IMMUNISATION COALITION

2023 WEBINAR

SHINGLES UPDATE

15 NOVEMBER 2023 | 6–7 PM AEDT

Presenter: A/Prof John Litt AM
Moderator: Dr Andrew Minton, PhD

What’s new in vaccination against Zoster?

Associate Professor John Litt AM

Flinders University

Immunisation Scientific Advisory Committee

Conflicts of interest

- John Litt has is or has been a member of a number of Immunisation Advisory Boards on various influenza vaccines for a range of vaccine manufacturers, including: GSK, Seqirus, Astra Zeneca and Sanofi Pasteur.

- He has received financial support for attending immunisation conferences, developing educational programs and materials for immunisation, as well as presenting Immunisation Vaccination updates to a variety of audiences including the Immunisation Coalition, GPs and Practice Nurses

- He was previously a member of ATAGI (2000-2004) and the National Centre for Immunisation Research and Surveillance Scientific Advisory Board (2007-2016) and has been a member of the Immunisation Coalition Scientific Advisory Board since 2007

Overview

- Who is at increased risk of zoster?
- Epidemiology and burden of morbidity
- Introducing a recombinant Zoster vaccine (RZV), Shingrix
  - Guidance
  - Vaccine efficacy and duration
  - Vaccine safety
  - Administration
  - Who should get RZV
- Immunocompromised patients
  - Guidance
  - Increased risk
  - Immunogenicity
  - Vaccine effectiveness
- Coverage
- What can improve zoster vaccine uptake?
- Survey results

Is the incidence of Zoster rising?

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

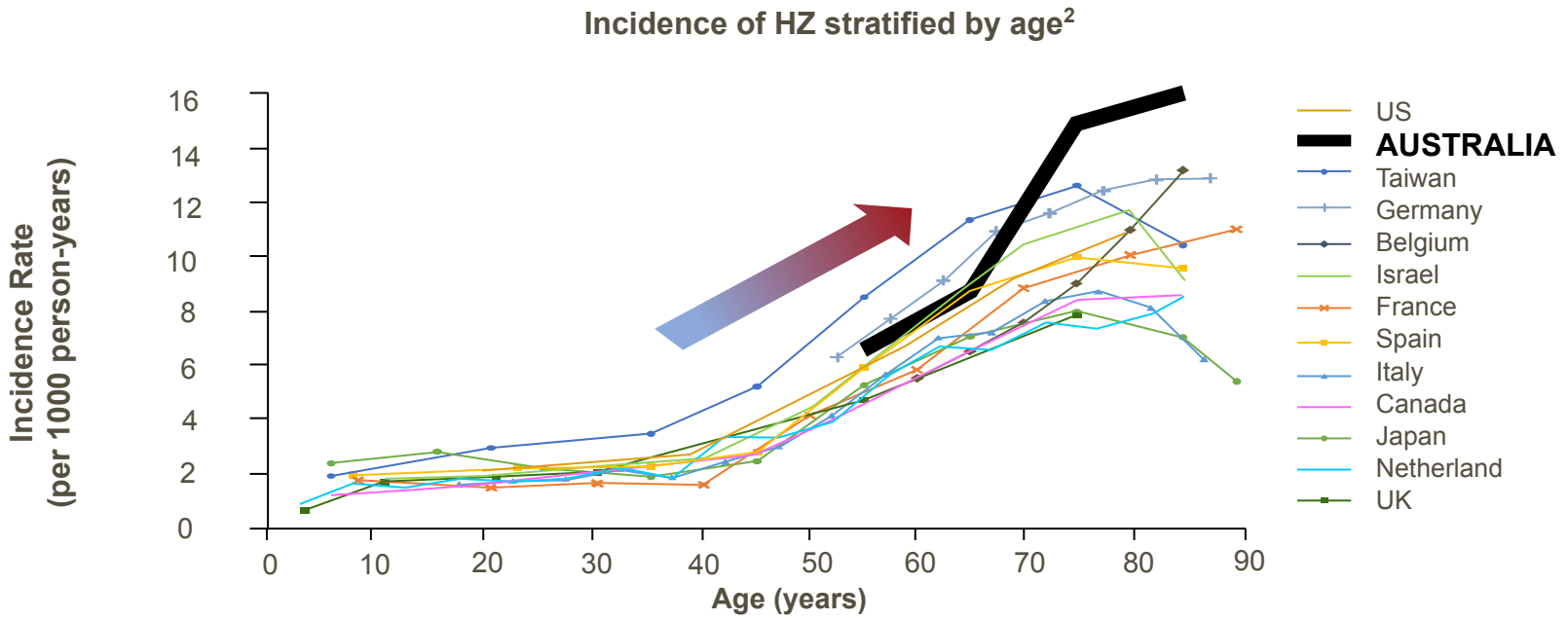


Figure reproduced from Kawai K *et al. BMJ* Open 2014;4:e004833 with permission from BMJ Publishing Group Ltd.

1. Update on Recommendations for Use of Herpes Zoster Vaccine: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6333a3.htm; accessed 11 March 2021. 2. Kawai K, et al. BMP Open 2014;4:e004833

Lifetime risk of Zoster

- Overall lifetime risk of zoster in the population is between 20% and 30%

	Lifetime risk (%) HZ	PHN (%)
• For a 60 year old[1,2]	40	9
• For an 85 year old[3]	50	21

- 120,000 cases of shingles per year in Australia[4]

- Less that 1 in 5 older adults believe they are likely or very likely to get shingles[5]

1. Stein AN et al. Vaccine 2009,24:520-29 . 2. Stein. Personal communication 2016. 3 Gauthier Epidemiol Infect. 2008;9:1–10 .4. MacIntyre R. PLoS ONE 2014; 10(4):e0125025. 5. Litt et al. Aust Zoster Study 2015

Who is at the highest risk of developing Zoster?

Zoster is more common in

- Older adults (>50 yrs)

Other groups (RR and 95% CI)

- Immunocompromise
  - HIV 3.22 (2.40–4.33)
  - Malignancies 2.17 (1.86–2.53)
- Family history 2.48 (1.70–3.60)
- SLE 2.08 (1.56–2.78)
- RA 1.51 (1.31–1.75)
- CVD disorders 1.34 (1.17–1.54)
- Diabetes 1.24 (1.14–1.35)
- Asthma 1.24 (1.16–1.31)

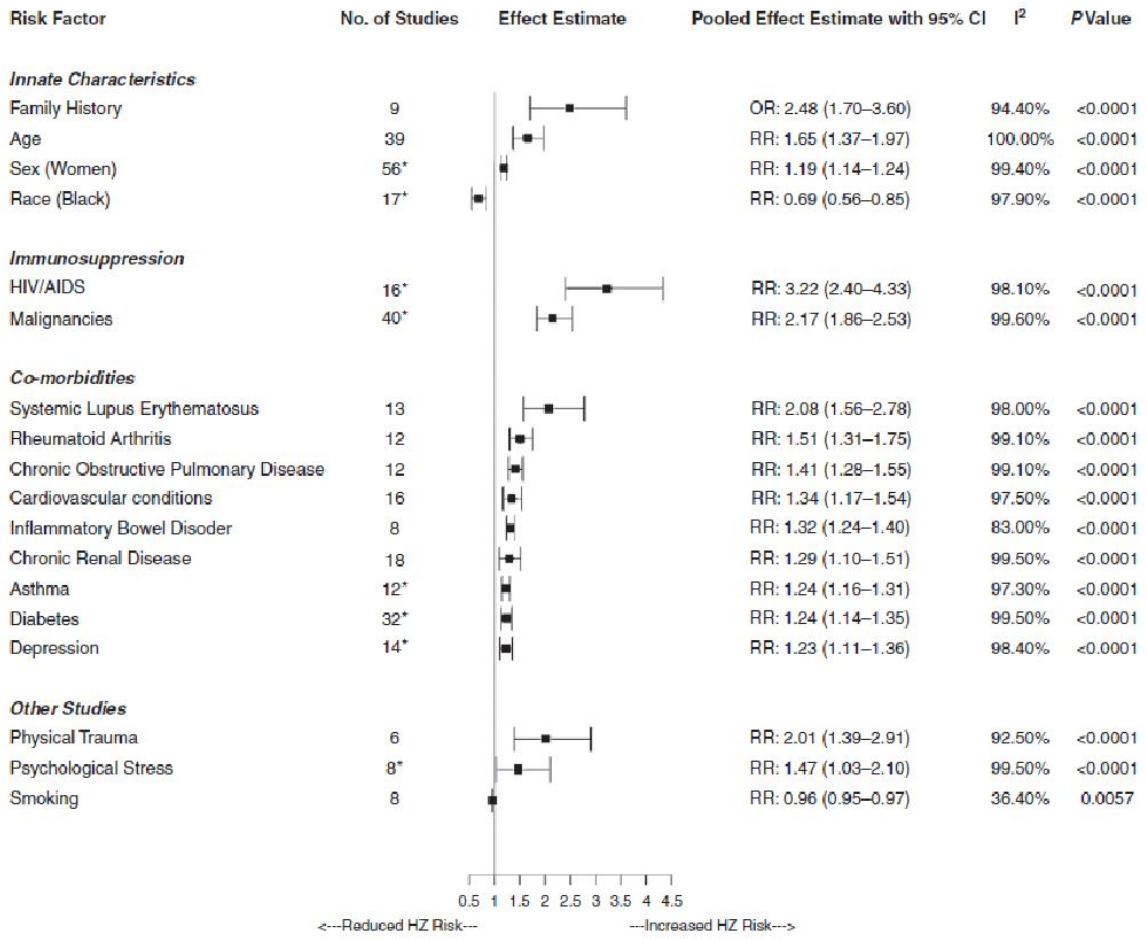
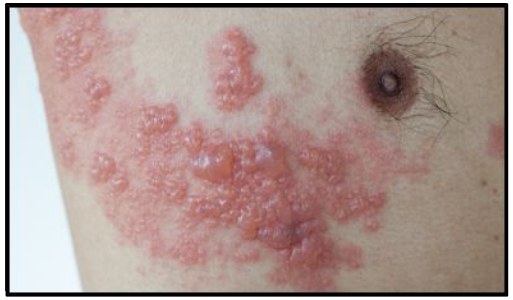
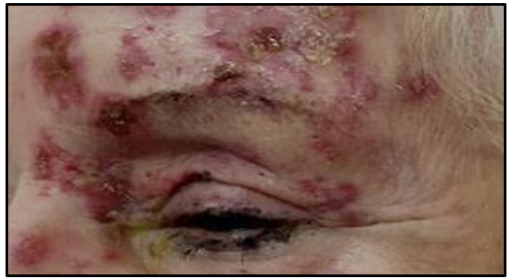


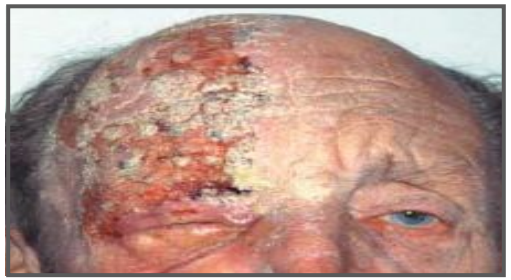
Figure 2. Pooled analysis of the risk of herpes zoster.

Marra Open Forum Infect Dis. 2020 Jan 9;7(1):ofaa005. doi: 10.1093

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

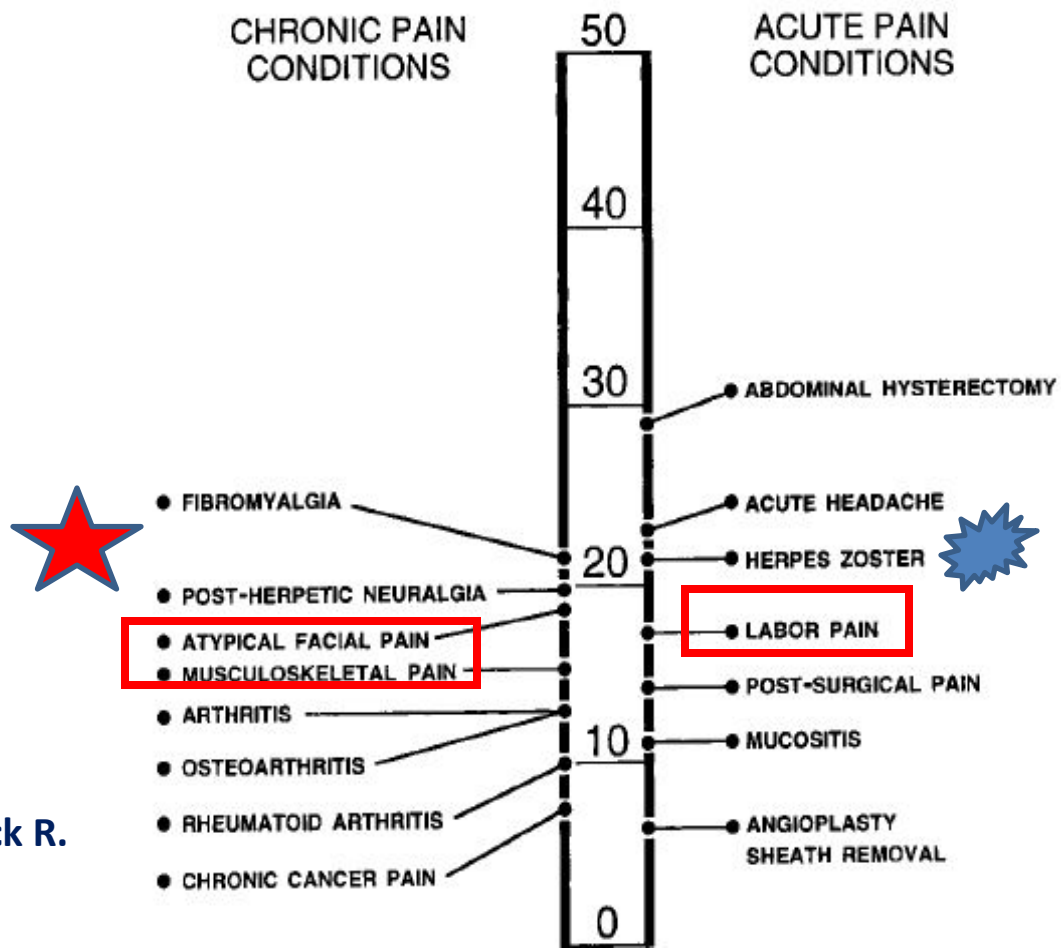
HZ symptoms and complications may be more frequent and of longer duration in immunocompromised patients[5,6]

Other complications

- Disseminated disease[3]

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. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2018, immunisationhandbook.health.gov.au 4. Erskine, N; PLoS One; 2017; 12:1-18 5. McKay SL, et al. Clin Infect Dis. 2019 Nov;ciz1090. 6. Kennedy PGE, et al. Viruses. 2018;10(11):609.

Comparison of total pain rating index scores; McGILL Pain Questionnaire



Katz J, Melzack R. Surg Clin NA 1999;79:230

What are the main complications of Zoster?

- Cutaneous
- Neurologic
  - PHN
  - Stroke
  - Other due to the involvement of the nervous system
    - cranial neuropathies,
    - polyneuritis, myelitis,
    - aseptic meningitis, or
    - partial facial paralysis occur
- Ophthalmic
  - epithelial and stromal keratitis.
  - uveitis
  - acute retinal necrosis
- Disseminated (immune compromised)

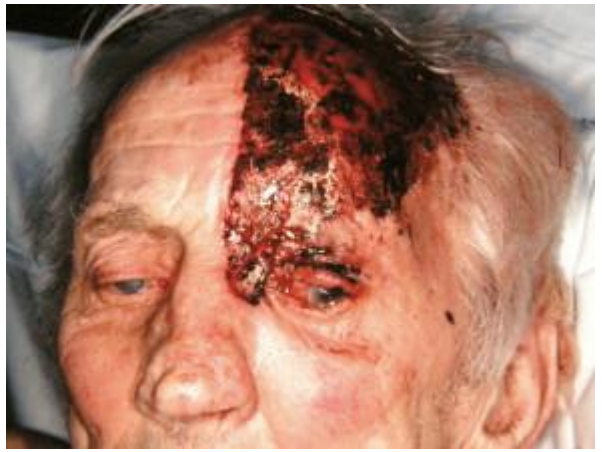
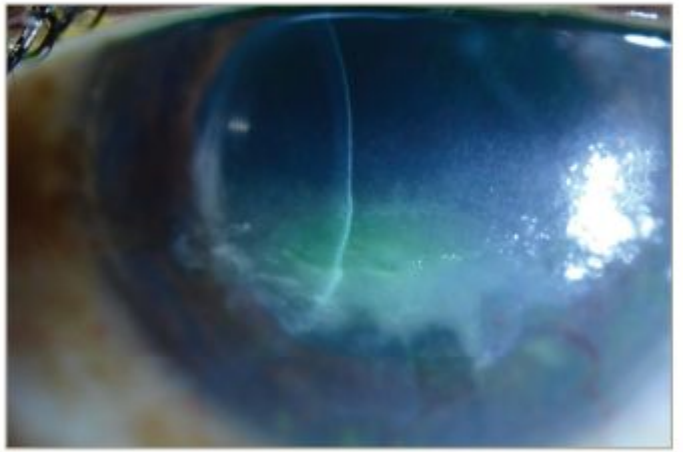


Figure 3: Persistent epithelial defect with early stromal melting in an eye with neurotrophic keratitis secondary to herpes zoster ophthalmicus



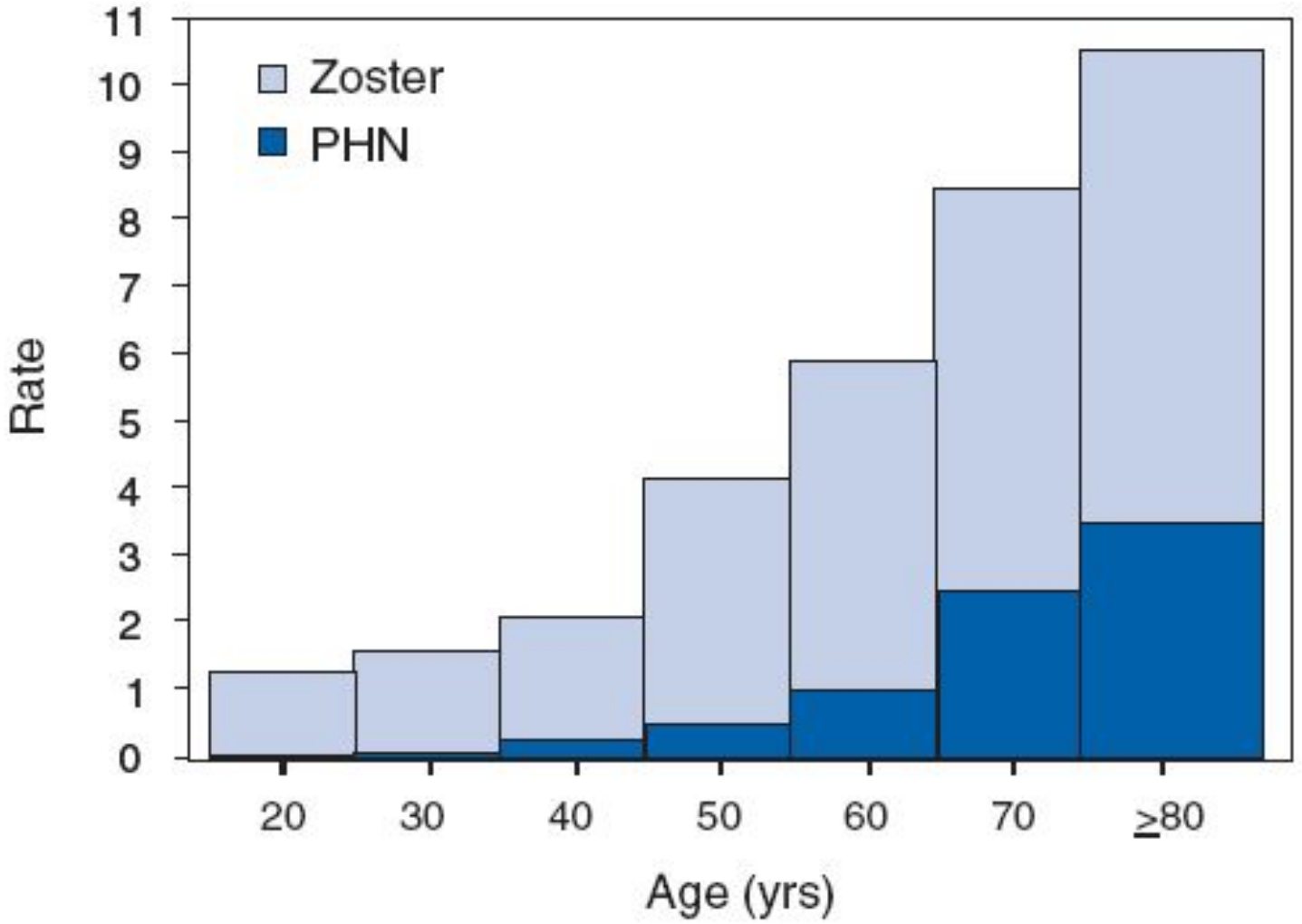
1. Kawai BMJ Open 2014:(6): e004833.
2. Johnson Prim Care 2015: **42**(3): 285-303
3. Yawn J Stroke Cerebrovasc Dis. 2023 Feb;32(2):106891

Risk factors for PNH[1-2]

- Advancing age
- Prodromal pain
- Greater severity of acute pain
- Greater rash severity
- Greater degree of sensory impairment in the affected dermatome
- No clear evidence for gender[3], immune compromise[4], or dermatome affected
- No evidence of higher PHN with depression or cancer[2]

1. Thomas and Hall Lancet Infect Dis. 2004 Jan;4(1):26-33.. 2. Forbes et al. Pain 2015;·157 : 30–54; 3. Zhou Ann Palliat Med. 2021 Dec;10(12):12181–12189 . 4 Yanni BMJ Open. 2018 Jun 7;8(6):e020528

Shingles and Postherpetic Neuralgia† Rates* by Age: United States



*per 1,000 person-years.
† Defined as pain for 30 days or longer

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

Post-herpetic neuralgia (PHN)[1-3]

- Most common and debilitating complication of zoster
- Chronic neuropathic pain in area of rash
  - Burning, throbbing, itching, tender, stabbing, shooting, sharp, tingling
  - May be triggered by even minor stimuli to the affected skin (allodynia) – in >90% of patients with PHN

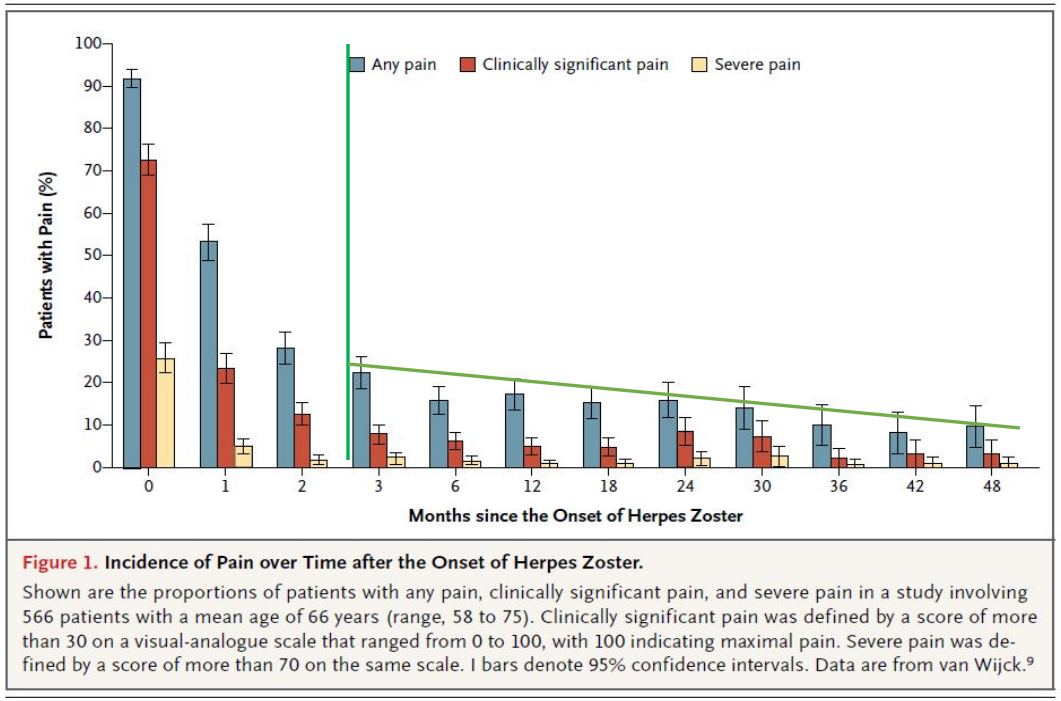


Figure 1. Incidence of Pain over Time after the Onset of Herpes Zoster.
Shown are the proportions of patients with any pain, clinically significant pain, and severe pain in a study involving 566 patients with a mean age of 66 years (range, 58 to 75). Clinically significant pain was defined by a score of more than 30 on a visual-analogue scale that ranged from 0 to 100, with 100 indicating maximal pain. Severe pain was defined by a score of more than 70 on the same scale. I bars denote 95% confidence intervals. Data are from van Wijck.[9]

1. Johnson et al NEJM 2014; 371(16)1526-33
2. Schmader CID 2001; 32(10) :1481-6
3. Chen May Clin Proc 2004: 79 (12):1533

Impact of shingles and PHN on Health

Physical
- Fatigue
- Anorexia
- Weight loss
- Reduced mobility
- Physical inactivity
- Insomnia

Psychological
- Depression
- Anxiety
- Emotional distress
- Difficulty concentrating
- Fear

Social
- Withdrawal
- Isolation
- Attendance at fewer social gatherings
- Loss of independence
- Change in social role

Functional
- Dressing, bathing, eating, mobility
- Travelling, cooking, housework, shopping

1. Johnson, R. The impact of herpes zoster and post- herpetic neuralgia on quality of life. *BMC Medicine*. 2010. 8:37. 2. Katz, J. Acute Pain in Herpes Zoster and Its Impact on Health-Related Quality of Life. *Clinical Infectious Diseases*. 2005. 39:342-8

Burden and complications of herpes zoster ophthalmicus (HZO)

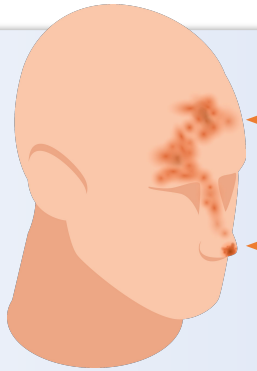
- incidence 8-20 % of VZV cases
- can affect all parts of the eye
- visual loss (1 in 10)
- antivirals can reduce HZO complications by 20-30%
- RZV >90% effective in preventing HZ (& complications)

&

Headache

Fever

Neuropathic pain



Herpetic rash

Hutchinson's sign (increased ocular involvement)

Without treatment, **50%** can progress to:

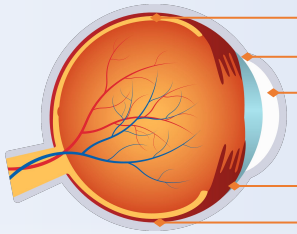
Discomfort

Pain

Photophobia

Redness

Discharge



Retinitis

Conjunctivitis

Keratitis

Uveitis

Episcleritis

8-20%

of patients with HZ will develop HZO

≤25%

develop chronic or recurrent HZO

1 in 10

moderate or severe vision loss, potentially permanent

Treatment

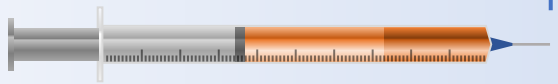
Antivirals within 72 h

complications by **20-30%**

Prevention

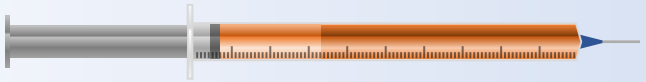
Live attenuated vaccine (**ZVL**)

27-63% effectiveness



Non-live recombinant vaccine (**RZV**)

67-93% effectiveness



RZV vs ZVL:

Reactogenicity

Contraindications

HZO is a painful ophthalmic emergency with potentially severe complications

Early identification and treatment is crucial

Primary care physicians should consider vaccination to reduce HZO incidence

Impact of Zoster on Stroke

- Adults developing shingles have a greater risk of both heart attack and stroke[1-3]
- The increased risk is greatest within the first 3 months of developing shingles, and decreases over time[1-3].
- The inflammatory response to shingles has been thought to account for this increase in heart attack and stroke[4,5]

1.Forbes. PloS one. 2018;13(11):e0206163.
2.Yang J Stroke Cerebrovasc Disease . 2017;26(2):301-7.
3.Marra. BMC Infect Dis. 2017;17(1):198.
4.Lin. Mayo Clinic proceedings. 2019;94(8):1649-50.
5.Nagel J Infect Dis. 2018;218(suppl_2):S107-s12.

Impact of Zostavax on risk of stroke

- Centers for Disease Control and Prevention's Behavioral Risk Factors Surveillance System, a cross-sectional nationwide telephone survey[1]
- 2014 survey data were from 265,568 adults 50-79 years old.
- HZ-vaccinated individuals had lower risk of reporting stroke those not vaccinated (hazard ratio [HR] = 1.73).
- A **decreased risk of stroke** was seen in patients who received the recombinant zoster vaccine (OR, 0.57 [95% CI, .46–.72] or the live zoster vaccine (OR, 0.77 [95% CI, .65–.91]; [2]

TABLE II. Unadjusted Odds Ratios Describing Associations Between Self-reported Stroke With Self-reported Zoster Vaccine Uptake

		95% Wald Confidence Limit		99% Wald Confidence Limit	
Age Group	Odds Ratio	Lower	Upper	Lower	Upper
50–54	0.96	0.62	1.48	0.54	1.70
55–59	0.86	0.60	1.23	0.54	1.38
60–64	1.29	1.06	1.58	1.00	1.68
65–69	1.56	1.33	1.83	1.27	1.92
70–74	1.30	1.11	1.53	1.06	1.61
75–79	1.24	1.05	1.46	1.00	1.54

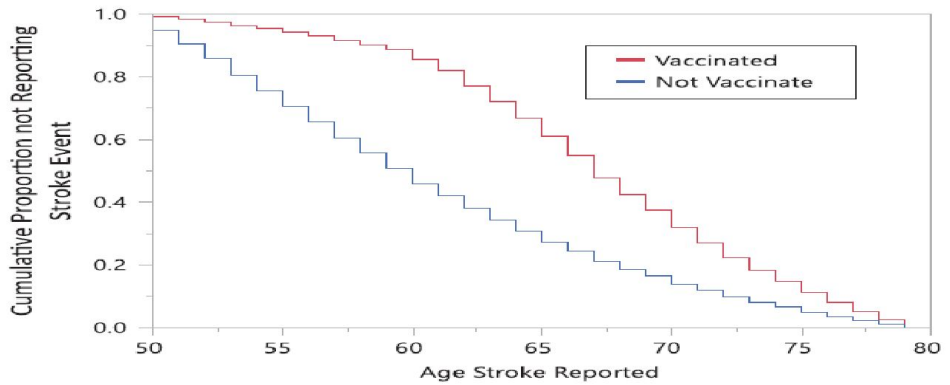


FIGURE 2. Estimated proportions of respondents within each age (ages 50–79) without a history of stroke, by zoster vaccination status. A different sample of respondents was used at each age. At age 79 despite vaccination status, the cumulative Kaplan–Meier proportions of age cross-sections where respondents were without a stroke history approach 0.0. Behavioral Risk Factor Surveillance System 2014.

1. Klaric Mil Med. 2019 Mar 1;184(Suppl 1):126-132
2. Parameswaran Clin Infect Dis. 2023 Feb 8;76(3):e1335-e1340.

HZ and the long-term risk of stroke

Table 2. HZ and Long-Term Risk of Stroke in the NHS, NHS II, and HPFS

Variable	Time since HZ, y				
	Never	1–4	5–8	9–12	≥13
NHS					
Cases/person-years	2181/879 821	95/35 929	99/25 106	61/15 037	25/6169
Age-adjusted HR (95% CI)	1.00 (Reference)	0.98 (0.80–1.21)	1.32 (1.08–1.62)	1.27 (0.98–1.64)	1.33 (0.89–1.99)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	0.96 (0.79–1.19)	1.29 (1.05–1.58)	1.25 (0.96–1.62)	1.33 (0.89–1.99)
NHS II					
Cases/person-years	472/1 151 523	17/28 235	22/20 942	16/17 473	10/17 583
Age-adjusted HR (95% CI)	1.00 (Reference)	1.29 (0.79–2.10)	2.23 (1.45–3.42)	1.89 (1.15–3.13)	1.11 (0.59–2.09)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.19 (0.73–1.94)	2.01 (1.31–3.10)	1.69 (1.03–2.79)	0.97 (0.52–1.82)
HPFS					
Cases/person-years	541/251 884	21/5577	15/5594	9/3974	19/6828
Age-adjusted HR (95% CI)	1.00 (Reference)	1.38 (0.89–2.13)	1.15 (0.69–1.93)	0.93 (0.48–1.79)	1.14 (0.72–1.81)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.39 (0.90–2.16)	1.14 (0.68–1.91)	0.90 (0.47–1.75)	1.14 (0.72–1.81)
Pooled					
Total No. of cases	3194	133	136	86	54
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.05 (0.88–1.25)	1.38 (1.10–1.74)	1.28 (1.03–1.59)	1.19 (0.90–1.56)

HPFS indicates Health Professionals Follow-Up Study; HR, hazard ratio; HZ, herpes zoster; NHS, Nurses' Health Study; and NHS II, Nurses' Health Study II.
*Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index, waist circumference (≤70, 71–79, 80–88, and >88 cm), physical activity, diabetes, hypertension, elevated cholesterol, regular use (≥2 days/week) of aspirin, thiazide diuretics, loop diuretics, "statins," or other cholesterol-lowering drugs, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, or "other" antihypertensive drugs, Alternative Healthy Eating Index 2010 score, menopausal status (in NHS and NHS II), oral contraceptive use (in NHS II), postmenopausal hormonal therapy use (in NHS and NHS II), history of coronary heart disease, and a report of ≥1 of the following: cancer (other than nonmelanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, or oral steroids/corticosteroid use.

Zoster increases the long-term risk of stroke

Curhan J Am Heart Assoc. 2022 Nov 16:e027451.

NIP-changes to shingles vaccination from 1 Nov 2023

- From 1 November 2023, the shingles vaccine RZV (Shingrix®) will replace LAIV (Zostavax®) on the National Immunisation Program (NIP) schedule for the prevention of shingles and post-herpetic neuralgia.
- It will be available for eligible people most at risk of complications from shingles.
- A 2-dose course of Shingrix® will be available for free for:
  - people aged 65 years and older
  - First Nations people aged 50 years and older
  - immunocompromised people aged 18 years and older with the following medical conditions:
    - haemopoietic stem cell transplant
    - solid organ transplant
    - haematological malignancy
    - advanced or untreated HIV.

https://www.health.gov.au/news/national-immunisation-program-changes-to-shingles-vaccination-from-1-november-2023

The recombinant zoster vaccine (RZV) was designed to help address age-related decline in immunity and immunocompromise [1-5]

Elicits a specific immune response against VZV[7]

- Primary target for VZV-specific immune response[9]
- Expressed on the surface of VZV-infected cells[9]
- Key to viral replication[9]

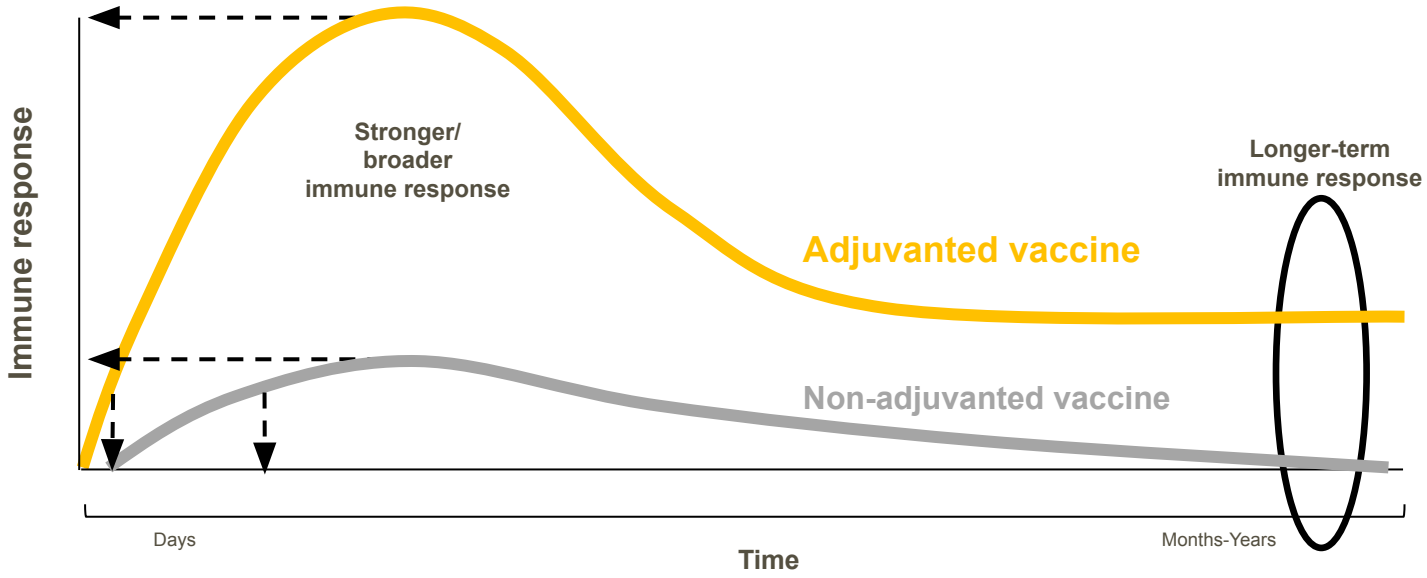
Enhances the immune response to the vaccine antigen[7,8]

- Designed to induce strong and sustained anti-gE immune response[9]
- The combination of MPL and QS-21 enhances both antibody and cellular immune response against gE[9]

MPL=monophosphoryl lipid A; QS-21=*Quillaja saponaria* Molina fraction 21; VZV=varicella zoster virus

References: 1. Chlibek R, et al. Vaccine. 2014 Mar;32(15):1745-53. **2.** Lal H, et al. N Engl J Med. 2015 May;372(22):2087-96. 3. Bharucha T, et al. Hum Vaccin Immunother. 2017 Aug;13(8):1789-97. 4. Garçon N, et al. Vaccine adjuvants. Amsterdam: Elsevier; 2011. 5. Shingrix Approved Product Information. 6. Bastidas A, et al. Open Forum Infect Dis. 2019 Oct;6(Suppl 2):S84-S85. **7.** Dendouga N, et al. Vaccine. 2012 Apr;30(20):3126-35. **8.** Leroux-Roels G, et al. Clin Immunol. 2016 Aug;169:16-27. **9.** Lecrenier N, et al. Exp Rev Vaccine. 2018 Jun;17(7):619-634.

Adjuvants help generate a strong and long-lasting immune response



For conceptual purposes only, not a comparison between herpes zoster vaccines.
Illustrative figure independently created by GSK based on Garçon N, et al. Understanding modern vaccines. 2011[1]

References: 1. Garçon N, et al. Understanding Modern Vaccines: Perspectives in Vaccinology. Vol 1. Amsterdam: Elsevier; 2011; Chapter 4: 89-113

RZV pivotal phase III program: ZOE-50 and ZOE-70 [1,2]

New England Journal of Medicine 2015[1], 2016[2]

	ZOE-50[1] (Zoster-006)	ZOE-70[2] (Zoster-022)
Study design	Randomised, observer-blind, placebo-controlled, multi-centre, multinational (North America, Europe, Latin America, Asia-Pacific [including Australia])	
Primary objectives	VE_{HZ} in subjects ≥50 years of age	VE_{HZ} in subjects ≥70 years of age
Dosing schedule	2 doses administered 2 months apart	
Actual Enrolment	16160	14816
Primary objectives (pooled analysis)	**VE_{PHN} in individuals ≥70 years of age** **VE_{HZ} efficacy in individuals ≥70 years of age**	
Actual enrolment (pooled analysis)	**16596**	

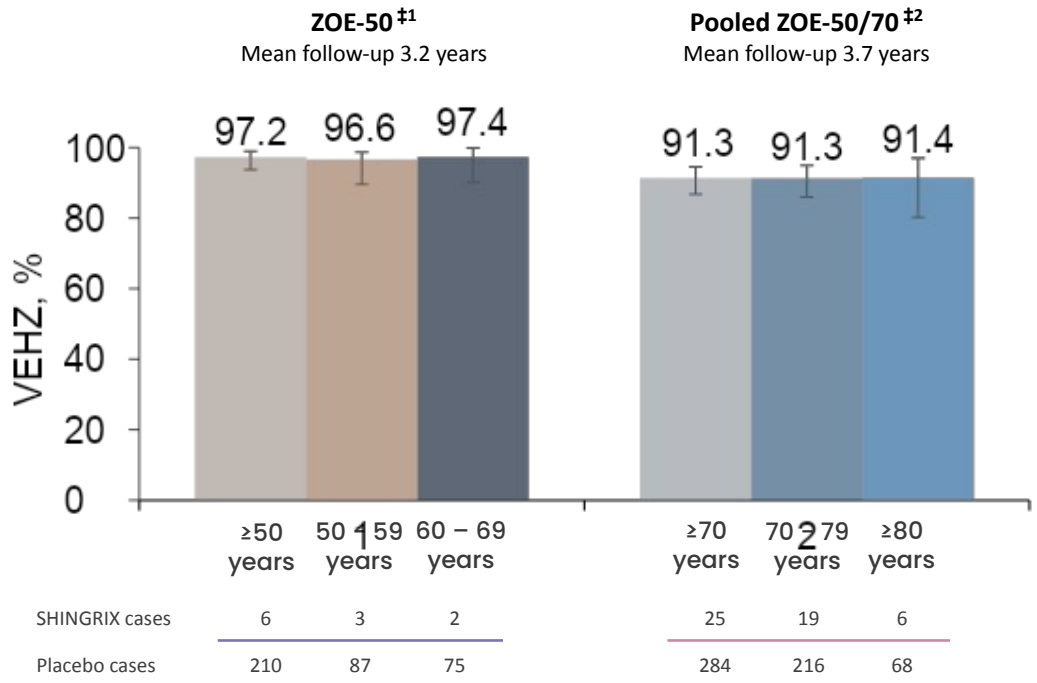
ZOE-50 and ZOE-70 studies conducted at the same sites

Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70

RZV Recombinant Zoster Vaccine; HZ Herpes Zoster; PHN post-herpetic neuralgia; VE vaccine efficacy

1. Lal H, *et al. N Engl J Med* 2015;372:2087–96; **2.** Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32

RZV demonstrated >90 % efficacy AGAINST herpes zoster in patients ≥50 Years of age [1-3*]



P<0.001 for all age groups vs. placebo

*Shingles case = a new unilateral rash with pain that had no other diagnosis and confirmed by PCR.[2] ‡Included 7344 randomized subjects ≥50 YOA who received second dose of the vaccine and did not develop shingles within 1 month after the second dose.[2,4] HZ=herpes zoster; PCR=polymerase chain reaction

References: 1. Shingrix Australian product information 2. Lal H, et al. N Engl J Med. 2015 May;372(22):2087-96. 3. Cunningham AL;N Engl J Med;2016;375;1019-32

RZV VE on HZ complications among groups ≥50 and ≥70 years of age [1,2*]

Prespecified, pooled analysis of ZOE-50 and ZOE-70*

Age (years)	PHN cases[1†]		VE_{PHN} ‡ (95% CI)	Other complications^[2]		VE_{other} (95% CI)
	RZV (n = 13881)	Placebo (n = 14035)		RZV (n = 13881)	Placebo (n = 14035)	
50+	4	46	**91%** (76, 98)	1	16	**94%** (60, 100)
70+	4	36	**88%** (69, 97)	1	12	**92%** (43, 100)

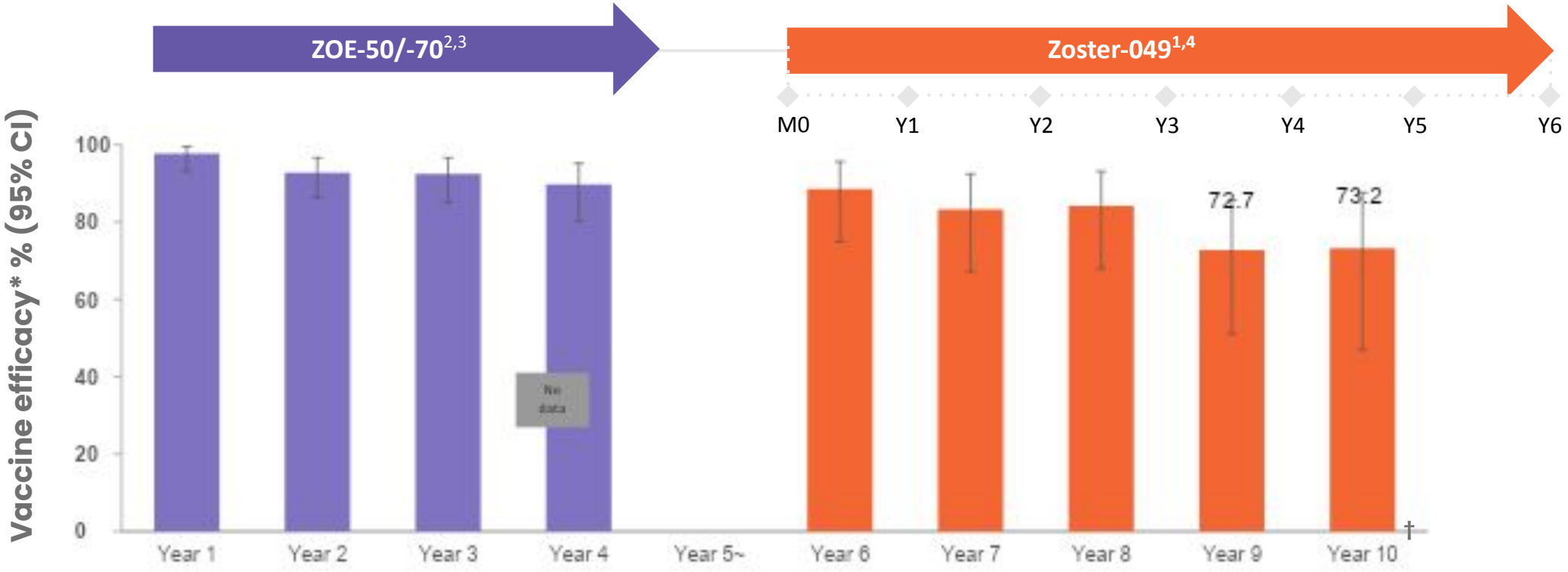
In RZV recipients aged 50-69, there were no cases of PHN or other HZ-related complications (i.e. all complications in the RZV group were in those aged 70+)

Mean follow-up 3.8 years in subjects ≥50 years old; *Modified vaccinated cohort (excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2); †PHN defined as HZ-associated pain ≥3 (on a 0–10 scale), occurring or persisting for ≥90 days following the onset of rash using Zoster Brief Pain Inventory (ZBPI); ‡$p<0.001$ for both comparisons versus placebo. ^other complications include HZ vasculitis, disseminated, ophthalmic and neurological disease.
CI confidence interval; HZ herpes zoster; n total number of subjects; PHN post-herpetic neuralgia; RZV recombinant zoster vaccine; VE_{PHN} vaccine efficacy against PHN VE_{other} vaccine efficacy against other HZ-related complications

1. Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32; **2.** Kovac M, *et al. Vaccine* 2018;36:1537–41

Zoster-049: Vaccine efficacy by year of follow-up[1]

mTVC (N=7277); from 1 month post-dose 2 to Year 4 interim analysis data lock point (August 2021)[1]



	Year 1	Year 2	Year 3	Year 4	Year 5~	Year 6	Year 7	Year 8	Year 9	Year 10
RZV n/ (N)	3 (13,881)	10 (13,569)	9 (13,185)	10 (12,757)		7 (7277)	10 (7100)	9/6878	15/6648	11/6258
Placebo/HC n/ (N)	130 (14,035)	136 (13,564)	116 (13,074)	95 (12,517)		61 (7277)	60 (7100)	57/6878	55/6648	41/6258

The graph has been independently created by GSK from the original data. The same results were first published in Lal et al.[2], Cunningham et al.[3], Boutry et al. [4], and Strezova A, et al.[1]

*RZV versus placebo recipients from the ZOE-50/-70 studies in years 1–4, then versus matched historical controls (HC) from the placebo group in the ZOE-50/-70 studies for years 6–10, adjusted for age and region at randomisation during the ZOE-50/-70 studies. The same N and follow-up period were considered for the historical control and vaccinated group. n for historical controls represents the projected number of included placebo group participants from ZOE-50-/-70 with at least one confirmed HZ episode based on the estimated incidence rate; ~Data were not available due to the gap between the ZOE-50/-70 and Zoster-049 studies; †Data collection for Year 10 was incomplete at the data lock point

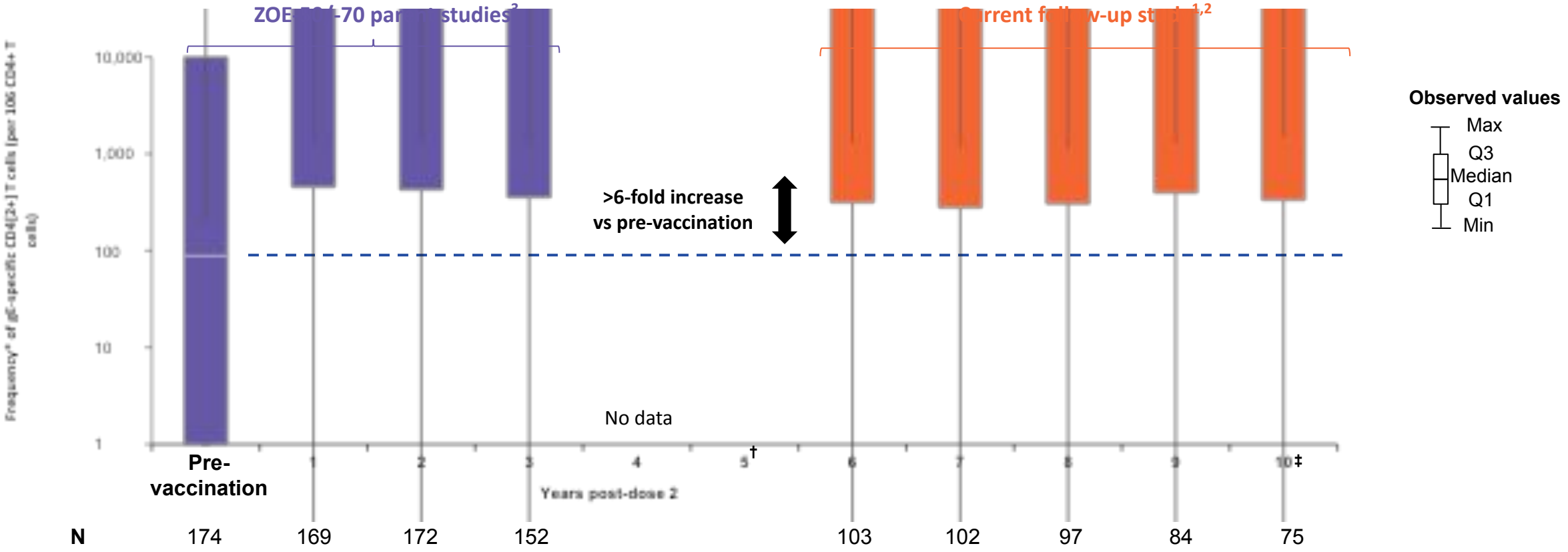
CI, confidence interval; HC, historical controls; HZ, herpes zoster; m, month; mTVC, modified total vaccinated cohort; N, number of individuals included in each group; n, number of individuals having at least one confirmed herpes zoster episode; RZV, recombinant zoster vaccine; Y, year.

1. Strezova A *et al. Open Forum Infect Dis* 2022; **2.** Lal H, *et al. N Engl J Med* 2015;372:2087–96; **3.** Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32; **4.** Boutry C et al. Clin Inf Dis. 2021;1-30; **5.** ClinicalTrials.gov. NCT02723773. https://clinicaltrials.gov/ct2/show/NCT02723773 (accessed October 2022)

Zoster-049: Long-term persistence of cell-mediated immune responses[1]

ATP cohort (N=108)[1,2]

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



*The frequency of gE-specific CD4[2+] T cells was assessed per 10^6 total CD4[2+] T cells;[1] †Data not shown because only three participants had available results for this analysis;[2] ‡Data collection was incomplete at the data lock point for the second interim analysis[2]
ATP, according-to-protocol; gE, glycoprotein E; max, maximum; min, minimum; N, number of participants with available results; Q, quartile

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

Any grade and grade 3 solicited local adverse reactions reported up to 7 days post-vaccination*[1–4]

Median duration of <u>any grade</u> solicited local reactions
ZOE-50: pain, redness and swelling = 3 days[3]
ZOE-70: pain = 2 days; redness and swelling = 3 days[2]

Median duration of <u>grade 3</u>‡ solicited local reactions
ZOE-50: pain = 1 day; redness and swelling = 2 days[1]
ZOE-70: pain = 1.5 days; redness = 2 days; swelling = 1 day[2]

Grade 3 solicited local reactions occurred in 10% of participants[1,2]

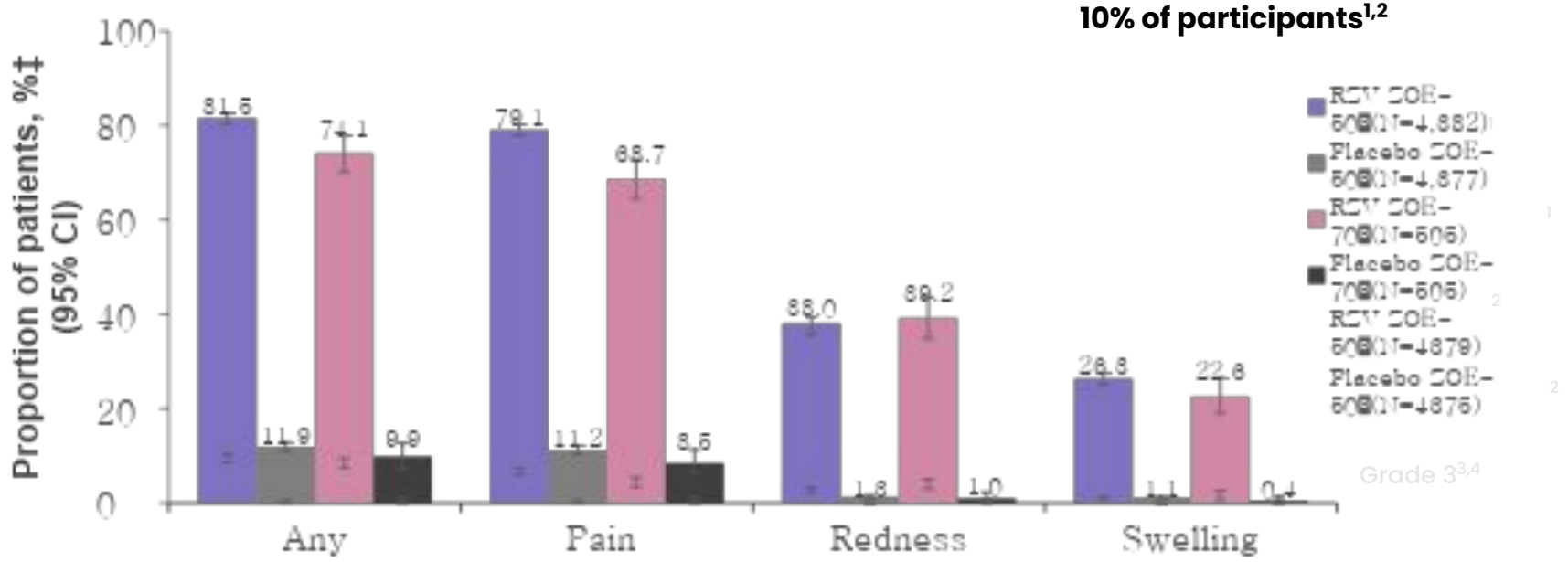


Figure drafted from raw data within article from Lal H, *et al. N Engl J Med* 2015;372:2087–96; Cunningham AL, *et al. N Engl J Med* 2016
*Subgroup of age stratified subjects recorded injection-site reactions and systemic reactions on diary cards for 7 days after each injection; †Grade 3, redness and swelling at the injection site were scored as grade 3 for those more than 100 mm. All other symptoms were scored as 3 for preventing normal activity; ‡Percentage of subjects reporting the symptom at least once when the intensity is maximum

1. Lal H, *et al. N Engl J Med* 2015;372:2087–96; **2.** Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32; **3.** Study 110390: GSK Clinical Study Report 2016. Available at: https://www.gsk-studyregister.com/study/3283; **4.** Study 113077: GSK Clinical Study Report 2016. Available at: https://www.gsk-studyregister.com/en/trial-details/?id=113077

Any grade and grade 3 solicited systemic adverse reactions reported post-vaccination*[1–4]

Median duration of <u>any grade</u> solicited systemic reactions
ZOE-50: fatigue, GI, headache and myalgia = 2 days; fever and shivering = 1 day[3]
ZOE-70: fatigue, fever GI, headache, and myalgia = 2 days; shivering = 1 day[2]

Median duration of <u>grade 3</u>‡ solicited systemic reactions
ZOE-50: all grade 3 adverse reactions = 1 day[1]
ZOE-70: fatigue, GI, headache and shivering = 1 day; myalgia = 2 days[2]

Grade 3 solicited local reactions occurred in 10% of participants[1,2]

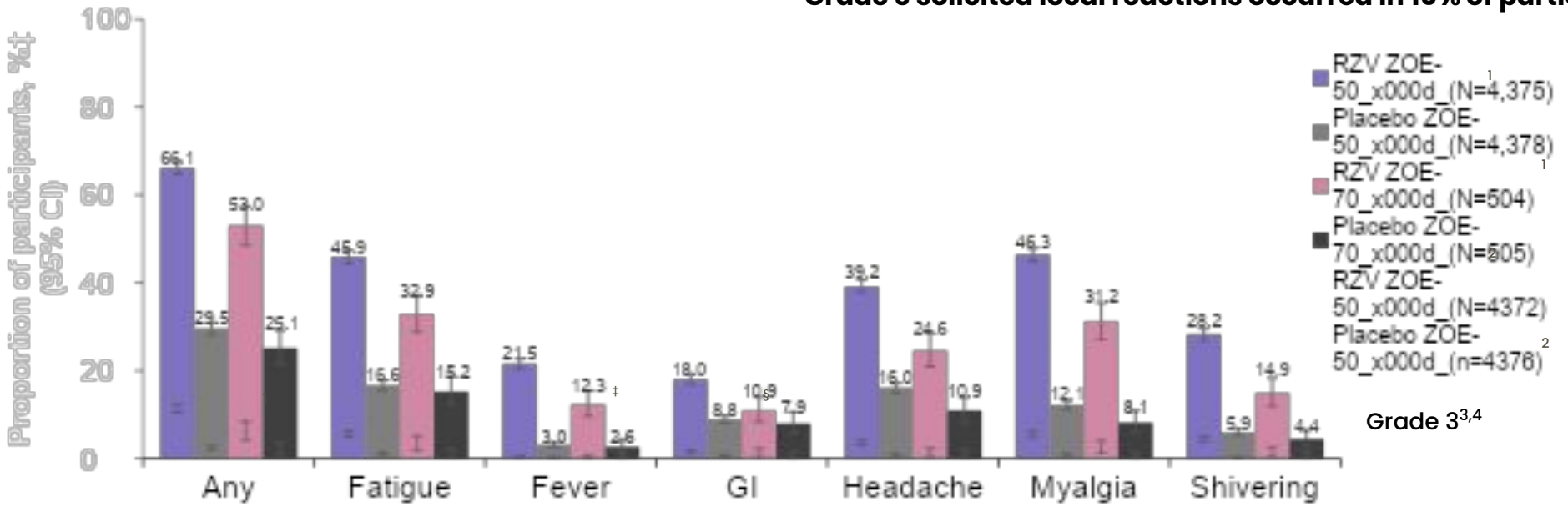
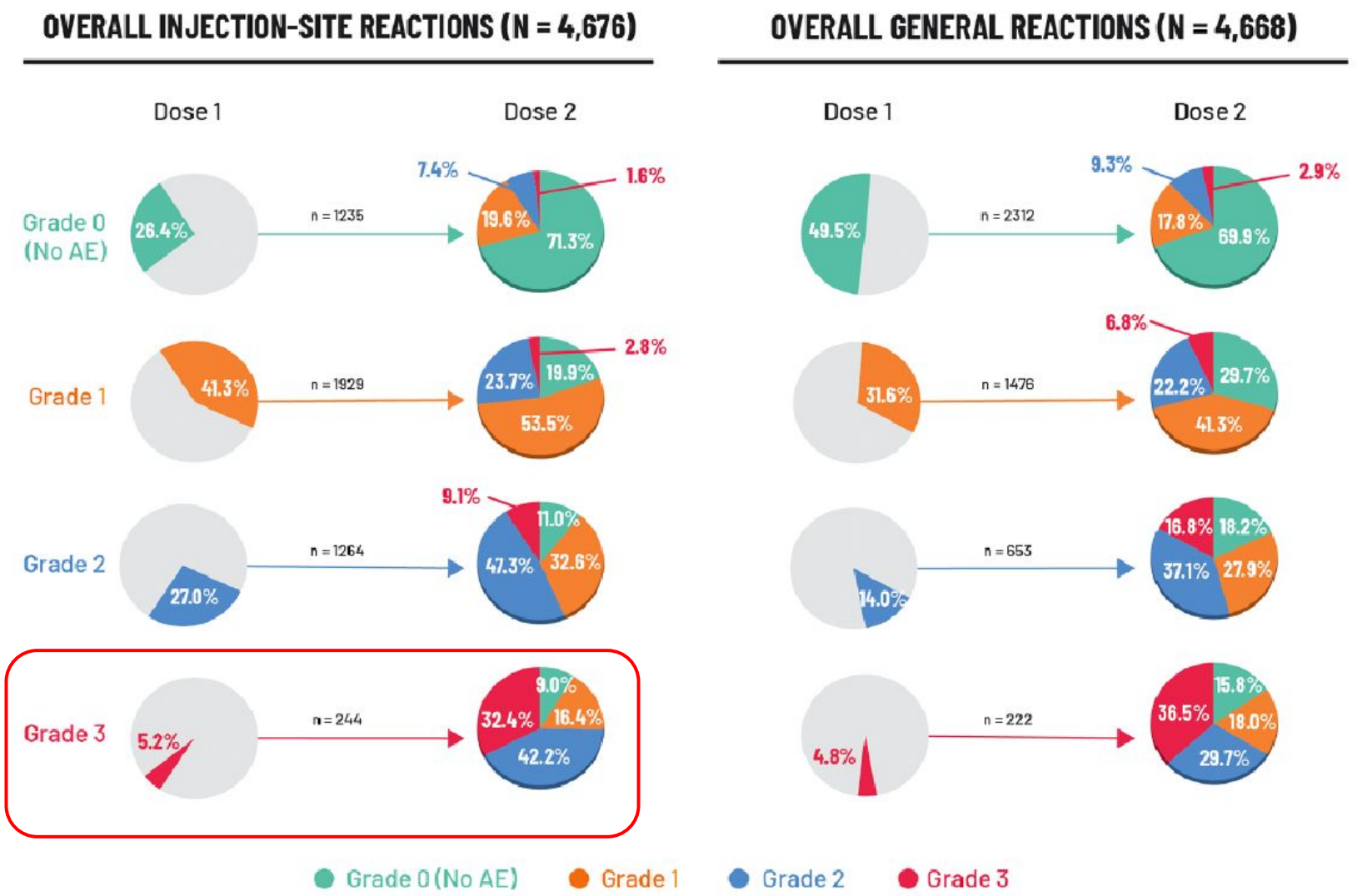


Figure drafted from raw data within article from Lal H, *et al. N Engl J Med* 2015;372:2087–96; Cunningham AL, *et al. N Engl J Med* 2016
*Subgroup of age stratified subjects recorded injection-site reactions and systemic reactions on diary cards for 7 days after each injection; †Grade 3: temperature >39°C (preferred route: oral); all other symptoms were scored as 3 for preventing normal activity. ‡Fever (≥37.5°C/≥99.5°F); §GI symptoms included nausea, vomiting, diarrhoea, and/or abdominal pain; GI, gastrointestinal; N, number of subjects with at least 1 documented dose; %, percentage of subjects reporting the symptom at least once when the intensity is maximum

1. Lal H, *et al. N Engl J Med* 2015;372:2087–96; **2.** Cunningham AL, *et al. N Engl J Med* 2016;75:1019–32; **3.** Study 110390: GSK Clinical Study Report 2016. Available at: https://www.gsk-studyregister.com/study/3283; **4.** Study 113077: GSK Clinical Study Report 2016. Available at: https://www.gsk-studyregister.com/en/trial-details/?id=113077

Are more severe adverse reactions more common with the second dose of RZV?

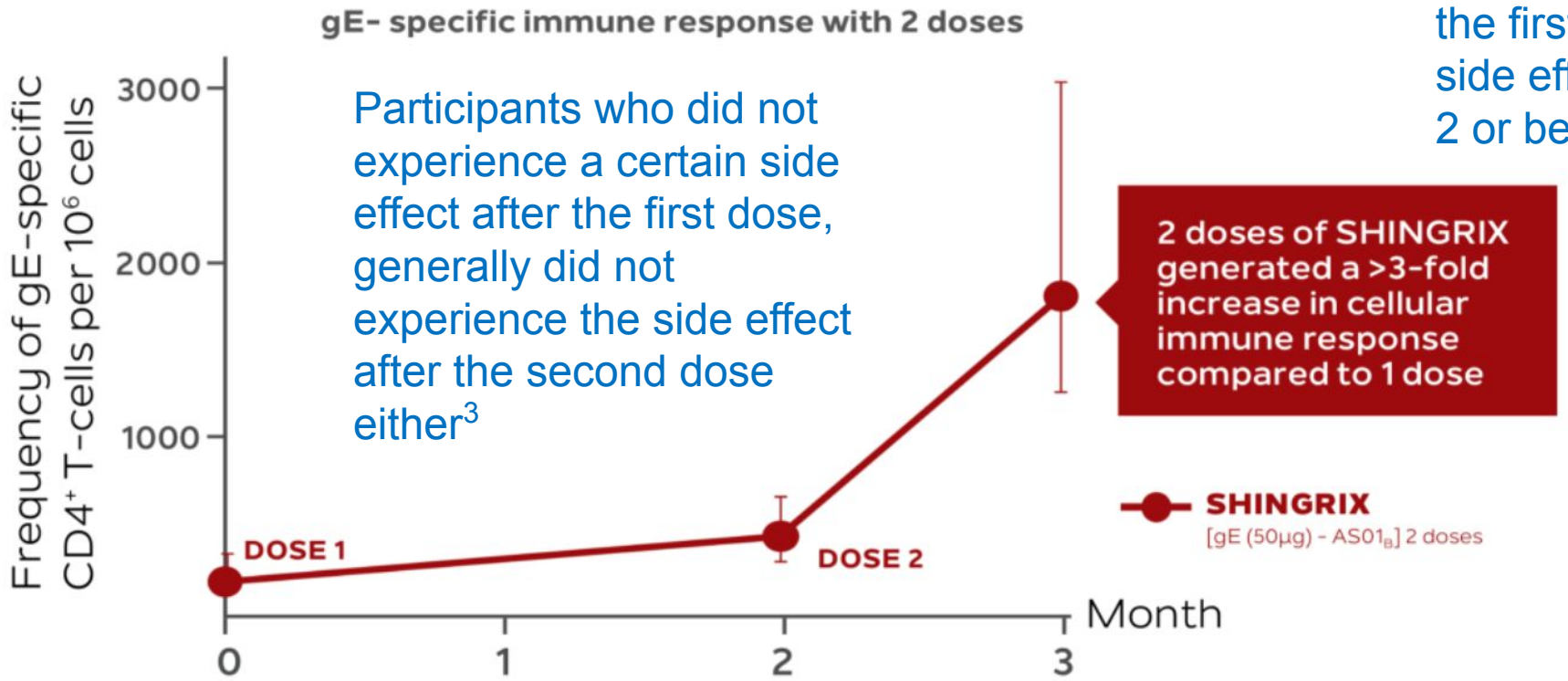


A total of 244 (5.2%) individuals reported a Grade-3 local AE after the first dose, of whom 165 (67.6%) experienced the same event at a lower intensity (grade ⩽ 2) after the second dose

Fiore Ther Adv Vaccines Immunother. 2021 Nov 30;9:

RZV EFFICACY IN ADULTS ≥50 YEARS OF AGE IS ONLY CONFIRMED IN A 2-DOSE SERIES[1,2]

Two-thirds of vaccine recipients reporting a specific side effect at the highest (grade 3) intensity after the first dose reported the same side effect at lower intensity (grade 2 or below) after the second dose [3]:



Participants who did not experience a certain side effect after the first dose, generally did not experience the side effect after the second dose either[3]

Colindres Hum Vaccin Immunother. 2020 Nov 1;16(11):2628-2633.

The same results were first published in Vaccine.*
*The graph has been independently created by GSK from the original data.[2]
gE=glycoprotein E.

1. Shingrix Australian Product Information 2. Chlibek R, et al. Vaccine. 2014 Mar;32(15):1745-53.

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against HZ is unknown

RZV in immunocompromised patients

Resource

https://immunisationhandbook.health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised#recombinant-zoster-vaccine-shingrix

The incidence of HZ is higher in immunocompromised populations[1]

A retrospective cohort study conducted in England using data (January 2000 to March 2012) from the Clinical Practice Research Datalink with linkage to the Hospital Episodes Statistics*.

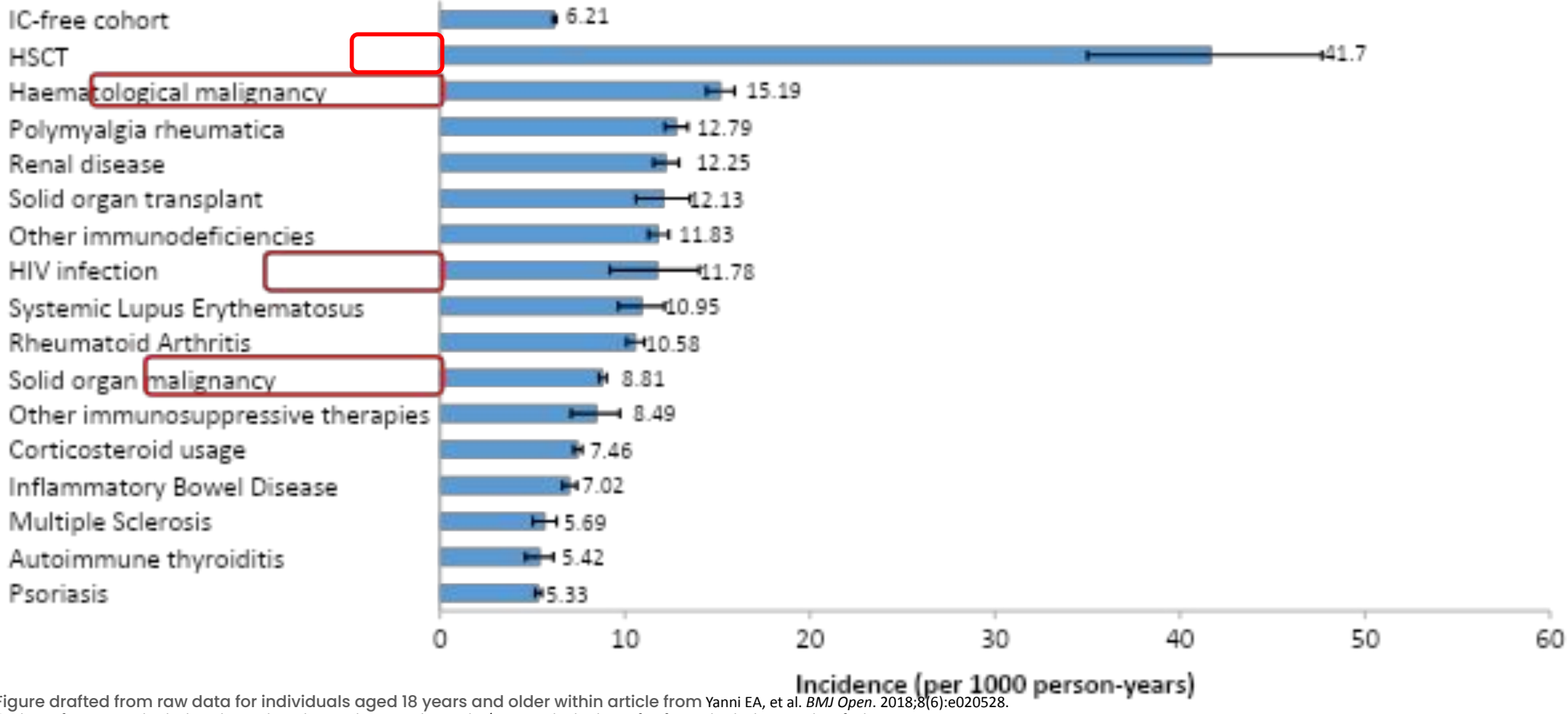


Figure drafted from raw data for individuals aged 18 years and older within article from Yanni EA, et al. *BMJ Open*. 2018;8(6):e020528.
*Cohort of 621 588 individuals with 16 selected IC conditions and a gender/age-matched cohort of IC-free individuals were identified.

HZ herpes zoster; HSCT haematopoietic stem cell transplant; HIV human immunodeficiency virus

1. Yanni EA, et al. *BMJ Open*. 2018;8(6):e020528.

TABLE 1. RECOMMENDED VACCINES AGAINST HERPES ZOSTER FOR IMMUNOCOMPROMISED PATIENTS

Level of immunocompromise	Disease or therapy	Recommended zoster vaccine
Severe	Patients with: • haemopoietic stem cell transplantation • solid organ transplantation • haematological malignancies • solid tumours and on chemotherapy • high-dose corticosteroid therapy (≥20mg/day) • AIDS • symptomatic HIV infection	Recombinant zoster vaccine (RZV; Shingrix)
Moderate	Patients taking biological or targeted synthetic DMARDs including: • TNF inhibitors • JAK inhibitors • T cell inhibitors (e.g. ciclosporin)	RZV (no evidence yet, awaiting results of current trials)
Mild	Patients taking: • hydroxychloroquine • sulfasalazine • low-dose corticosteroids (<20mg/day) • azathioprine • methotrexate	RZV recommended over live attenuated zoster vaccine (Zostavax)

Abbreviations: DMARDs = disease modifying antirheumatic drugs; JAK =janus kinase; TNF = tumour necrosis factor.

Cunningham Medicine Today 2022 :23(7): 53-6

Vaccine immune response rates to RZV in IC populations[1-10]

Condition (anti-GE antibody, CD4(2⁺) count in overall cohort)	Overall (%, 95% CI)		18-49 years(%, 95% CI)		50+ years(%, 95% CI)	
	Anti-gE antibody	CD4(2⁺) count	Anti-gE antibody	CD4(2⁺) count	Anti-gE antibody	CD4(2⁺) count
HIV[1,2] (n=53, 20)	**96%** (87, 100)	**90%#** (68, 99)	**n/a**	**n/a**	**n/a**	**n/a**
Autologous HSCT[3,4] (n=82, 42)	**67%** (56, 77)	**93%** (81, 99)	**58%** (37, 77)	**100%** (77, 100)	**71%** (58, 83)	**89%** (72, 98)
Renal transplant[5,6] (n=121, 28)	**80%** (72, 87)	**71%** (51, 87)	**85%** (71, 94)	**82%** (48, 98)	**77%** (66, 86)	**65%** (38, 86)
Haematological malignancy[7,8] (n=217, 43)	**65%** (59, 72)	**84%** (69, 93)	**73%** (60, 84)	**88%** (47, 100)	**63%** (55, 70)	**83%** (66, 93)
Solid tumours with chemotherapy^[9,10] (n=65, 22)	**94%** (85, 98)	**50%** (28, 72)	**95%** (74, 100)	**56%** (21, 86)	**94%** (82, 99)	**46%** (19, 75)

*Subjects tested 1 month after receiving the final dose. HIV patients received three doses at 0, 2, 6 months. All other studies received two doses at 0 and 1-2 months.
^Data obtained pre-chemotherapy. #Subgroup of patients with high CD4⁺ count.
RZV recombinant zoster vaccine; HIV Human Immunodeficiency Virus; HSCT haematopoietic stem cell transplant; gE, glycoprotein E; CD4(2+) CD4 T cells with at least two activation markers from interferon γ, interleukin 2, tumor necrosis factor α, and CD40 ligand.

1. Berkowitz EM et al. *J Infect Dis*. 2015;211(8):1279-1287. **2.** Study 112673: GSK Clinical Study Report 2015. **3.** Bastidas A, et al. JAMA 2019;132(2):123-133; **4.** Study 115523: GSK Clinical Study Report 2019. **5.** Vink P, et al. Clin Infect Dis 2020;70(2):181-190; **6.** Study 116428: GSK Clinical Study Report 2019. **7.** Dagnew AF, *et al. Lancet Infect Dis.* 2019 Sep;19(9):988-1000; **8.** Study 116428 : GSK Clinical Study Report 2019.. **9.** Vink P, et al. Cancer 2019;125(8):1301-1312. **10.** Study 116427: GSK Clinical Study Report 2018. All GSK Clinical Study Reports are available at: https://www.gsk-studyregister.com/en/

Efficacy of RZV in immunocompromised patients*[1-4]

Condition	Overall VE_{HZ}	Overall VE_{PHN}	VE_{HZ} in individuals aged 18–49	VE_{HZ} in individuals aged 50+
Autologous HSCT[1,2] (N=1721)	**68%** (56, 78)	**89%** (23, 100)	**72%** (39, 88)	**67%** (53, 78)
Haematological malignancy[3,4] (N=515)	**87%** (44, 99)	Not reported	Not reported	Not reported

GSK RZV in immunocompromised populations- internal documents

*Subjects tested 1 month after receiving the second dose. Efficacy was not an endpoint for the HIV, renal transplant or solid tumour IC populations.

Figures in parentheses represent 95% CI. All studies were randomised, controlled phase III clinical trials in which patients were given two doses of RZV one-two months apart.

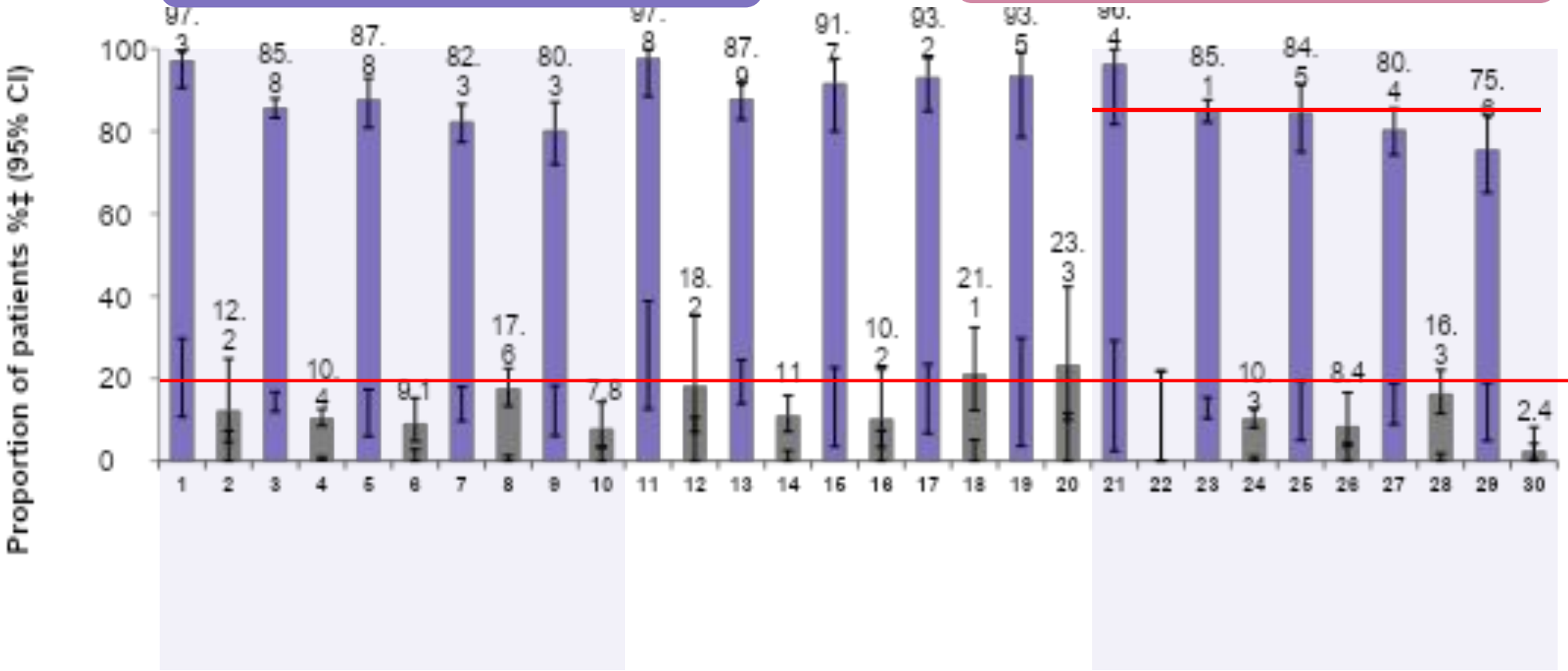
HZ herpes zoster; PHN post-herpetic neuralgia; VE_{HZ}, vaccine efficacy against HZ; VE_{PHN} vaccine efficacy against PHN; auHSCt autologous haematopoietic stem cell transplant.

1. Bastidas A, et al. JAMA 2019;132(2):123-133; **2.** Study 115523: GSK Clinical Study Report 2019. **3.** Dagnew AF, *et al. Lancet Infect Dis.* 2019 Sep;19(9):988-1000; **4.** Study 116428 : GSK Clinical Study Report 2019. All GSK Clinical Study Reports are available at: https://www.gsk-studyregister.com/en/

Solicited **local** AEs reported in IC populations*[1–10]

Median duration of any grade solicited local reactions was <= 4 days

Median duration of grade 3‡ solicited local reactions was <= 2 days



HIV = human immunodeficiency virus
auHSCT = autologous haematopoietic stem cell transplant
RT = renal transplant
HM = haematological malignancy
ST = solid tumours

Solicited local reactions are
- Pain
- Redness
- Swelling

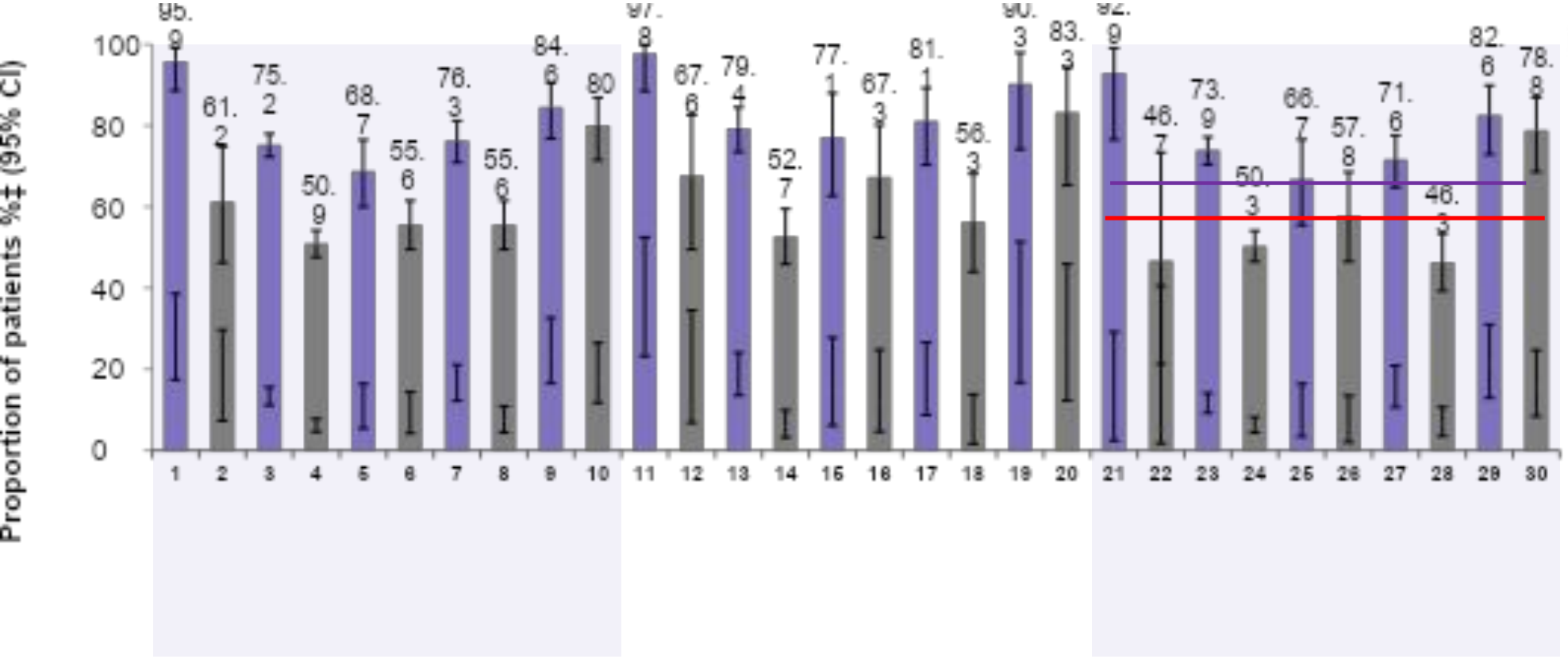
*Subgroup of age stratified subjects recorded injection-site reactions and systemic reactions on diary cards for 7 days after each injection; Grade 3, redness and swelling at the injection site were scored as grade 3 for those more than 100 mm. All other symptoms were scored as 3 for preventing normal activity. ‡Percentage of subjects reporting the symptom at least once when the intensity is maximum. AE adverse events; RZV recombinant zoster vaccine; IC immunocompromised;

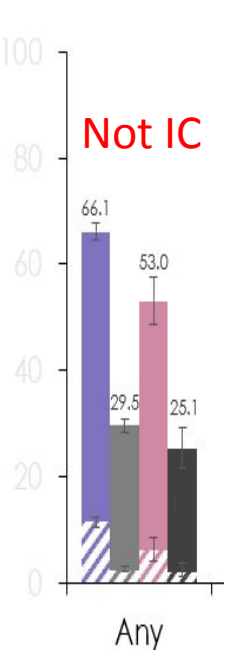
1. Berkowitz EM et al. *J Infect Dis*. 2015;211(8):1279-1287. **2.** Study 112673: GSK Clinical Study Report 2015. **3.** Bastidas A, et al. JAMA 2019;132(2):123-133; **4.** Study 115523: GSK Clinical Study Report 2019. **5.** Dagnew AF, *et al. Lancet Infect Dis.* 2019 Sep;19(9):988-1000; **6.** Study 116886: GSK Clinical Study Report 2019. **7.** Vink P, et al. Clin Infect Dis 2020;70(2):181-190; **8.** Study 116428: GSK Clinical Study Report 2019. **9.** Vink P, et al. Cancer 2019;125(8):1301-1312. **10.** Study 116427: GSK Clinical Study Report 2018. All GSK Clinical Study Reports are available at: https://www.gsk-studyregister.com/en/

Solicited systemic^ AEs reported in IC populations*[1–11]

Median duration of any grade solicited systemic reactions was <= 4 days

Median duration of grade 3‡ solicited systemic reactions was <= 2 days other than fatigue in RT which was = 7 days





Any ■ RZV ■ Placebo

Grade 3 ▨ RZV ▨ Placebo

HIV = human immunodeficiency virus
HSCT = haematopoietic stem cell transplant
RT = renal transplant
HM = haematological malignancy
ST = solid tumours

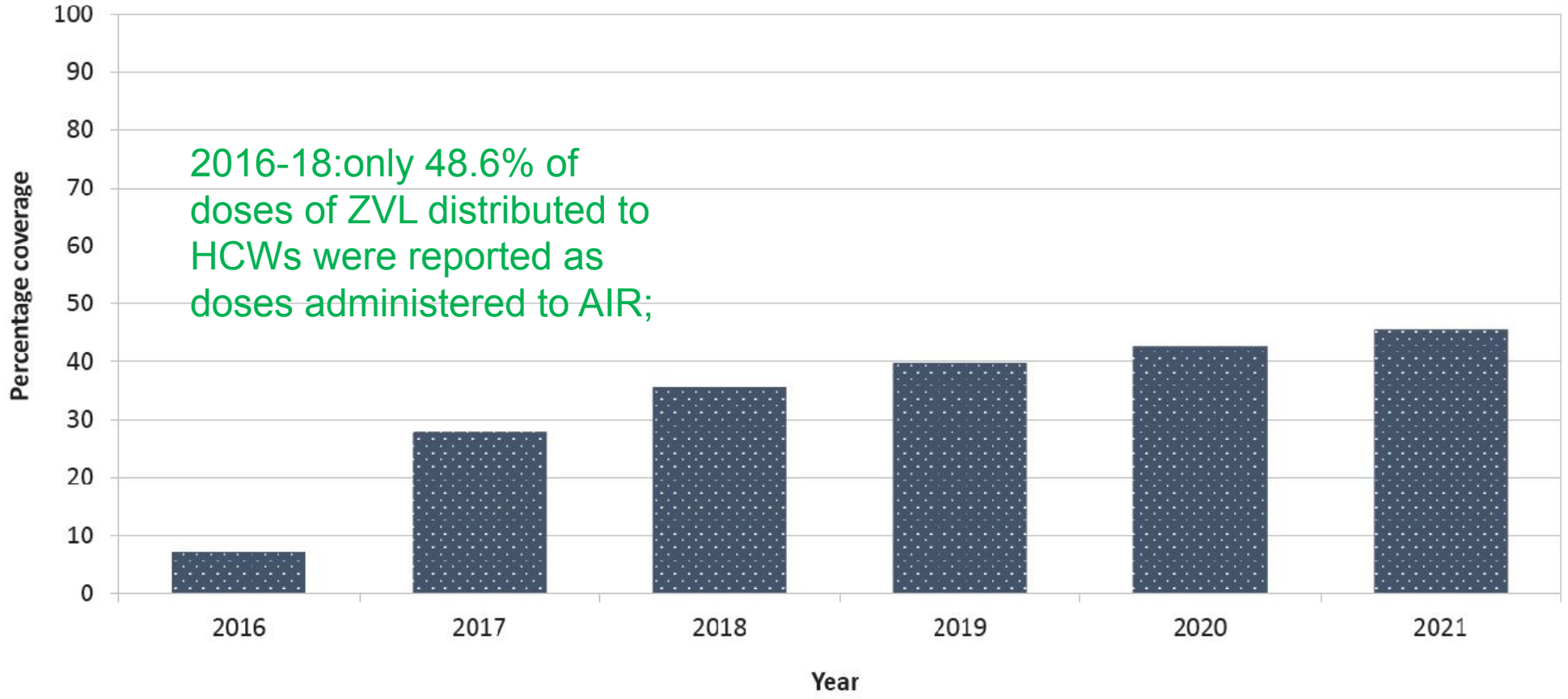
Solicited systemic reactions are: Fatigue, Gastrointestinal Headache, Myalgia, Shivering Fever

^HIV adverse reactions for age stratified patients includes solicited and unsolicited reactions. *Subgroup of age stratified subjects recorded injection-site reactions and systemic reactions on diary cards for 7 days after each injection; †Fever was scored as grade 3 if over 39, 39.5 for auHSCT, all other symptoms were scored as 3 for preventing normal activity. ‡Percentage of subjects reporting the symptom at least once when the intensity is maximum.
AE adverse events; RZV recombinant zoster vaccine; IC immunocompromised.

1. Berkowitz EM et al. *J Infect Dis*. 2015;211(8):1279-1287. **2.** Study 112673: GSK Clinical Study Report 2015. **3.** Bastidas A, et al. JAMA 2019;132(2):123-133; **4.** Study 115523: GSK Clinical Study Report 2019. **5.** Dagnew AF, *et al. Lancet Infect Dis.* 2019 Sep;19(9):988-1000; **6.** Study 116886: GSK Clinical Study Report 2019. **7.** Vink P, et al. Clin Infect Dis 2020;70(2):181-190; **8.** Study 116428: GSK Clinical Study Report 2019. **9.** Vink P, et al. Cancer 2019;125(8):1301-1312. **10.** Study 116427: GSK Clinical Study Report 2018. **11.** Lopez-Fauqued et al, 2021, drug safety 44:811-823 All GSK Clinical Study Reports are available at: https://www.gsk-studyregister.com/en/

Vaccine Coverage

Cumulative proportion of individuals aged 70–79 years who have had a single dose of LAZV, as assessed by calendar year, 2016 –2021[a]



a Source: Australian Immunisation Register.

Huang Commun Dis Intell (2018). 2023 Apr 27;47.

Summary: RZV

- Lifetime incidence of zoster is 1 in 3
- Zoster complications:
  - not prevented by prompt use of anti-virals
  - are problematic to treat
- RZV is the favoured zoster vaccine
  - Will be replacing LAZV for immunocompetent individuals age 65 yrs and older
  - Updated guidance for high-risk IC groups
  - RZV is immunogenic in high-risk groups
- Zoster vaccine coverage has plateaued
  - GP recommendation is the main influence on zoster vaccine acceptance

Indications AND Contraindications[1]

INDICATION

The recombinant Zoster vaccine (RZV) is indicated for the prevention of herpes zoster and post-herpetic neuralgia in individuals:

- aged 50 years and older
- aged 18 years and older at increased risk of herpes zoster

CONTRAINDICATION

Do not administer recombinant Zoster vaccine to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX[1]

Please refer to SHINGRIX Approved Product Information for further information on contraindications, precautions and safety

Interval between 2 doses

- 2-6 months in immunocompetent
- A shorter interval of 1-2 months can be used in individuals who are currently or shortly expected to be immunocompromised.

Note: The vial stoppers are not made with natural rubber latex.

1. Shingrix Australian Product Information

Factors improving RZV uptake

What increases patient's intentions to get the Zoster vaccine?

Table 2. Factors influencing the uptake of the herpes zoster vaccine.[a]

Factors associated with decreased uptake of herpes zoster vaccine		
Beliefs about shingles or immunity		Low perceived risk of getting herpes zoster
		Belief that vaccine is not needed/rarely get sick
		Belief that they already have good immunity to herpes zoster
		Belief that natural immunity is better/vaccines weaken the immune system
Beliefs about the herpes zoster vaccine		Concerns about the effectiveness of the herpes zoster vaccine
		Concerns about adverse effects from the herpes zoster vaccine
		Concerns about a possible allergic reaction to the herpes zoster vaccine
		Belief that the herpes zoster vaccine can cause shingles
Healthcare provider		GP has not discussed the need for the herpes zoster vaccine
		Difficulty getting to see GP
Factors associated with increased uptake of herpes zoster vaccine		
Demographic		Older age
		Female
		Higher level of education
Health knowledge and behavior	Adj OR 1.81 (1.18, 2.79)	Regularly gets influenza or pneumococcal vaccines
		Higher awareness of shingles and the herpes zoster vaccine
Beliefs about herpes zoster[#]	Adj OR 3.64 (2.61, 5.07)	Belief that herpes zoster can be a severe condition
Healthcare provider		Has a usual GP
	Adj OR 10.61 (6.28, 17.95)	Strong recommendation from GP to get the herpes zoster vaccine
Other		Family or friends have previously been affected with herpes zoster or PHN
		Herpes zoster vaccine available

GP, general practitioner; PHN, postherpetic neuralgia.
[a]Adapted from Litt et al.[27]

In contrast, vaccine believers have a higher uptake of the zoster vaccine adj OR 2.33 (1.66, 3.29) <0.001

includes other beliefs: concerned about getting shingles or its complications; shingles vax prevents getting shingles; shingles vax would prevent PHN; likely to get shingles in the near future; the shingles vaccine injection was free; know how serious shingles could be

1. Litt et al. Human Vaccines & Immunotherapeutics 2020;16(2): 1-9. Litt GP and patient views about Herpes Zoster (Shingles) its complications, and the likely acceptance of a Zoster vaccine . Poster International Conference on Infectious Diseases, Cape Town, April 2014

Influence of GP recommendation on patient beliefs to get vaccinated with ZVL (Zostavax)

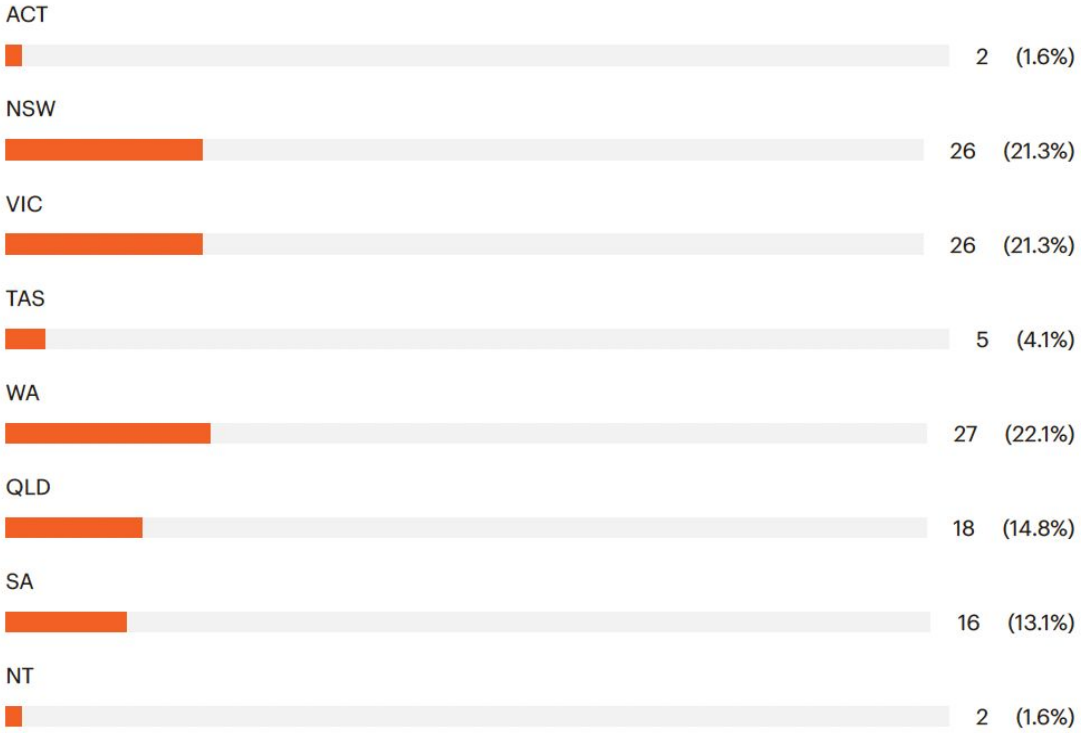
variable	coding	Prevalence (%)*	Percentage intending to get shingles vaccine: definitely/probably		Adjusted odds ratio (95%CI) of impact on getting a zoster vaccine	Comment
			No GP recommendation	If GP recommended		
concerned that a shingles vaccine injection may be painful or cause side effects	Disagree	53.3	66.5	91.8		Local side effects are common but most last less than two to three days Severe (grade 3 reactions) local reactions occur in <10% of the recipients Severe (grade 3 reactions) systemic reactions occur in <5% of the recipients
	Unsure, agree	46.6	46.6	72.3		
I trust the advice on vaccination that I receive from health professionals	Agree	93.6	60.0	86.2		Reassuringly, a very small percentage in the population overtly distrust health care professionals
	Unsure, disagree	6.4	18.1	30.3		
shingles vaccine injection would reduce my risk of becoming seriously ill from the complications of shingles	Agree	83.9	63.4	87.9	1.82 (1.04-3.19)	Very good evidence (ie VE >90%) in preventing both Zoster and PHN Anti-virals modify acute Zoster severity but do not reduce the incidence of PHN
	Unsure, disagree	16.2	27.6	57.5		
prefer to get natural immunity from getting the disease (eg Shingles) rather than from a vaccine	Disagree	68.3	69.4	92.0	1.69 (1.21-2.37)	Natural infection is associated with significant acute and long-term morbidity, including PHN which is very hard to treat
	Unsure, agree	31.7	32.6	64.0		
vaccines weaken the body's defense	Disagree	72.5	66.3	90.1		No evidence that vaccines weaken the immune system
	Unsure, agree	27.5	35.4	64.5		
Too many immunisations will weaken my immune system	disagree	67.3	69.2	91.0		The available evidence reviewed by Global Vaccine Advisory Committee on Vaccine Safety (GACVS) does not support the hypothesis that vaccines, as currently used, weaken or harm the immune system.
	Unsure, agree	32.6	35.6	67.7		

Influence of GP recommendation on patient beliefs to get vaccinated with ZVL (Zostavax)

Influence of GP recommendation on patient beliefs to get vaccinated with ZVL (Zostavax)						
variable	Coding	Prevalence (%)*	Percentage intending to get shingles vaccine: definitely/probably		Adjusted odds ratio (95%CI) of impact on getting a zoster vaccine	Comment
			No GP recommendation	If GP recommended		
I could get shingles from the shingles vaccine	Disagree	56.5	64.9	89.9		RZV- not possible as inactivated vaccine LAZV- possible but uncommon to get VZV
	Unsure, agree	43.5	48.0	73.8		
shingles vaccine injection would prevent me from getting shingles	Agree	77.2	63.8	87.6	1.47 (1.04-2.10)	Both LAZV and RZV are very effective against Zoster and PHN: RZV > LAZV
	Unsure, disagree	23.9	37.6	68.1		
is likely that I would feel unwell for a few days after having a shingles vaccine	Disagree	22.7	62.8	89.9		Local side effects like pain and swelling are common after RZV but subside within 2-3 days
	Unsure, agree	77.3	55.9	80.7		
concerned about having an allergic reaction from the shingles vaccine	Disagree	58.0	67.2	92.2		Anaphylaxis is extremely rare following a zoster vaccine (https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/about-vaccine.html#severe-allergic-reactions)
	Unsure, agree	42.0	44.8	70.8		
I do not need a shingles vaccine injection as I rarely get sick	Disagree	60.4	76.2	92.7	3.19 (2.44-4.17)	Car engine oil and preventive maintenance; zoster virus, which is present in nearly all older patients DRG, can emerge if immune system declines; Immune system decline is largely beyond the control of the patient. Best E-B protection against immune decline is vaccination
	Unsure, agree	39.6	29.9	68.4		

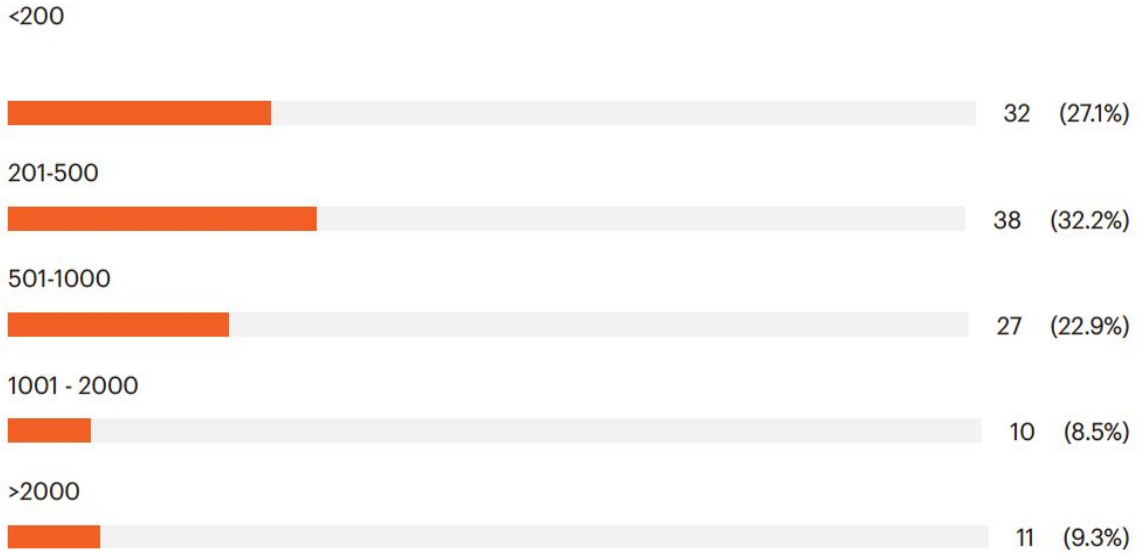
Survey results

"Q1. Which state do you work in?"



122 responders

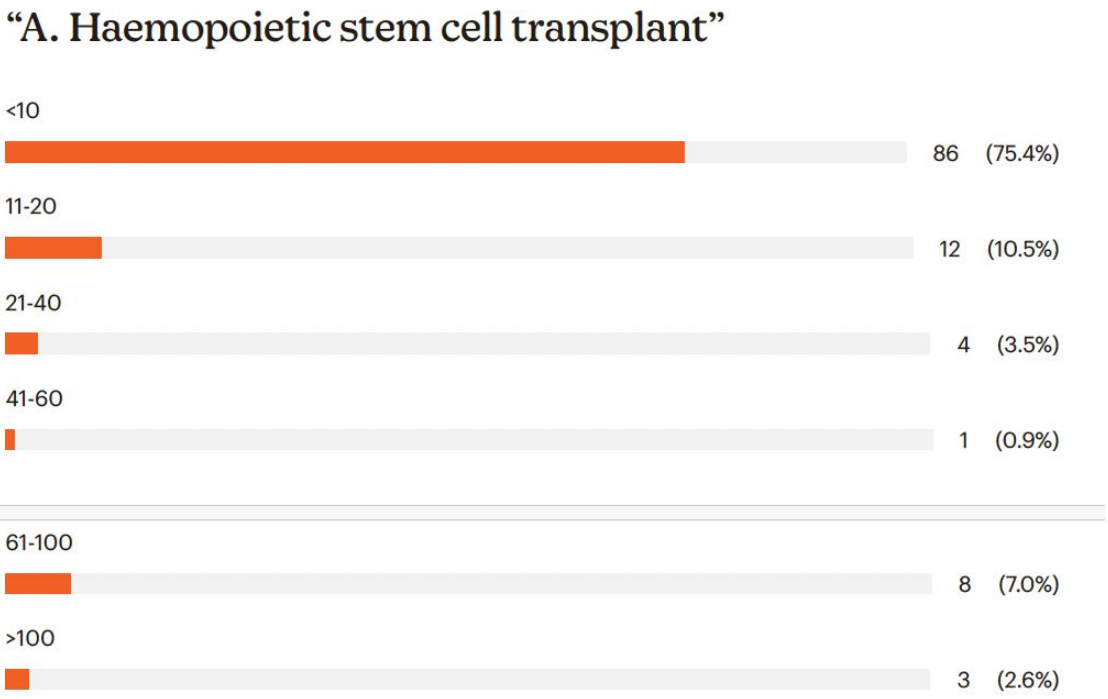
"Q2. How many patients in your practice are eligible for a free Shingrix vaccine in those 65 years and older"



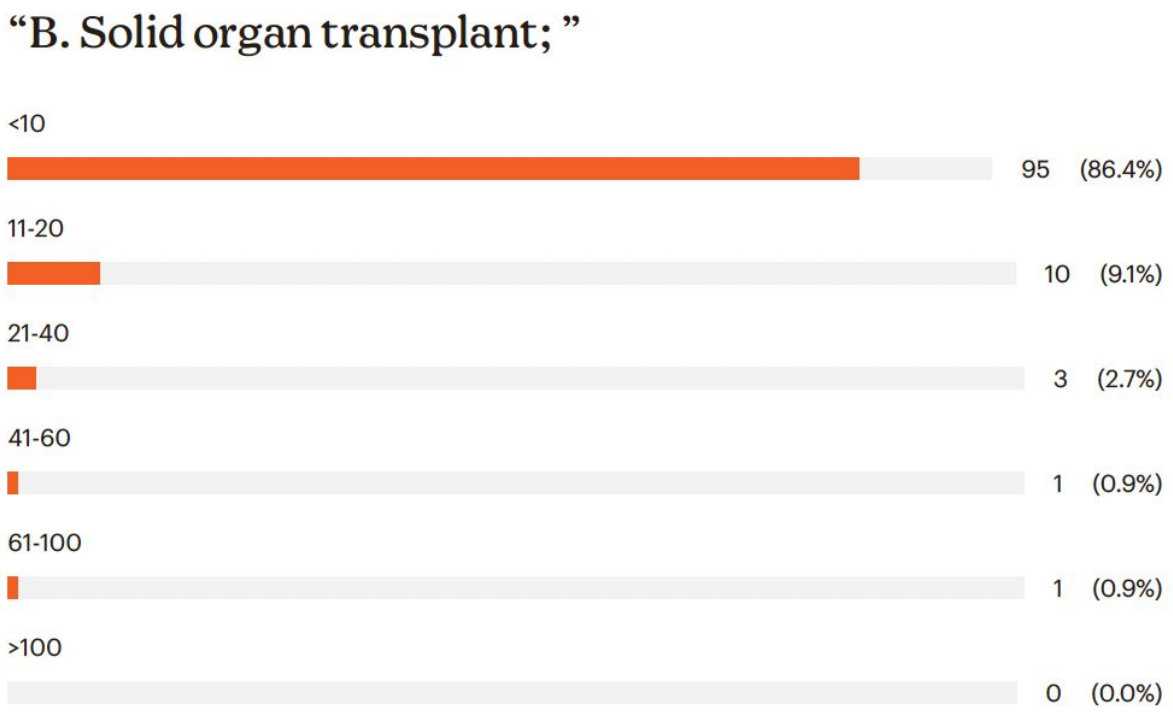
118 responders

Survey results

In those that have one of the 4 identified immunocompromising conditions, how many are eligible for a free Shingrix vaccine in your practice?



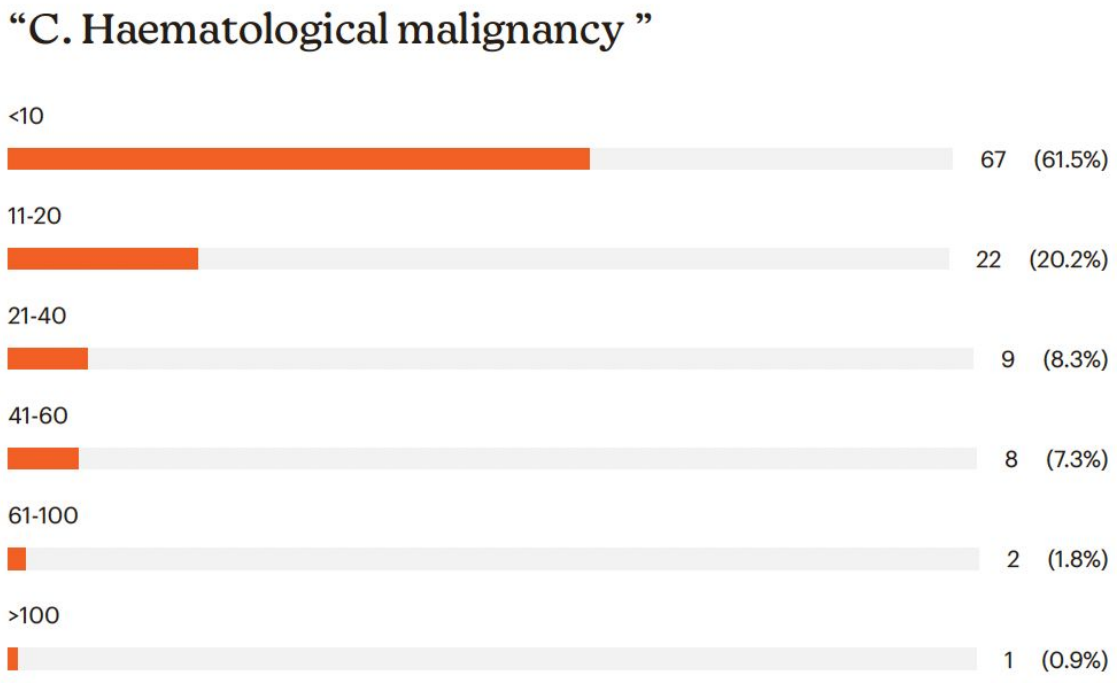
114 responders



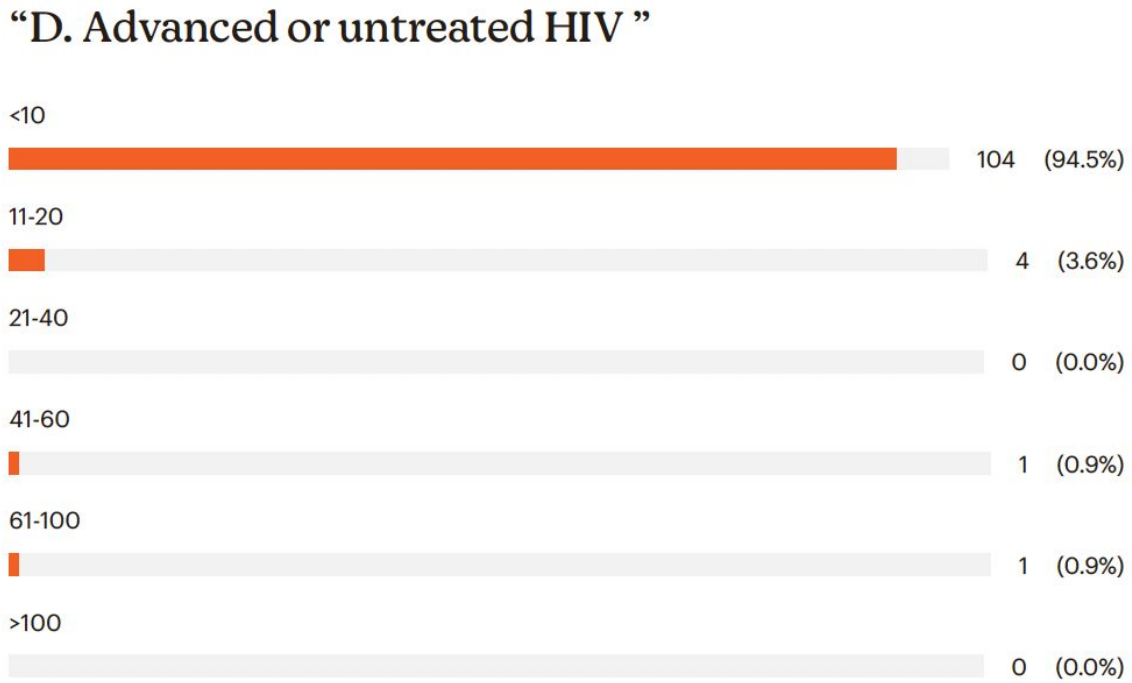
110 responders

Survey results

In those that have one of the 4 identified immunocompromising conditions, how many are eligible for a free Shingrix vaccine in your practice?



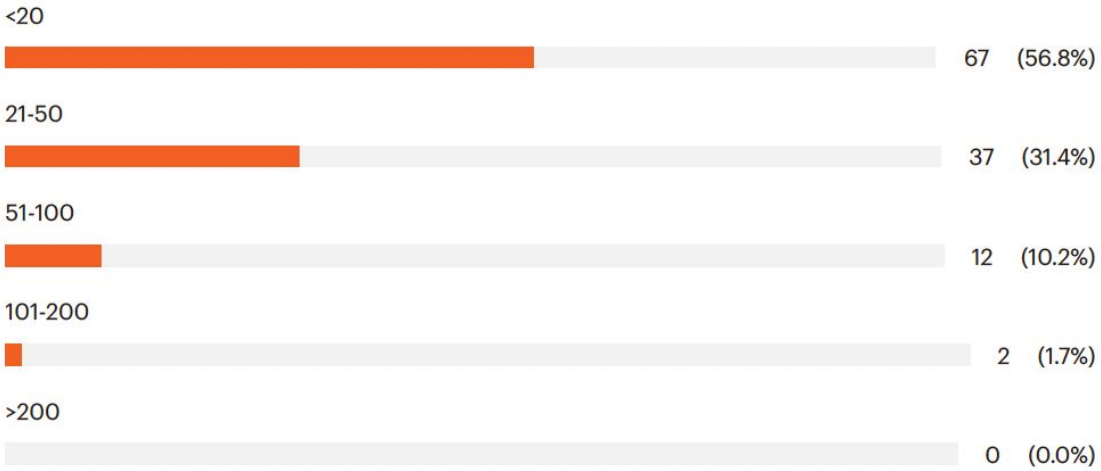
109 responders



110 responders

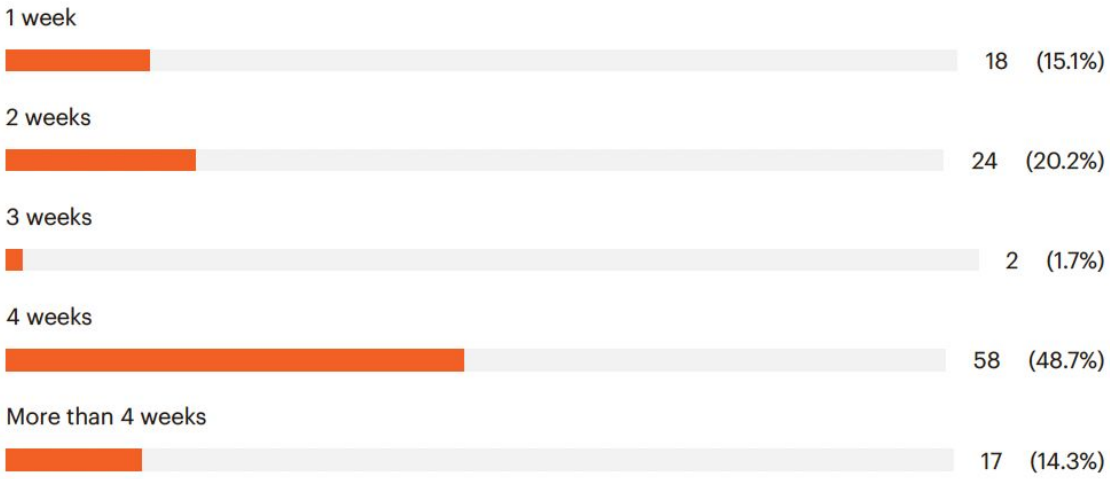
Survey results

"Q4. What is the maximum quantity of Shingrix vaccines that you can order at one time?"



118 responders

"Q5. What is the time interval before you can order the same amount of Shingrix again?"



119 responders

Q and A

ATAGI and NCIRS: FAQs for herpes zoster vaccination in adults aged ≥50 years of age

Can I vaccinate someone who has had shingles?	• The safety and immunogenicity of Zostavax® and SHINGRIX is similar between those with or without a past history of shingles.[1,2,3] • As the optimal time for vaccination following an episode of shingles is unknown, it is suggested that the vaccine be given at least 12 months after an episode of shingles.[1,2,3]
Can patients who have previously received Zostavax® receive SHINGRIX?	• Evidence in this population is limited, a single study identified no safety concerns when SHINGRIX was given >5 years earlier.[1-4] • In the absence of evidence to support a minimum interval, administration of SHINGRIX 12 months following receipt of Zostavax® is currently recommended.[1,2,3]
How should I vaccinate a patient with an immune-modulating condition?	• Refer to the NCIRS FAQ for guidance on vaccination of immunocompromised patients, including those receiving chemo/radiotherapies, DMARDs, corticosteroids, immune modulating therapies, blood products or those with HIV.[2]
Can SHINGRIX be given to people with immunocompromise?	• SHINGRIX is a non-live vaccine and is not contraindicated in immunocompromised patients.[2]

NCIRS=National Centre for Immunisation Research & Surveillance; ATAGI= Australian Technical Advisory Group for Immunisation; FAQ=frequently asked questions; HZ=herpes zoster; DMARD=disease-modifying antirheumatic drug; HIV=human immunodeficiency virus.

1. National Centre for Immunisation Research and Surveillance. Zoster vaccine for Australian adults - fact sheet. November 2021, http://www.ncirs.org.au/health-professionals/ncirs-fact-sheets-faqs.
2. National Centre for Immunisation Research and Surveillance. Zoster vaccines: Frequently asked questions. November 2021. **3.** Australian Technical Advisory Group for Immunisation. Statement on the clinical use of Zoster Vaccines in older adults in Australia. October 2021, Statement of the Clinical use of Zoster vaccines in older adults in Australia (health.gov.au). 4. Shingrix Australian Product Information

Does RZV increase the risk of Guillain-Barre syndrome (GBS)?

- Recent epidemiologic data suggested a potentially elevated risk of GBS following an episode of HZ in the U.S. adult population.[1]
  - relative incidence of GBS was increased during the 42-day risk window as compared to the primary control window (100–365 days after HZ) both for those:
    - 18–64 years (6.3; 95% CI, 1.8–21.9, *p* = .0035) and those ≥65 years (4.1; 95% CI, 1.9– 8.7, *p* = .0003)
- A subsequent CDC review[2] contrasted the incidence of GBS post zoster and compared this with the incidence of GBS post vaccination with RZV

RZV vaccination averted 43,000–63,000 cases of HZ, including GBS complications, per million vaccinated per 10-y age cohort compared to 3–6 additional cases of GBS projected following RZV per million vaccinated in the same

(b) Projected HZ cases averted compared to incremental GBS cases

		Incremental GBS cases (per million vaccinated)**		Averted HZ cases (per million vaccinated*)				
Age group (years)	Strategy	GBS (VSD)	GBS (FDA)	Uncomplicated	PHN	Ocular Complications	Deaths	Total HZ
50–59	Vaccinated	2.9	5.9	37,559	5,524	4,266	47	47,397
60–69	Vaccinated	2.6	5.6	46,648	9,350	5,544	62	61,604
70–79	Vaccinated	2.5	5.5	45,375	11,938	5,685	171	63,170
80–89	Vaccinated	2.6	5.6	39,774	12,421	5,178	155	57,528
90–99	Vaccinated	2.8	5.7	28,171	10,753	3,861	116	42,902

*Cases per million RZV vaccinated (1-dose or 2-dose series).
†Cases per cohort. Each cohort includes 1 million individuals, some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60–69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20-y time horizon.
**Cases of GBS|RZV + GBS|HZ per million RZV vaccinated (1-dose or 2-dose series).
HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine; VSD=Vaccine Safety Datalink; FDA=U.S. Food and Drug Administration.

1. Anderson Hum Vaccin Immunother. 2021 Dec 2;17(12):5304-5310
2. Janusz Hum Vaccin Immunother. 2022 Nov 30;18(5):2060668.

Is zoster associated with an increased risk of cancer?

- Taiwanese nationwide population-based matched-controlled prospective study using the National Health Insurance Research Database[1]:
  - adjusted HR: 1.68 (95%CI: 1.35-2.42) for lymphoid malignancies
- National Health Insurance Research Database in Taiwan, 35 871 patients with newly diagnosed herpes zoster during 2000-2008[2]
  - Patients with herpes zoster were not at increased risk of cancer (standardized incidence ratio 0.99, 95% CI 0.93-1.06)
- Netherlands ongoing GP-based morbidity registration network[3]
  - Hazard ratio (HR) in women >65 years of age for any malignancy, 1·82 (95% CI 1·25–2·66).
- Large UK primary care database containing the general practice information of over 3.6 million patients from 4450 practices; retrospective cohort study[4]
  - The hazard ratio for cancer diagnosis after zoster was 2.42 (95% CI 2.21, 2.66)
- Aust prospective cohort of 241497 adults, with mean age 62.0 years at recruitment (2006–2009), linked to health datasets from 2006 to 2015[5]
  - Compared to those without cancer, zoster risk was also elevated prior to a haematological cancer diagnosis (aHR for 1–2 years prior, 2.01 [95% CI, 1.31–3.09]
- Systematic RV (N=46 studies)[6]
  - pooled relative risk for any cancer was 1.42 (95% confidence interval: 1.18, 1.71) overall and 1.83 (95% confidence interval: 1.17, 2.87) at one year after zoster
  - highest estimates were generally reported for occult haematological cancer

1 Liu et al BMC Cancer 2012:12:503. 2. Wang et al CMAJ 2012 Oct 16;184(15):E804-9. 3. Buntinx et al Epidemiol Infect 2013: 1-10. 4. Cotton et al Br J Cancer 2013;108(3):721-6. 5. Qian J Infect Dis. 2019 Jun 5;220(1):3-11. 6, Schmidt J Infect. 2017 Mar;74(3):215-235.

Incidence of cancer associated with solid organ cancer and haematological malignancy

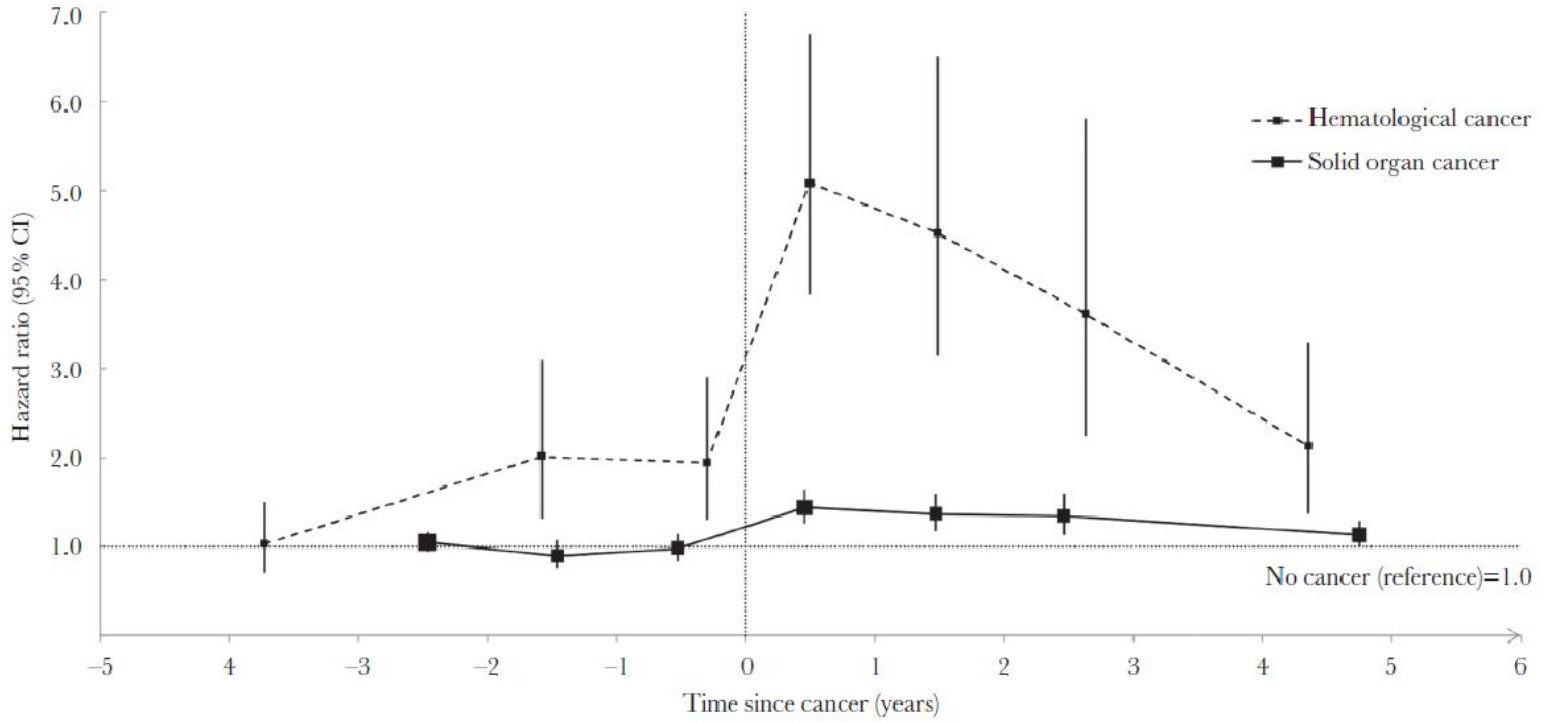


Figure 2. Adjusted hazard ratios (HRs) of herpes zoster by time before and after a cancer diagnosis. HRs are plotted according to the mean time in each category (see Methods). Person-years of reference group is 1 621 322, compared with 1 698 601 in other analyses due to follow-up time attributed to time before cancer. HRs are adjusted for age, sex, income, residence, marital status, private health insurance, smoking, cancer screening, supplement use, heart disease/stroke, asthma/hay fever, and physical limitations.

Qian J Infect Dis. 2019 Jun 5;220(1):3–11.

Does SARS-COV-2 increase the risk of zoster in subjects ≥ 50 years?

Increased Risk of Herpes Zoster in Adults ≥50 Years Old Diagnosed With COVID-19 in the United States

Amit Bhavsar,[1] Germain Lonnet,[2] Chengbin Wang,[3] Konstantina Chatzikonstantinidou,[4] Raunak Parikh,[1] Yves Brabant,[1] Nathalie Servotte,[1] Meng Shi,[3] Robyn Widenmaier,[3] and Emmanuel Aris[1]

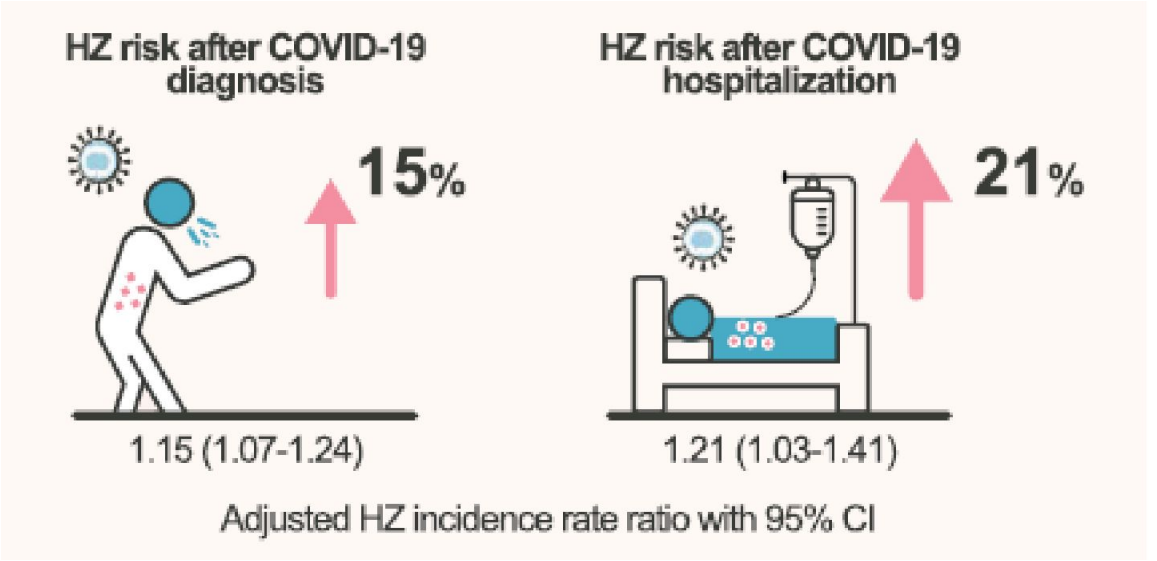
[1]GSK, Wavre, Belgium, [2]Business & Decision Life Sciences, Brussels, Belgium, c/o GSK, Wavre, Belgium, [3]GSK, Rockville, Maryland, USA, and [4]Aixial, an Alten Company, Brussels, Belgium, c/o GSK, Wavre, Belgium

Background. Case reports have described herpes zoster (HZ) in patients with coronavirus disease 2019 (COVID-19). However, this constitutes low-quality evidence for an association. We therefore performed a retrospective cohort study to assess the risk of developing HZ following a COVID-19 diagnosis.

Methods. We compared the HZ incidence in ≥50-year-olds diagnosed with COVID-19 vs those never diagnosed with COVID-19. We used data from the US MarketScan Commercial Claims and Encounters and Medicare Supplemental (3/2020–2/2021) and Optum Clinformatics Data Mart (3–12/2020) databases. Individuals with COVID-19 were exact-matched 1:4 to those without COVID-19 by age, sex, presence of HZ risk factors, and health care cost level. Adjusted incidence rate ratios (aIRRs) were estimated by Poisson regression.

Results. A total of 394 677 individuals ≥50 years old with COVID-19 were matched with 1 577 346 individuals without COVID-19. Mean follow-up time after COVID-19 diagnosis and baseline characteristics were balanced between cohorts. Individuals diagnosed with COVID-19 had a 15% higher HZ risk than those without COVID-19 (aIRR, 1.15; 95% CI, 1.07–1.24; $P < .001$). The increased HZ risk was more pronounced (21%) following COVID-19 hospitalization (aIRR, 1.21; 95% CI, 1.03–1.41; $P = .02$).

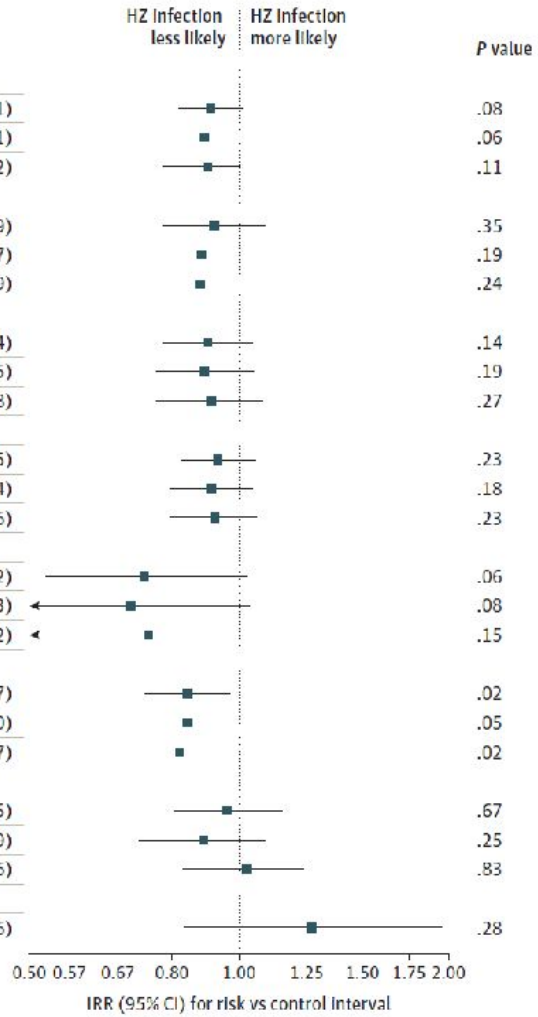
Conclusions. We found that COVID-19 diagnosis in ≥50-year-olds was associated with a significantly increased risk of developing HZ, highlighting the relevance of maintaining HZ vaccination.



Bhavsar Open Forum Infect Dis. 2022 Mar 9;9(5):ofac118.

Figure 2. Incidence Rate Ratio of Herpes Zoster After COVID-19 Vaccination With Subgroup Analyses

Subgroup	Total patients In subgroup	HZ cases in risk interval	IRR (95% CI)	P value
Overall				
Any dose	1451	891	0.91 (0.82-1.01)	.08
Dose 1	1019	459	0.89 (0.78-1.01)	.06
Dose 2	992	432	0.90 (0.78-1.02)	.11
Age <50 y				
Any dose	602	374	0.92 (0.78-1.09)	.35
Dose 1	419	191	0.88 (0.72-1.07)	.19
Dose 2	411	183	0.88 (0.72-1.09)	.24
Age ≥50 y				
Any dose	845	517	0.90 (0.78-1.04)	.14
Dose 1	600	268	0.89 (0.76-1.05)	.19
Dose 2	581	249	0.91 (0.76-1.08)	.27
Not immunocompromised				
Any dose	1305	811	0.93 (0.83-1.05)	.23
Dose 1	913	419	0.91 (0.80-1.04)	.18
Dose 2	886	392	0.92 (0.80-1.06)	.23
Immunocompromised				
Any dose	146	80	0.73 (0.53-1.02)	.06
Dose 1	106	40	0.70 (0.46-1.03)	.08
Dose 2	106	40	0.74 (0.49-1.12)	.15
BNT162b2 vaccine				
Any dose	789	468	0.84 (0.73-0.97)	.02
Dose 1	544	223	0.84 (0.70-1.00)	.05
Dose 2	566	245	0.82 (0.69-0.97)	.02
mRNA-1273 vaccine				
Any dose	575	373	0.96 (0.81-1.15)	.67
Dose 1	388	186	0.89 (0.72-1.09)	.25
Dose 2	389	187	1.02 (0.83-1.26)	.83
Ad26.COV2.S vaccine				
Dose 1	87	50	1.27 (0.83-1.96)	.28



Incidence rate ratios (IRRs), 95% CIs, and *P* values were calculated using conditional Poisson regression models. Age and immunocompromised status were determined at baseline before the first vaccine dose. Immunocompromising conditions included HIV or AIDS, cancer, solid organ transplant, systemic corticosteroid use, and immunosuppressive medication use. Individuals who received the Ad26.COV2.S vaccine, which has a 1-dose regimen, were included in the *any dose* and *dose 1* models but not in the *dose 2* models. Thus, the subgroup results for both models among individuals who received the Ad26.COV2.S vaccine were the same and are only presented once in the figure. HZ indicates herpes zoster. Markers indicate IRRs, and horizontal lines indicate 95% CIs.

Does getting a COVID vaccine increase the risk of zoster?

No increase in the risk of herpes zoster was found after a single dose or full (2-dose) primary series of a COVID-19 vaccine

0.91, (95%CI, 0.82-1.01) *P* = .08

Akpandak JAMA Netw Open. 2022 Nov 1;5(11)

Does SARS-COV-2 vaccination increase the risk (reactivation) of zoster?

Real-world evidence from over one million COVID-19 vaccinations is consistent with reactivation of the varicella-zoster virus

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[2]Institute of Pathology, Universitätsklinikum Leipzig, Universität Leipzig, Leipzig, Germany
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[4]Institute of Physiology and Science-IT, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
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Abstract

Background Reactivation of the varicella-zoster virus (VZV), which causes herpes zoster (HZ, synonym: shingles) in humans, can be a rare adverse reaction to vaccines. Recently, reports of cases after COVID-19 vaccination have arisen.

Objectives The aim of this study was to assess whether the frequency of HZ is found to increase after COVID-19 vaccination in a large cohort, based on real-world data. As a hypothesis, the incidence of HZ was assumed to be significantly higher in subjects who received a COVID-19 vaccine (Cohort I) vs. unvaccinated individuals (Cohort II).

Methods The initial cohorts of 1 095 086 vaccinated and 16 966 018 unvaccinated patients were retrieved from the TriNetX database and were matched on age and gender in order to mitigate confounder bias.

Results After matching, each cohort accounted for 1 095 086 patients. For the vaccinated group (Cohort I), 2204 subjects developed HZ within 60 days of COVID-19 vaccination, while among Cohort II, 1223 patients were diagnosed with HZ within 60 days after having visited the clinic for any other reason (i.e. not vaccination). The risk of developing shingles was calculated as 0.20% and 0.11% for cohort I and cohort II, respectively. The difference was statistically highly significant ($P \leq 0.0001$; log-rank test). The risk ratio and odds ratio were 1.802 (95% confidence interval [CI] = 1.680; 1.932) and 1.804 (95% CI = 1.682; 1.934).

Conclusions Consistent with the hypothesis, a higher incidence of HZ was statistically detectable post-COVID-19 vaccine. Accordingly, the eruption of HZ may be a rare adverse drug reaction to COVID-19 vaccines. Even though the molecular basis of VZV reactivation remains murky, temporary compromising of VZV-specific T-cell-mediated immunity may play a mechanistic role in post-vaccination pathogenesis of HZ. Note that VZV reactivation is a well-established phenomenon both with infections and with other vaccines (i.e. this adverse event is not COVID-19-specific).

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Hertel Journal of the Eur Acad Dermatol Venereol 2022 (Aug(

Does SARS-COV-2 vaccination increase the risk (reactivation) of zoster?

Herpes Zoster Reactivation After mRNA and Adenovirus-Vectored Coronavirus Disease 2019 Vaccination: Analysis of National Health Insurance Database

Jin Gu Yoon,[1,a] Young-Eun Kim,[2,a] Min Joo Choi,[3] Won Suk Choi,[4] Yu Bin Seo,[5] Jaehun Jung,[6] Hak-Jun Hyun,[1] Hye Seong,[1] Eliel Nham,[1] Ji Yun Noh,[1] Joon Young Song,[1] Woo Joo Kim,[1] Dong Wook Kim,[7] and Hee Jin Cheong[1,©]

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Background. Our study aimed to determine the risk of herpes zoster reactivation and coronavirus disease 2019 (COVID-19) vaccination (mRNA vaccine [BNT162b2] and adenovirus-vectored vaccine [ChAdOx1 nCoV-19]).

Methods. This retrospective study analyzed herpes zoster cases diagnosed between 26 February 2021 and 30 June 2021 and registered in the National Health Insurance Service database. A matched case-control study with a 1:3 matching ratio and a propensity score matching (PSM) study with a 1:1 ratio of vaccinated and unvaccinated individuals were performed.

Results. In the matched case control analysis, BNT162b2 was associated with an increased risk of herpes zoster reactivation (first dose adjusted odds ratio [aOR], 1.11; 95% confidence interval [CI], 1.06–1.15; second dose aOR, 1.17; 95% CI, 1.12–1.23). PSM analysis revealed a statistically significant increase in risk within 18 days following any vaccination (adjusted hazard ratio [aHR], 1.09; 95% CI, 1.02–1.16). BNT162b2 was associated with an increased risk at 18 days postvaccination (aHR, 1.65; 95% CI, 1.35–2.02) and second dose (aHR, 1.10; 95% CI, 1.02–1.19). However, the risk did not increase in both analyses of ChAdOx1 vaccination.

Conclusions. mRNA COVID-19 vaccination possibly increases the risk of herpes zoster reactivation, and thus close follow-up for herpes zoster reactivation is required.

Keywords. COVID-19 vaccination; herpes zoster; mRNA vaccines.

This retrospective study analyzed herpes zoster cases diagnosed between 26 February 2021 and 30 June 2021 and registered in the Korean National Health Insurance Service database
. A matched case-control study with a 1:3 matching ratio and a propensity score matching (PSM) study with a 1:1 ratio of vaccinated and unvaccinated individuals were performed.

BNT162b2 was associated with an increased risk at 18 days postvaccination (aHR, 1.65; 95% CI, 1.35–2.02) and second dose (aHR, 1.10; 95% CI, 1.02–1.19).

mRNA COVID-19 vaccination possibly increases the risk of herpes zoster reactivation

Table 4. Propensity Score Matching Analysis: Incidence, Relative Risk, and Absolute Risk Difference of Herpes Zoster Reactivation

Characteristic	Total No.	No. of Herpes Zoster Reactivations		*P* Value	Relative Risk	Absolute Risk Difference (Cases Per 100 000 People)
		Vaccinated	Unvaccinated			
All	2 993 584	5072 (0.17)	5272 (0.18)	.049	0.96	−6.7*
ChAdOx1 first dose	2 479 236	4149 (0.17)	4709 (0.19)	<.001	0.88	−2.3*
ChAdOx1 second dose	457 702	690 (0.15)	736 (0.16)	.223	0.94	−10.1
BNT162b2 first dose	653 585	1073 (0.16)	871 (0.13)	<.001	1.23	30.9*
BNT162b2 second dose	629 781	1353 (0.21)	1181 (0.19)	.001	1.15	27.3*
Age group, y						

Yoon J Infect Dis. 2023 Nov 11;228(10):1326-1335

Does SARS-COV-2 vaccination increase the risk (reactivation) of zoster?

Herpesviruses reactivation following COVID-19 vaccination: a systematic review and meta-analysis

Arman Shafiee[1,2], Mohammad Javad Amini[2], Razman Arabzadeh Bahri[3], Kyana Jafarabady[2], Seyyed Amirhossein Salehi[4], Hamed Hajishah[5] and Sayed-Hamidreza Mozhgani[6,7*]

Abstract

Background The reactivation of herpesviruses (HHV) in COVID-19 patients is evident in the literature. Several reports have been published regarding the reactivation of these viruses (HSV, VZV, EBV, and CMV) among those who got COVID-19 vaccines. In this study, we aimed to review the current evidence to assess whether HHVs reactivation has any association with the prior administration of COVID-19 vaccines.

Methods A systematic search was conducted on 25 September 2022 in PubMed/MEDLINE, Web of Science, and EMBASE. We included all observational studies, case reports, and case series which reported the reactivation of human herpesviruses following administration of COVID-19 vaccines.

Results Our systematic search showed 80 articles that meet the eligibility criteria. Among the evaluated COVID-19 vaccines, most of the vaccines were mRNA based. Evidence from observational studies showed the possible relation between COVID-19 vaccine administration and VZV and HSV reactivation. The results of our proportion meta-analysis showed that the rate of VZV reactivation among those who received the COVID-19 vaccine was 14 persons per 1000 vaccinations (95% CI 2.97–32.80). Moreover, our meta-analysis for HSV reactivation showed the rate of 16 persons per 1000 vaccinations (95% CI 1.06–46.4). Furthermore, the evidence from case reports/series showed 149 cases of I II IV reactivation. There were several vaccines that caused reactivation including BNT162b2 mRNA or Pfizer–BioNTech ($n=76$), Oxford AstraZeneca ($n=22$), mRNA 1273 or Moderna ($n=17$), Sinovac ($n=4$), BBIBP CorV or Sinopharm ($n=3$), Covaxin ($n=3$), Covishield ($n=3$), and Johnson and Johnson ($n=1$). Reactivated HHVs included varicella-zoster virus (VZV) ($n=114$), cytomegalovirus (CMV) ($n=15$), herpes simplex virus (HSV) ($n=14$), Epstein-Barr virus (EBV) ($n=6$), and HHV-6 ($n=2$). Most cases reported their disease after the first dose of the vaccine. Many patients reported having comorbidities, of which hypertension, diabetes mellitus, dyslipidemia, chicken pox, and atrial fibrillation were common.

Conclusion In conclusion, our study showed the possible association between COVID-19 vaccination and herpesvirus reactivation. The evidence for VZV and HSV was supported by observational studies. However, regarding other herpesviruses (EBV and CMV), further research especially from observational studies and clinical trials is required to elucidate the interaction between COVID-19 vaccination and their reactivation.

Keywords SARS-CoV-2, COVID-19, Vaccination, Herpesvirus, HHV

Conclusion

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Does herpes zoster increase the risk of dementia?

A Population-Based Danish Cohort Study used data from linked nationwide Danish registries to conduct a cohort study of the association between zoster and dementia during 1997–2017.

- Methods
  - Cohort included people aged ≥40 years with zoster and a general population comparison cohort matched 5:1 by sex and birth
  - Zoster and dementia were identified in the registries using prescription records in the community and hospital diagnoses
  - Cox regression was used to compute confounder-adjusted hazard ratios (HRs) with 95% CIs for dementia associated with zoster during 0–1 year and 1–21 years of follow-up.
- Results
  - Study included 247,305 people with zoster and 1,235,890 matched general population comparators
  - The hazard ration (HR) of all-cause dementia was 0.98 (95% CI 0.92–1.04) during the first year and 0.93 (95% CI 0.90–0.95) thereafter in people with zoster vs matched comparators.
  - Dementia was diagnosed in 9.7% of patients with zoster and 10.3% of matched comparators by the end of follow-up. Analyses of Alzheimer disease as a separate outcome showed similar results.
- Conclusion
  - HZ is not associated with an increased risk of dementia, but patients with CNS involvement had an almost 2-fold increased relative risk of dementia.
- A Taiwanese health insurance database had a slight increase in risk of dementia RR 1.11 (95%CI 1.04-1.17[2]
- In a UK primary care-based cohort in 'fit' subjects HZ was not associated with increased dementia diagnosis (adjusted HR 0.97, 95% CI 0.92–1.02).[3]

Mixed evidence that HZ is associated with an increased risk of dementia

1. Johannesdottir Schmidt Neurology. 2022 Jun 8;99(7):e660-8. 2. Chen J Clin Psychiatry. 2018 Jan/Feb;79(1):16. 3.Warren-Gash Ann Clin Transl Neurol. 2022 Mar;9(3):363-374.

Does receipt of the herpes zoster vaccine reduce the risk of dementia?

- Welsh cohort, discontinuity design, eligibility for the herpes zoster vaccine: pre vs post born September 2 1933[1]
  - Subjects born after Sept 2nd 1933 who received the herpes zoster vaccine (Zostavax):
    - reduced the probability of a new dementia diagnosis over a follow-up period of seven years by 3.5 percentage points (95% CI: 0.6 – 7.1, p=0.019), corresponding to a 19.9% relative reduction
    - protective effects from the Zoster vaccine for dementia were stronger among women than men.
- A related Welsh study[2] that included the complete population of Wales born after September 1, 1933 who were registered with a primary care provider (GP) reviewed the retrospectively collected national health data between 2013 and 2020 and analyzed the association of shingles vaccination with incident dementia
  - Vaccinated individuals were at reduced risk of dementia (adjusted hazard ratio: 0.72; 95% CI 0.69 to 0.75).
- A US DVA retrospective cohort study showed a similar level of reduced risk of dementia in subjects who had received a zoster vaccine
  - HZ vaccination was associated with a 31% lower risk for dementia HR 0.69 (95% CI 0.67-0.72)[3]

1. Eyting Med Rxiv 2023 preprint doi: https://doi.org/10.1101/2023.05.23.23290253;
2. Schnier Alzheimers Dement (N Y). 2022 Apr 13;8(1):e12293.
3. Scherrer PLoS One. 2021 Nov 17;16(11):e0257405

THANK YOU

- Professor John Litt and the audience for your engagement and questions.
- Again, the Q&As and webinar recording will be available next week via email.
- Our next webinar is on **28 November - Online Peer Learning: Travel Vaccination in General Practice**
  This webinar will be CPD accredited for Reviewing Performance with patient cases chaired by Dr Anita Munoz – A GP Educator.
- First event in 2024: **25th ASM on 4-5 February**
  Details can be found on our website: www.immunisationcoalition.org.au

Good night, stay safe!