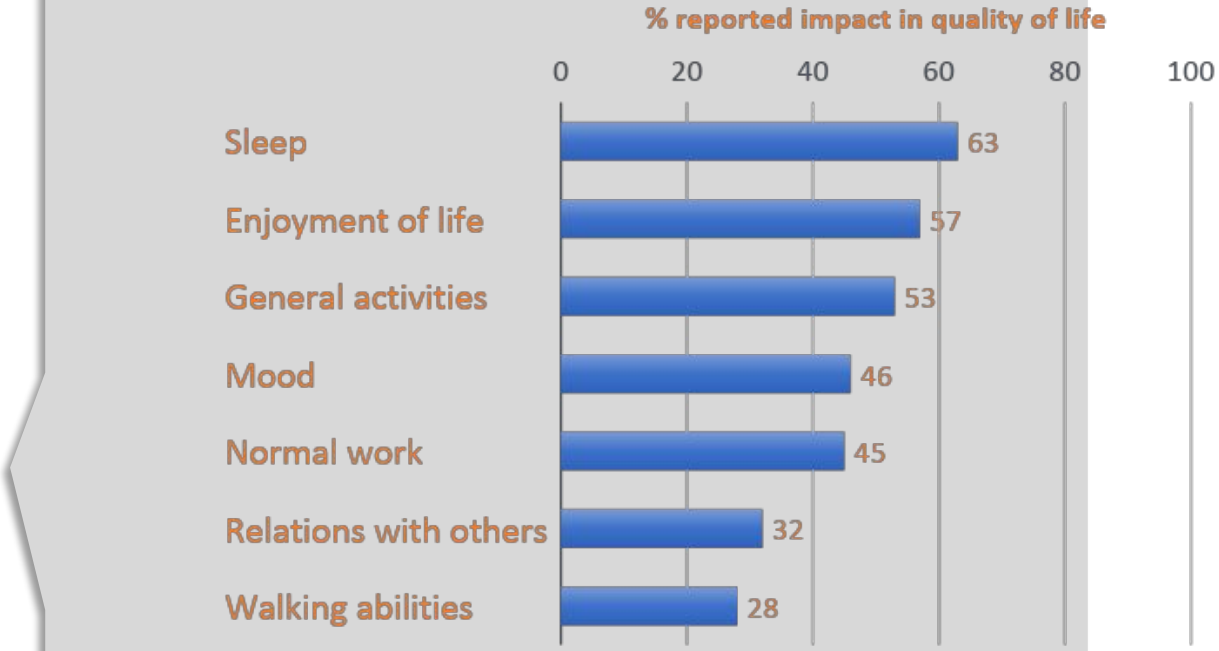
Shingles can cause a burning, stabbing, deep aching pain[1]



Comparison of total pain rating index scores using the short-form McGill Pain Questionnaire for acute and chronic pain conditions[2*]

Figure modified from Katz J et al.[2] with permission from Elsevier

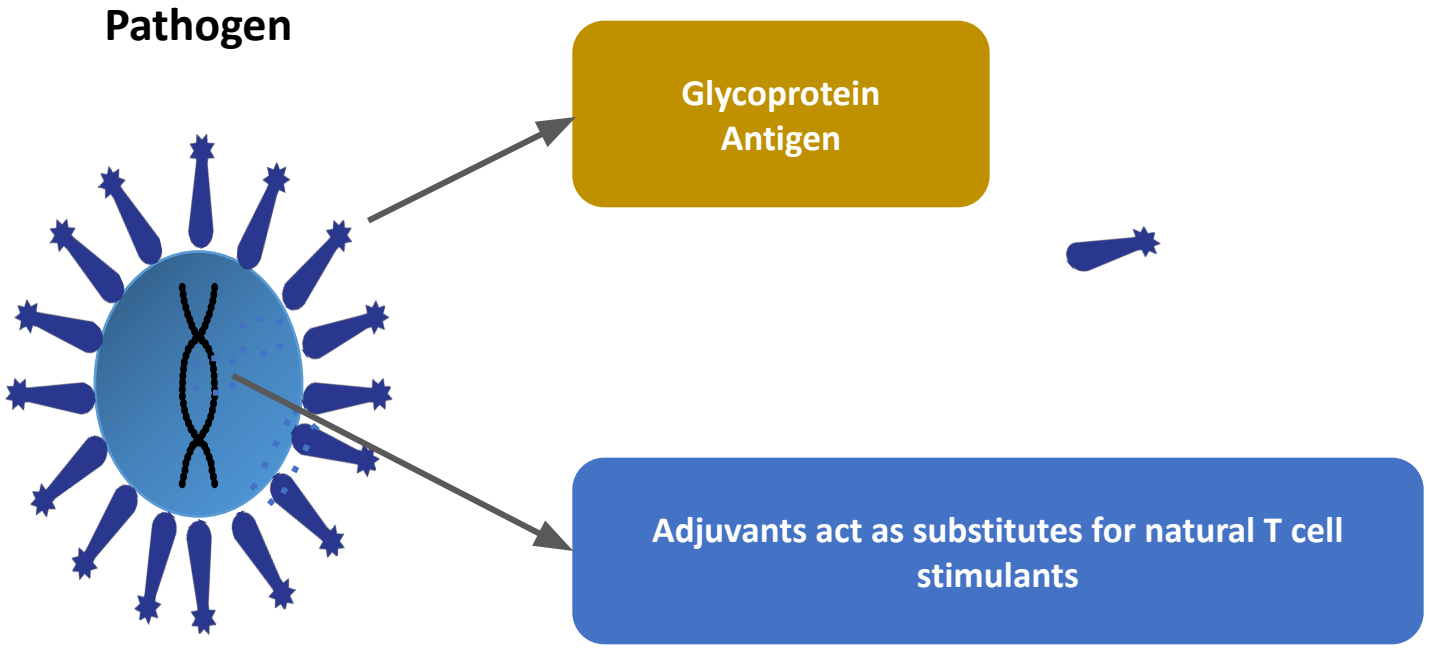
MORE THAN JUST A RASH, CAN BE DEBILITATING TO DAILY LIFE[3,4]



Impact of HZ on activities of daily living from 261 newly diagnosed patients: rated by interference of pain ≥5 (out of 10)

1. Johnson RW, et al. BMC Med. 2010 Jun;8:37. 2. Katz J, et al. Surg Clin North Am. 1999;79(2):231-252.
3. Curran D, et al. BMC Infect Dis. 2018 Aug 4. Watson CP, et al. Adis (Spring Nature), 2017. P 127.

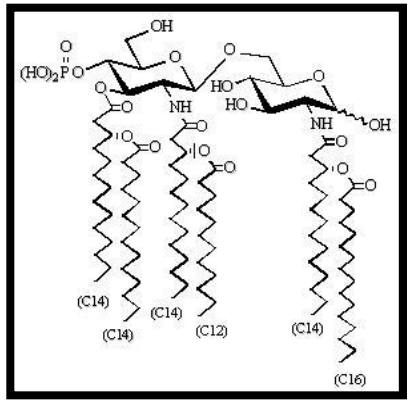
Recombinant Zoster Vaccine, Shingrix



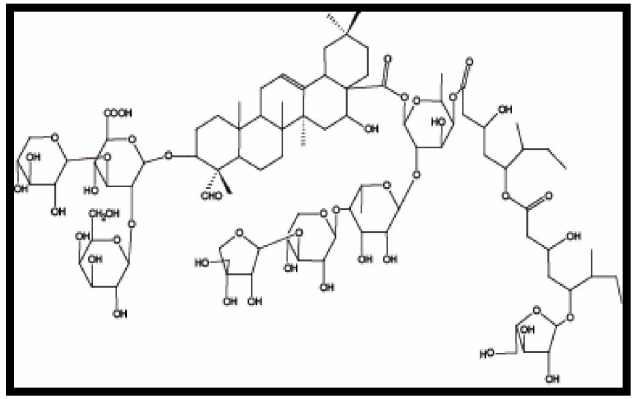
- Viral proteins alone may be insufficiently immunogenic
- Adjuvants act as substitutes for viral immune stimulants enhancing and directing the immune response

Adjuvant System AS01

- Combination of Adjuvants:

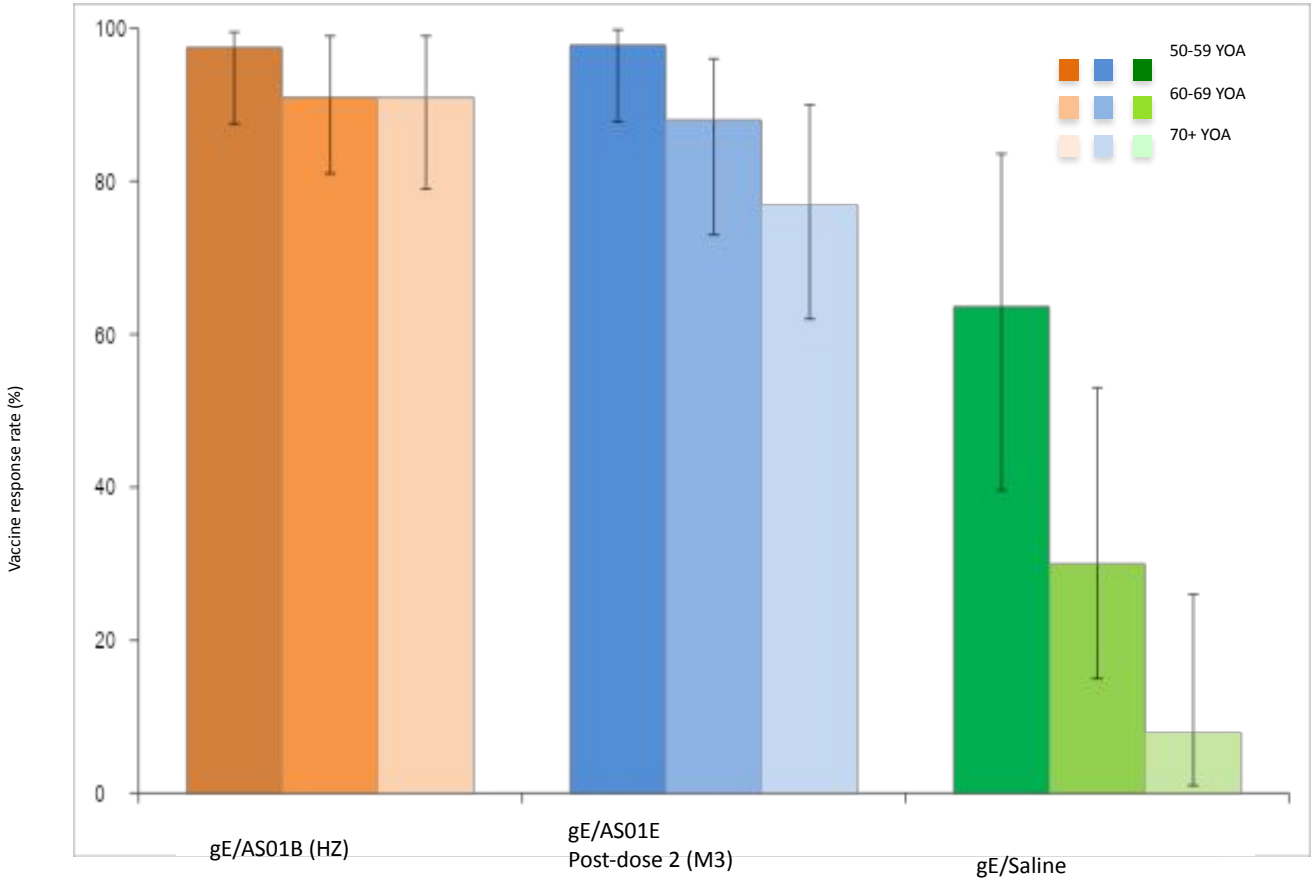


MPL: TLR4 agonist; from bacterial cell wall



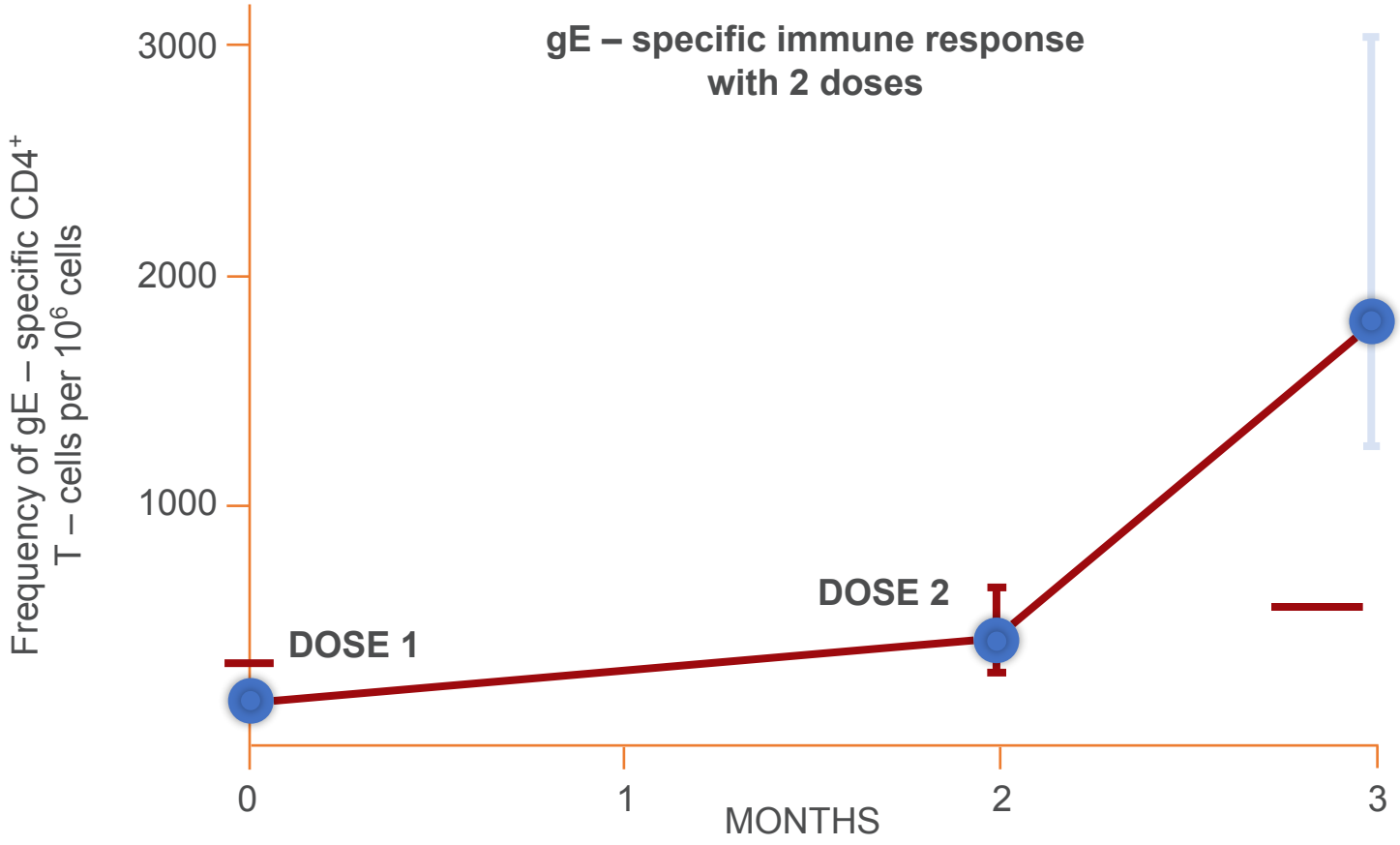
QS21: saponin; from tree bark

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



Chlibek et al J Infect Dis 2013

2 Doses of RZV are needed to enhance the cellular immune response



2 doses of SHINGRIX generated a >4-fold increase in cellular response compared to 1 dose

1. Chlibek R et al. Vaccine. 2014 Mar 26;32(15):1745-53; 2. Chlibek R et al. Vaccine. 2014 Mar 26;32(15 Suppl):1745-53

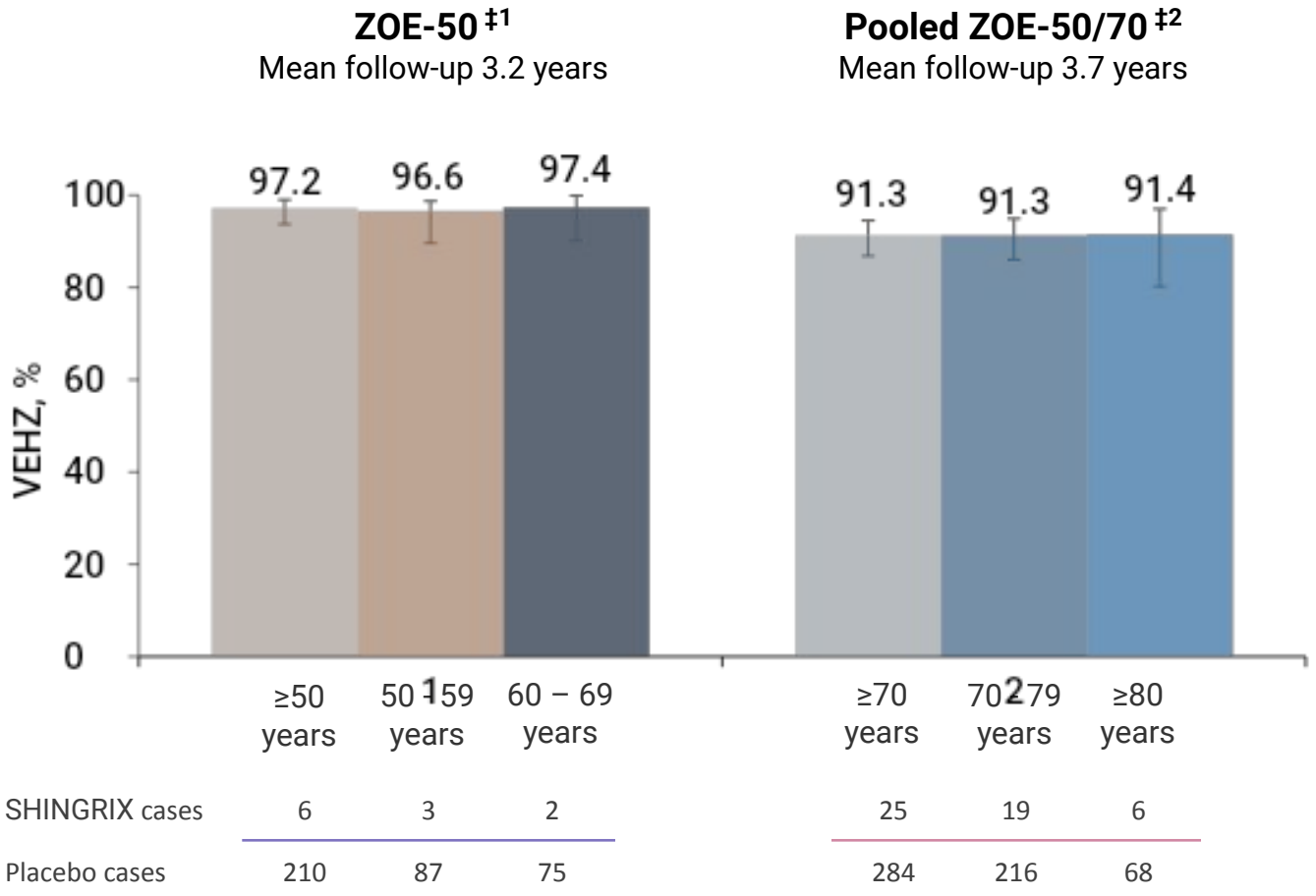
The two pivotal phase III clinical trials of RZV efficacy and reactogenicity

Study Design and Objectives	ZOE-50[1,2] (Zoster-006)	ZOE-70[3] (Zoster-022)
Experimental design	Randomised, observer-blind, placebo-controlled, multi centre, multinational (North America, Europe, Latin America, Asia-Pacific)	
Primary objective	HZ efficacy in persons ≥50 YOA	HZ efficacy in persons ≥70 YOA
Dosing schedule	Vaccine or placebo administered (0.5 mL) intramuscularly at 0 and 2 months	
Primary objectives in pooled analysis	PHN efficacy in persons ≥70 YOA HZ efficacy in persons ≥70 YOA	
Actual enrolment	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.

1. Lal H, et al. N Engl J Med. 2015 May;372(22):2087-96. **2.** Cunningham AL, et al. N Engl J Med. 2016 Sep;375(11):1019

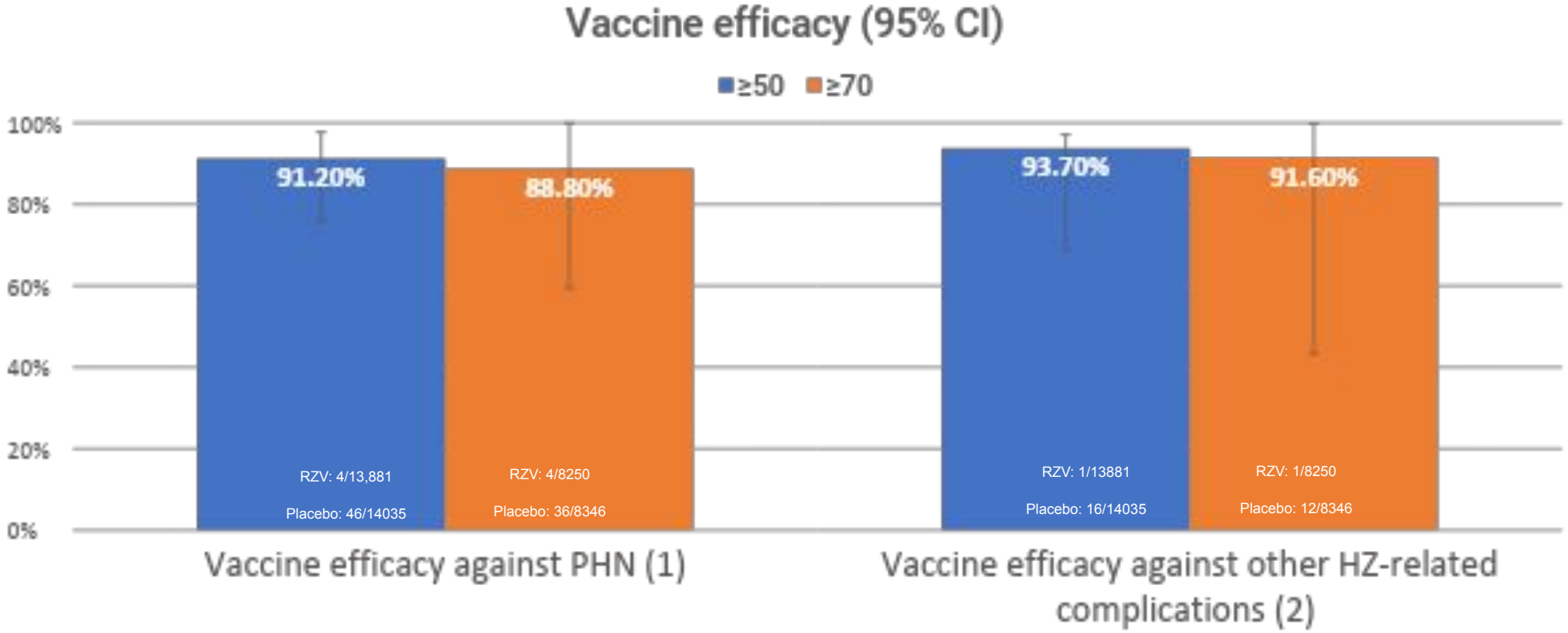
RZV delivered >90 % efficacy against herpes zoster in patients ≥50 years of age[1,2]



P<0.001 for all age groups vs. placebo

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

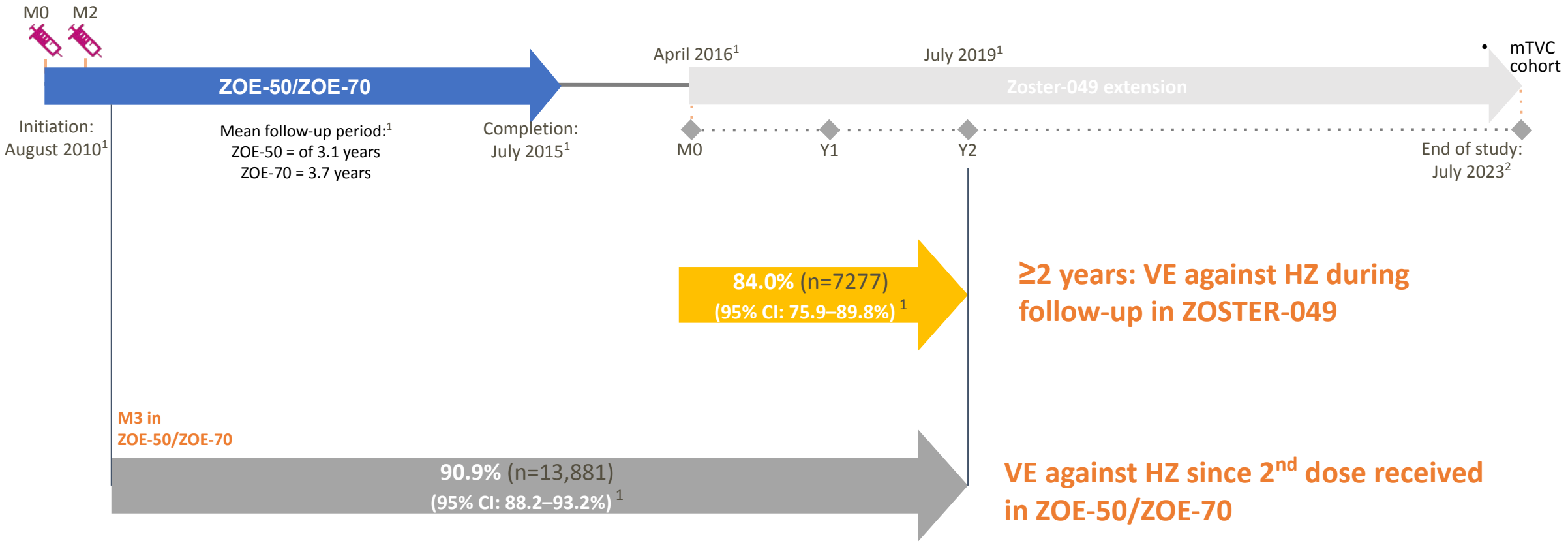
By preventing shingles, SHINGRIX significantly reduced risk of PHN and other complications[1,2]



disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke, HZ vasculitis

Pooled data from ZOE-50 (subjects ≥50 years old) and ZOE-70 (subjects ≥70 years old). 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 2. Kovac et al. 2018

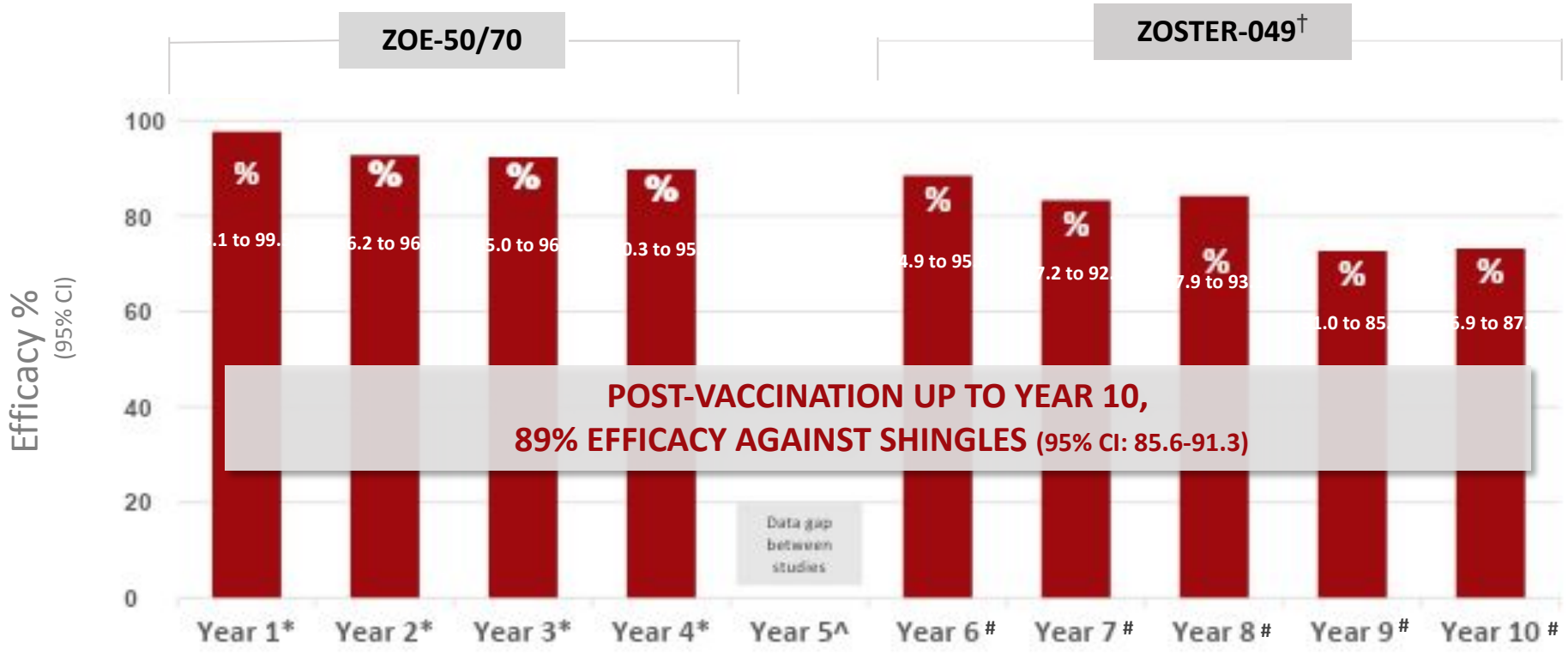
Long-term follow-up of RZV efficacy against HZ: sustained >7 years[1]



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 Cunningham AL. Clinical Infectious Diseases;2021;1-30

SHINGRIX: Shingles Protection that Lasts for Up to Year 10 and Continues to be Monitored[1]



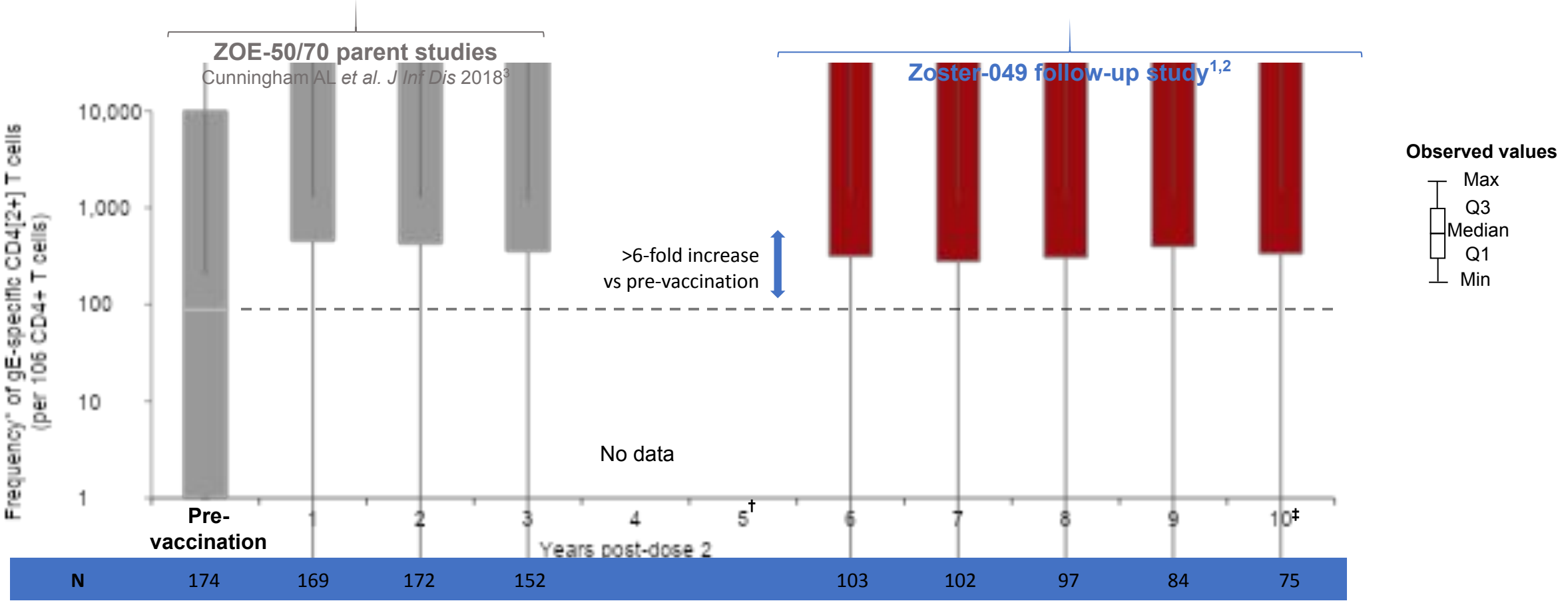
	OVERALL										
SHINGRIX n/ (N)	59 (13,881)	3 (13,881)	10 (13,569)	9 (13,185)	10 (12,757)	No data	7 (7277)	10 (7100)	9 (6878)	15 (6648)	11 (6258)
PLACEBO n/ (N)	651 (13,881)	130 (14,035)	136 (13,564)	116 (13,074)	95 (12,517)	No data	61 (7277)	60 (7097)	57 (6878)	55 (6648)	41 (6258)

^ No data are available for Year 5 b-50/70 studies.[2] because that period corresponds to the gap between ZOE-50/70 and the current follow-up study.[†]At the data lock point for the second interim analysis in the current follow-up study, data collection for year 10 was still incomplete.

1.Strezova A, et al. Open Forum Infectious Diseases, 2022 2. Boutry C, et al. Clin Infect Dis. 2022;74(8):1459-1467

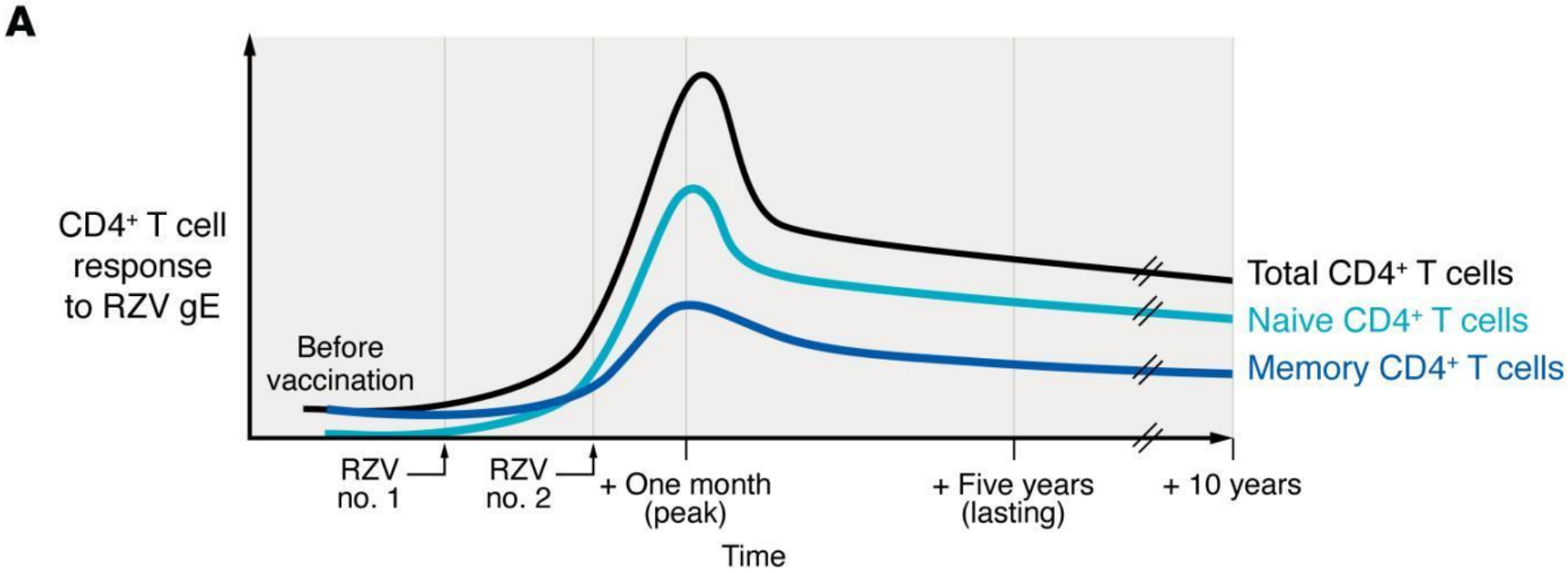
Long-term persistence of cell-mediated immune responses

The frequency of gE-specific CD4[2+] T cells remained above baseline from Year 6 to Year 10 after vaccination[1,2]



1. Boutry C, et al. Clin Infect Dis. 2022;74(8):1459-1467 2. Strezova A. et al.. 3. Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32

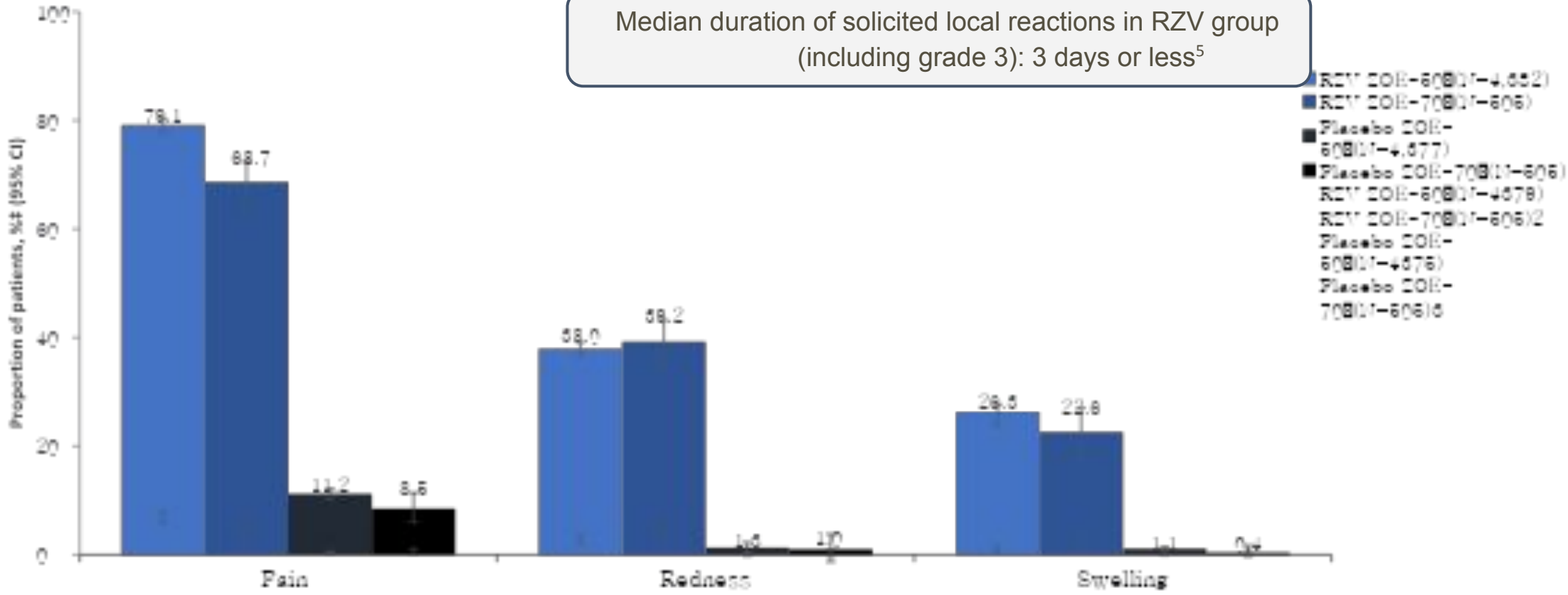
RZV stimulates naïve VZV gE specific CD4 T cells



Cunningham AL, Sandgren K, Truong N, Commentary on Laing K et al J Clin Invest 2023

Solicited local adverse reactions reported up to 7 days post-vaccination

Median duration of solicited local reactions in RZV group (including grade 3): 3 days or less[5]

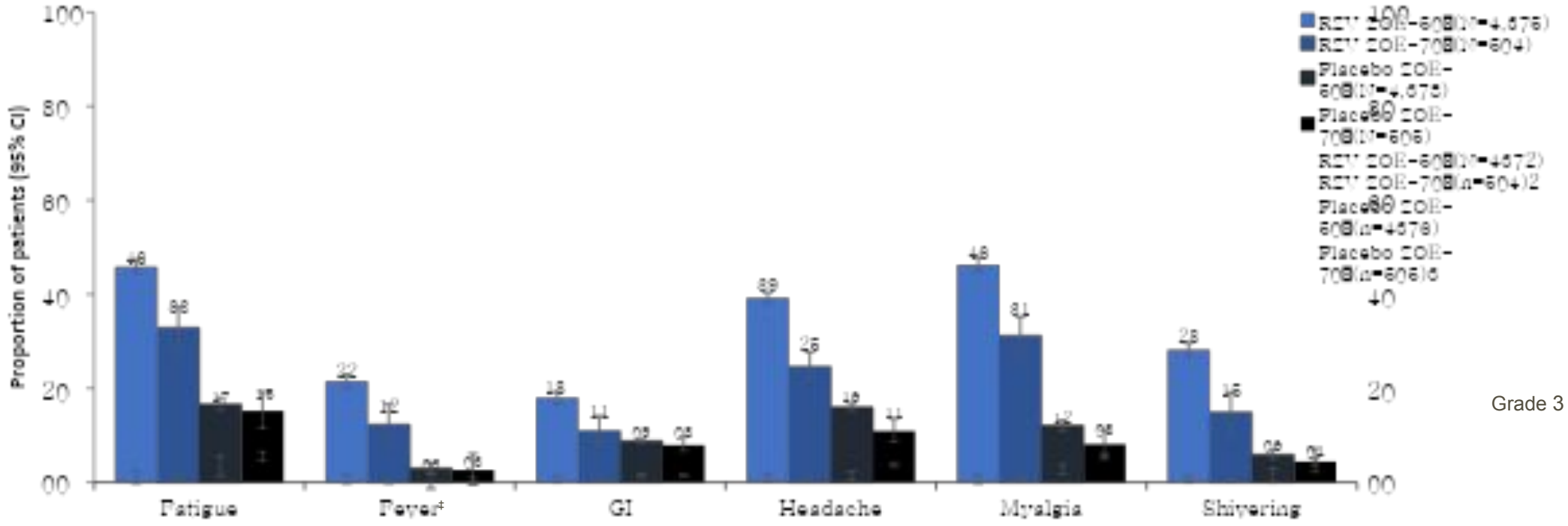


Grade 3

.Lal H, Cunningham et al. N Engl J Med 2015;372:2087–96; Cunningham AL, et al. N Engl J Med 2016

Solicited systemic adverse reactions reported post-vaccination

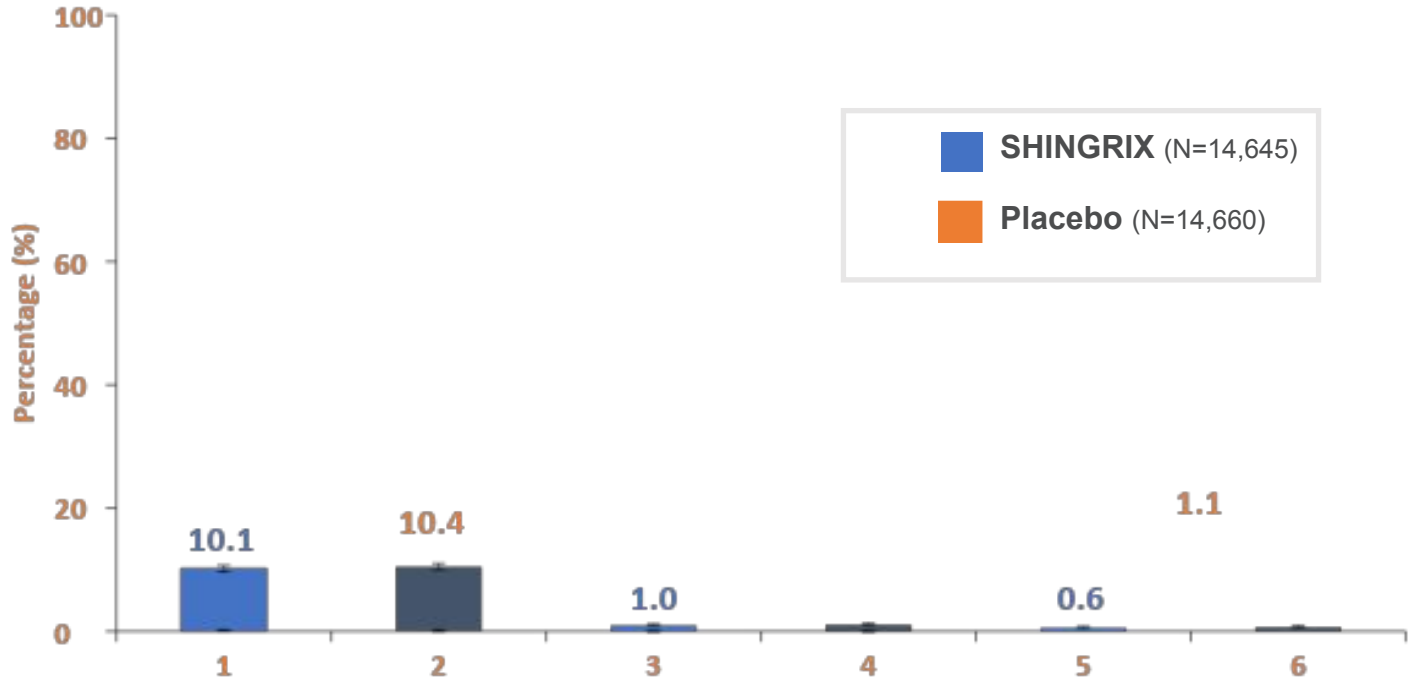
Median duration of solicited systemic reactions in SHINGRIX group (including grade 3): 2 days or less



Grade 3

Lal H, et al. N Engl J Med 2015;372:2087–96; Cunningham AL, et al. N Engl J Med 2016
.

Safety profile in RZV recipients >50 YOA



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

Lopez-Fauqued M, et al. Vaccine 37 (2019) 2482–2493

Poo:Lopez-Fauqued M, et al. Vaccine 37 (2019) 2482–2493.

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 reactogenicity after first dose had grade 3 after second dose
- Less reactogenicity with advancing age
- HZ or Zostavax in previous 5 years did not influence safety or reactogenicity

Colindres et al Hum Vacc Immunother 2020

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 164: 741, 2023; Callegero A J Infect Dis 2021

RZV as a booster following Zostavax or Herpes zoster?

- Important where high ZV coverage:
  - RZV administered 5 years after ZVL:
  - equally immunogenic and safe,
  - recommendation: 1 year post ZVL

- RZV after natural herpes zoster (physician documented):
  - safe but high reactogenicity as for ZOE 50/70
  - antibody to vaccine in patients >50: 90.2%
  - recommendation: > 1 year post HZ

Godeaux O et al Hum Vacc Immuno 2017

RZV can be co-administered with the following vaccines

- ✔ **Influenza** (unadjuvanted inactivated seasonal)[1,2]
- ✔ **Pneumococcal** (PPV23)[1,3]
- ✔ **COVID-19 RNA vaccines**
- ✔ **Diphtheria-Tetanus-Pertussis** (DTaP)[1,4]

Co-administration generally well tolerated [1-3]

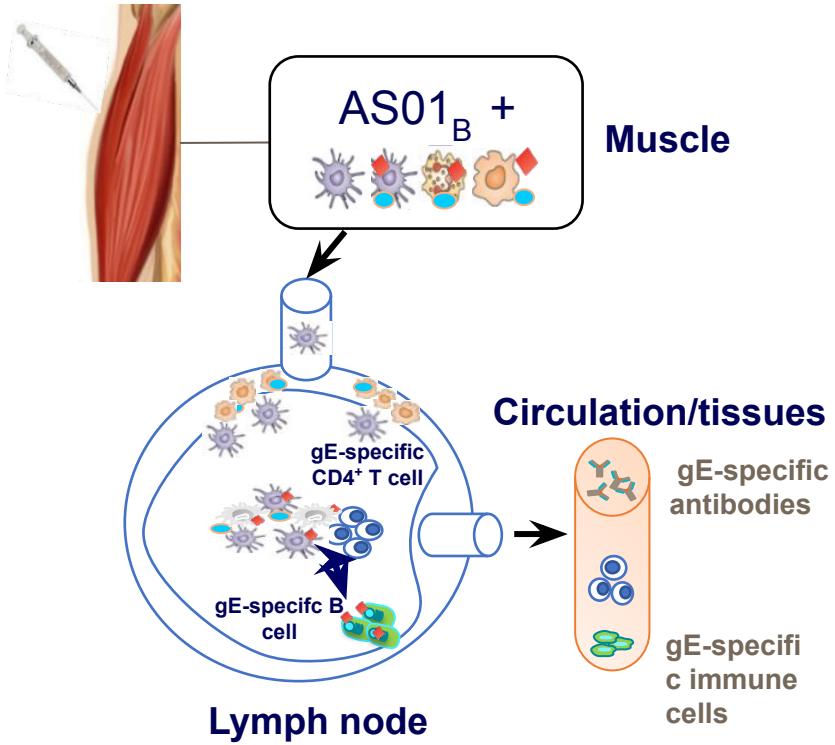
No safety issues [1-3]

No immunologic interference observed [1-3]

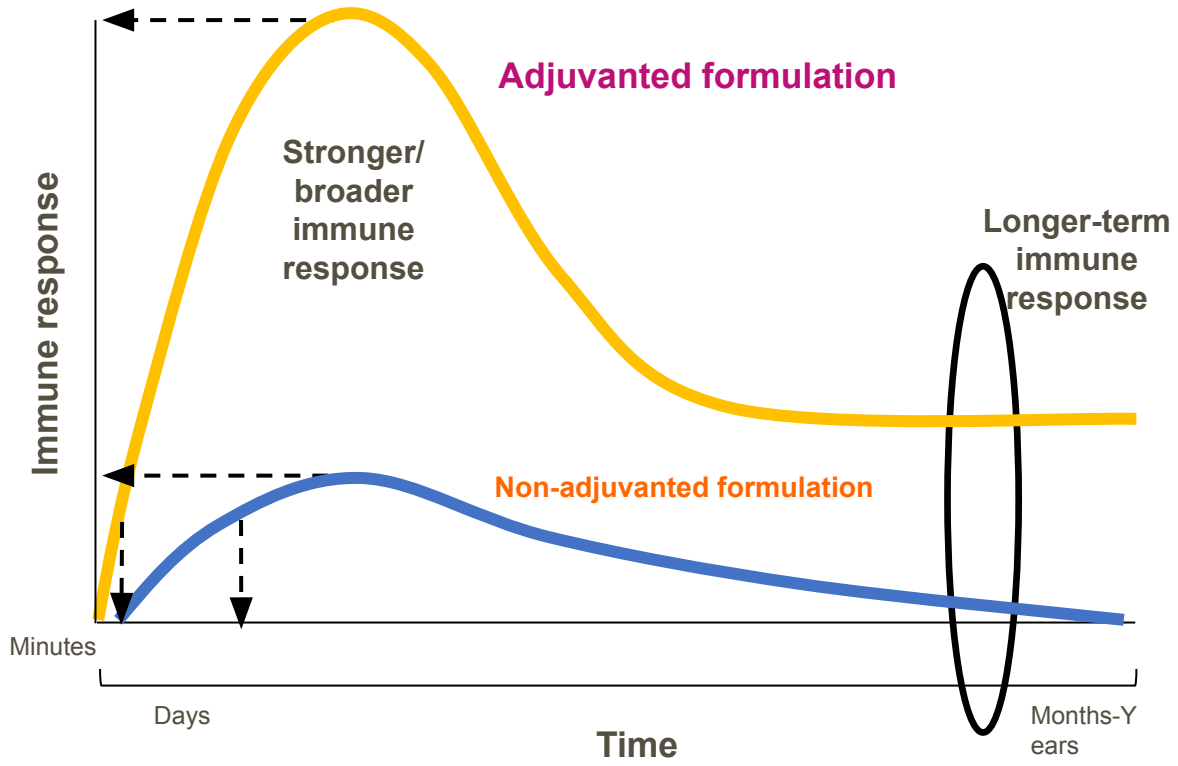
References: 1. Schwarz TF, et al. J infect Dis. 2017;216(1):1352–1361; **2.** Marechal C, et al. Vaccine. 2018;38(29):4278–86. **3.** Strezova A, et al. Vaccine. 2019;37(39):5877–85.

Adjuvant system $AS01_B$ enhances immune responses to gE

AS01 induces a rapid and transient activation of the innate immune response[1]



The early and transient response is followed by a high and durable VZV-specific response[,3]



1. Didierlaurent AM, *et al. Expert Rev Vaccines* 2017;15:55–63;; 3. Burny W et al. Vaccine. 2019 Mar 28;37(14):2004-2015; 4. Zubeldia JM, et al. J Investig Allergol Clin Immunol 2019; 29:103-111, Cunningham AL Brit Med J 2021.

Immunisation for Herpes zoster in the immune compromised

- **Three grades of immune-compromise:**
  - Mild, moderate and severe

- Risk of Herpes zoster only markedly increased in the severe group (and JAK inhibitors)

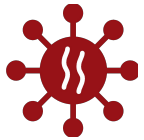
- Live attenuated HZ vaccine (Zostavax) contraindicated in severe and moderate groups.

Risk of Herpes zoster in severely immune compromised subjects

Condition	Incidence of HZ (per 1000 person years)
Haemopoietic stem cell transplant	43-94
Haematologic malignancy	31 (esp myeloma)
Solid organ transplant	17-32
Solid organ malignancy + chemotherapy	14
HIV (CD4<200)	6 (32)
General population	4.8

RZV/ SHINGRIX has been trialled in 5 severely immune-compromised populations[1-5]

Adults ≥18 years of age

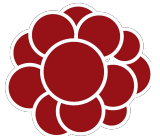


HUMAN IMMUNODEFICIENCY VIRUS[1]
Living with HIV

AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANT[2]
Post transplant

HAEMATOLOGIC MALIGNANCIES[3]
Receiving immunosuppressive chemotherapy*

RENAL TRANSPLANTS[4]
Post-renal transplant



SOLID TUMOUR[5]
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 1year post-vaccination.[1-5]

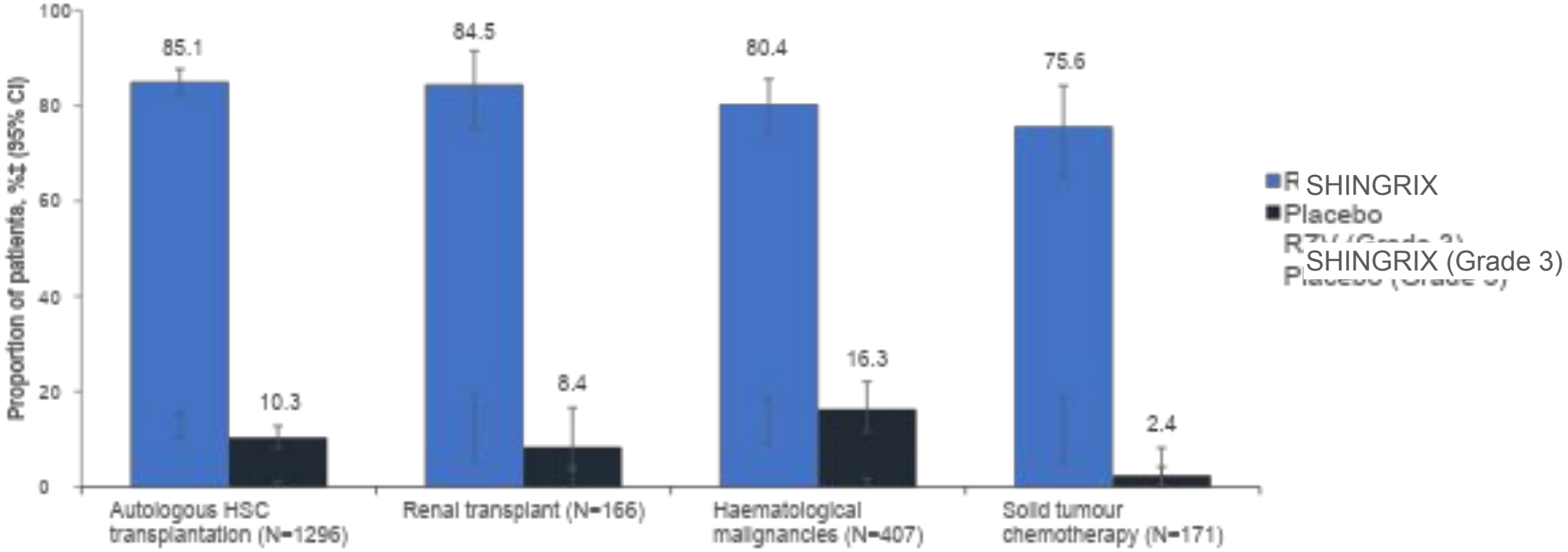
References: 1. Berkowitz EM, et al. J Infect Dis. 2015 Apr;211(8):1279-87. **2.** Bastidas A, et al. Open Forum Infect Dis. 2019 Oct;6(Suppl 2):S84-S85. **3.** Dagnew AF, Lancet Infect Dis. 2019 Jan;19(9):988-1000. **4.** Vink P, et al. Clin Infect Dis. 2020 Jan;70(2):181-190. **5.** Vink P, et al. Cancer.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

Immunogenicity and Efficacy of Recombinant Zoster Vaccine in Immunocompromised Patients

Condition or patient group	Vaccine response (gE antibody)	Vaccine response (CD4+ T-cell count)	Vaccine efficacy against HZ	Vaccine efficacy against PHN
Patients with haematological malignancy	60%	84%	87%	NA
Patients receiving autologous HSCT	71%	89%	68%	89%
Patients with solid tumours receiving chemotherapy	92%	46%	NA	NA
Patient receiving solid organ transplantation	74%	64%	68% (renal)	NA
Patients with HIV (two to three doses)	97 to 100%	86 to 90%	NA	NA

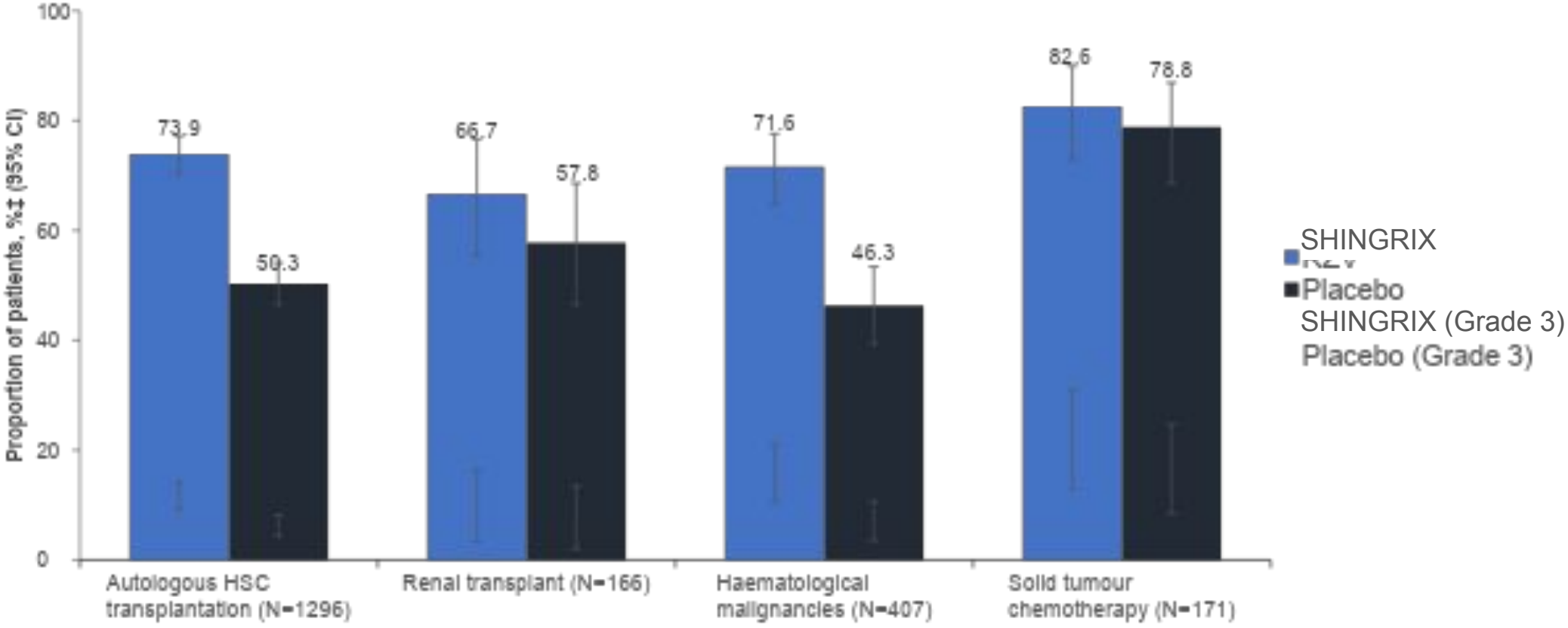
Abbreviations: HSCT = haemopoietic stem cell transplantation; HZ = herpes zoster; PHN = post-herpetic neuralgia

LOCAL reactogenicity to RZV in immune-compromised patients?



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

SYSTEMIC reactogenicity worse in immune-compromised patients?



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

RZV, Shingrix: summary and issues

- Immune-competent:
  - ~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

  - Duration of efficacy: 89% >10 years (longer term trials in progress)
  - High reactogenicity: severe, impairing everyday activity: local, 9%; systemic 11%; but lasts only ~2 days, only one-third are severe with second dose

  - Risk of auto immunity (and gout) with new adjuvants: none seen in trials. Guillain Barre Syndrome: slight (3/M) excess in first 42 days after second dose

- Severely immune-compromised
  - Efficacy where studied, 68-87%, local reactogenicity similar, systemic increased due to underlying disease

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