

# Update on Zoster

Associate Professor John Litt  
Flinders University

# Conflict of Interests

- Member of various Immunisation Advisory Boards
  - Seqirus,
  - Sanofi
  - Astra Zeneca

# Overview

## **Zoster: prevalence and burden of illness**

### **Zoster**

- Burden of illness and complications
- Treatment versus vaccination
- Efficacy/safety of ZOSTAVAX
- Zostavax in groups with immunocompromise

### **Practical aspects of adult vaccination**

- Strategies to improve uptake/coverage
- **Frequently asked questions**

# Addition of ZOSTAVAX to the NIP from 1<sup>st</sup> November 2016

Disease	Age group	Vaccine brands
Influenza	65 years and over	Fluad, Fluvax, FluQuadri, Fluarix Tetra Agrippal, Fluarix, Influvac, Vaxigrip
Pneumococcal disease	65 years and over 50 years and over (Aboriginal and Torres Strait Islander peoples)	Pneumovax 23 Prevnar 13
Herpes-zoster (shingles)	70-79 years <sup>^</sup>	Zostavax

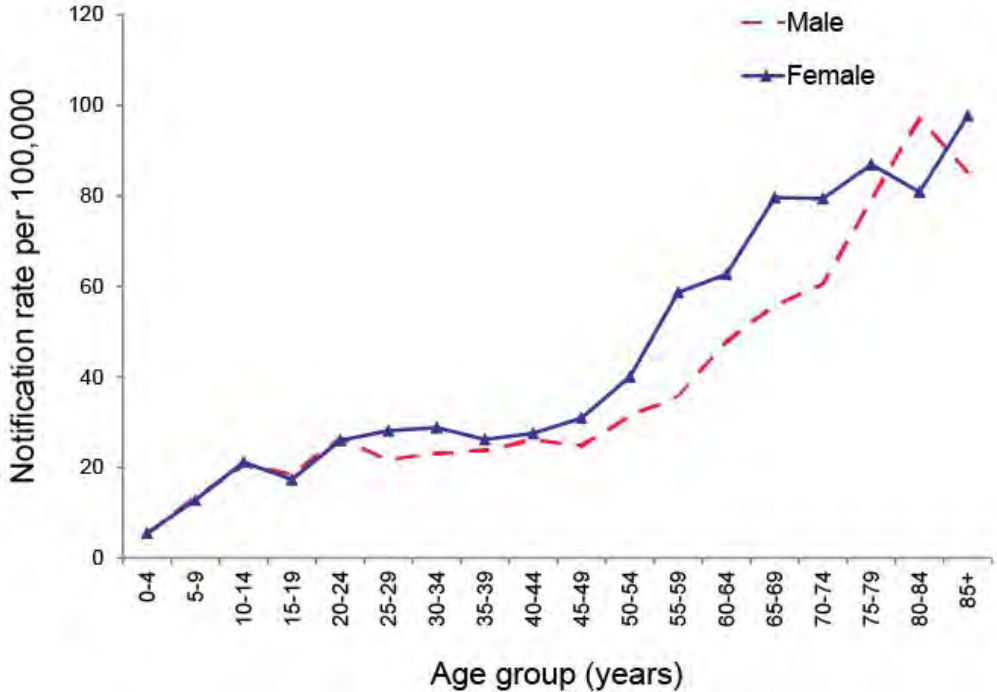
<sup>^</sup>Zostavax provided free for 70 year olds, with a catch-up program for 71-79 year olds

\*People over 65 years are also advised to have dTpa, a diphtheria-tetanus-whooping cough booster, if they have not received one in the previous 10 years, although this is not funded under the NIP.

# Shingles in Australia

Can we achieve shingles vaccine coverage comparable to flu vaccine coverage?

Notification rate for shingles, Australia,\* 2014, by age group and sex†1

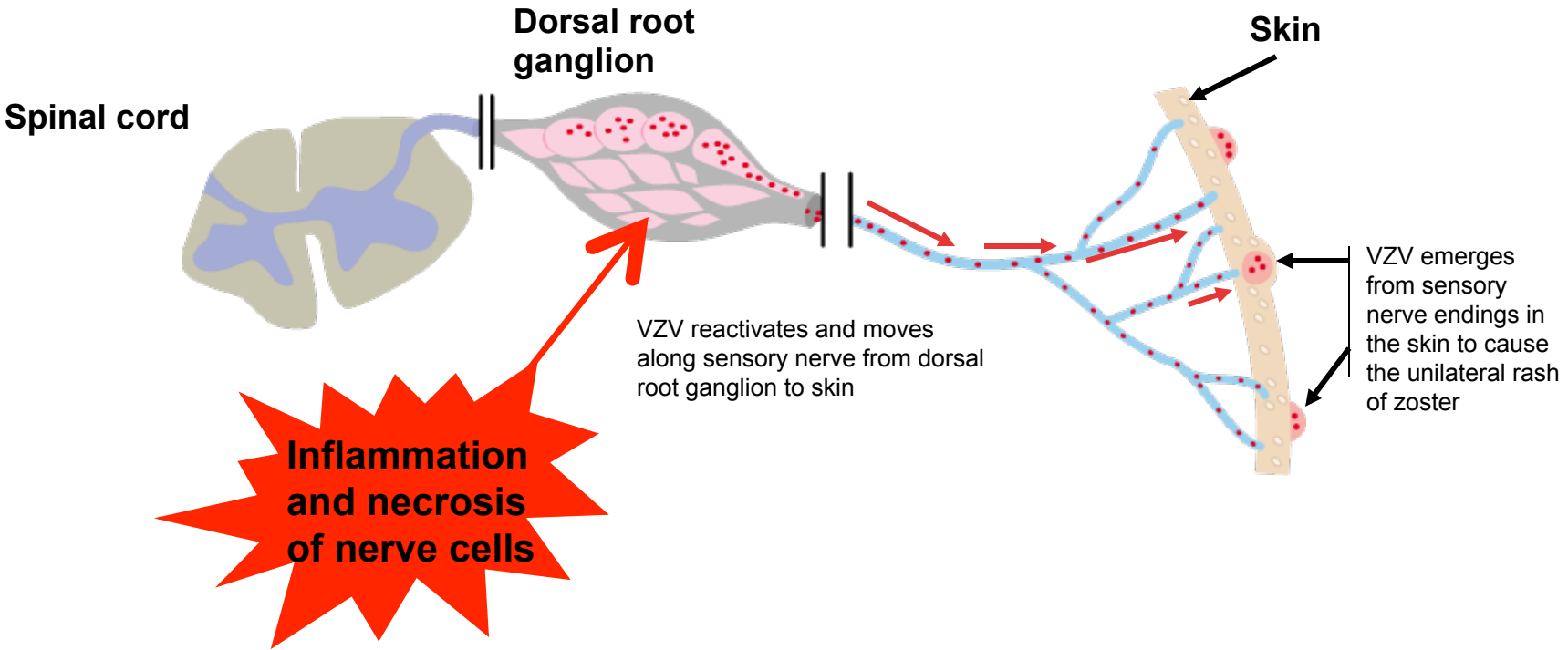


\*Excludes NSW

†Age of onset missing for 59 notifications and sex missing for 1 notification.

1. NNDS,S Commun Dis Intell 2016;40:E48-E145.

# VZV: REACTIVATION



# ZOSTER: CLINICAL FEATURES, RASH

- **Vesicular, “grape-like” lesions clustered on an erythematous base**
- **Unilateral distribution in 1-2 adjacent sensory dermatomes**
  - **Thoracic dermatome (~50-70%)**
  - **Cervical dermatome or ophthalmic branch of trigeminal (each ~10-20%)**
- **Vesicles crust in 7-10 days; full healing may take up to 1 month**

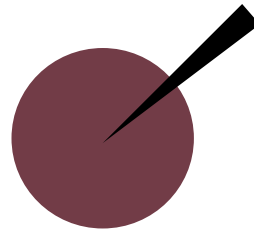


# The risk of developing shingles is unpredictable<sup>1</sup>



**97% of adults** have the virus that causes shingles within them<sup>1</sup>

40% of people age 70-79 years will develop Shingles



**4% of adults aged 60+** believe they are at high risk of developing shingles<sup>2</sup>

Less than 1 in 5 older adults believe they are likely or very likely to get shingles<sup>3</sup>

- 1. Stein AN *et al. Vaccine* 2009,24:520-29 . 2. Shingles Study 150930 n=1,025. Seqirus data on file. September 2015. 12:92. 3.
- Litt JCB, *et al. Int J Infect Diseases* 2014; 21:436-7

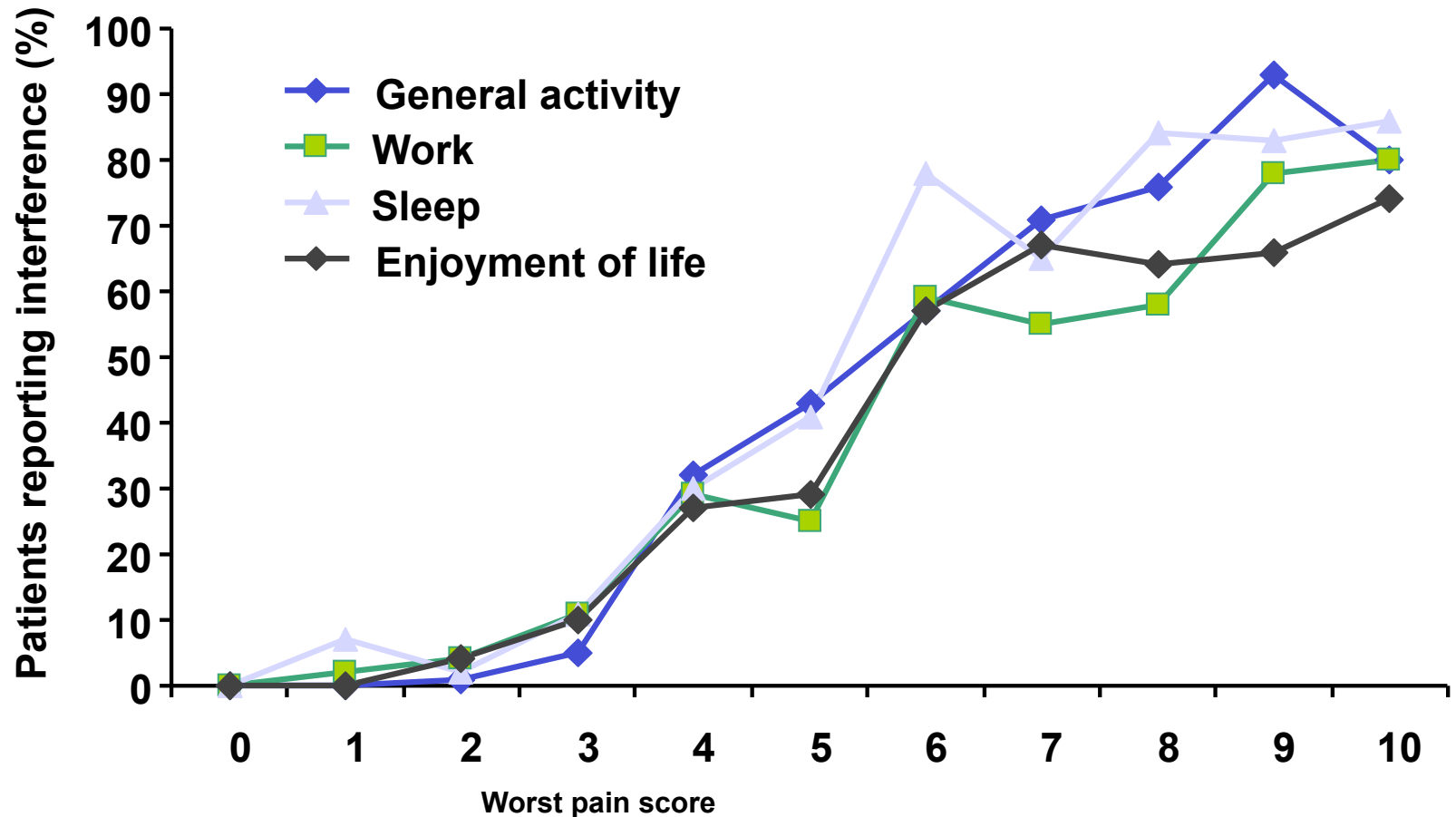


# Risk factors for Zoster<sup>1-5</sup>

- Increasing age
- Female
- Family history
- Stress
- stress in the 3 months before HZ to be a risk factor, but there was no evidence of a dose response
- People with compromised or suppressed immune systems who have an increased risk for herpes zoster include those:
  - with cancer, especially leukemia and lymphoma,
  - with human immunodeficiency virus,
  - who have undergone bone marrow or solid organ (renal, cardiac, liver, and lung) transplantation, or
  - who are taking immunosuppressive medications, including steroids, chemotherapy, or transplant-related immunosuppressive medications.

Thomas & Hall Lancet Infect Dis 2004;4(1):26-33;. 2. Liesegang et al Curr Opin Ophthalmol 2004;15:531-6: 3. Donohue et al Arch Int Med 1995;155(15):1605-9; 4. Gershon et al J Clin Virol 2010; 48: suppl2-7. 5. Marin et al United States Open Forum Infect Dis. 2016 Jun 11;3(3)

# EFFECT OF SHINGLES PAIN ON DAILY LIVING ACTIVITIES



# Shingles complications can be serious<sup>1</sup>

Shingles pain can be excruciating, described as stabbing and burning

## Ophthalmic zoster

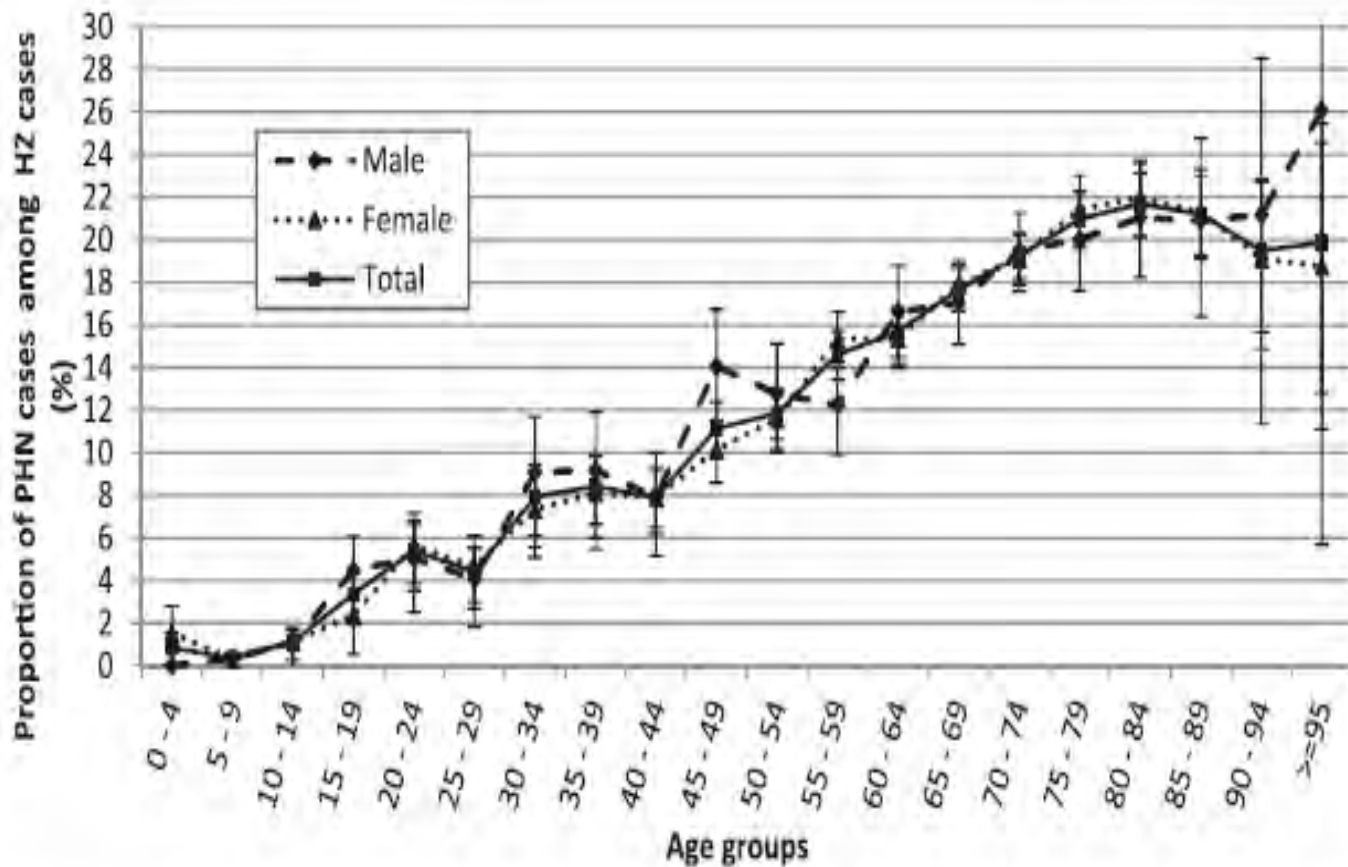
- Occurs in up to 25% of shingles cases<sup>1</sup>
- Complications may include facial scarring and loss of vision<sup>1,2</sup>



## Stroke Risk

- Shingles may also increase the risk of stroke in the following 6 months<sup>3</sup>
- There is a 63% higher risk in the 4 weeks after shingles vs. baseline period<sup>3</sup>

# Incidence of PHN



**Figure 3** Proportion of PHN cases among all HZ cases by 5-year age groups and sex in 2009.

# RISK FACTORS FOR PHN<sup>1-2</sup>

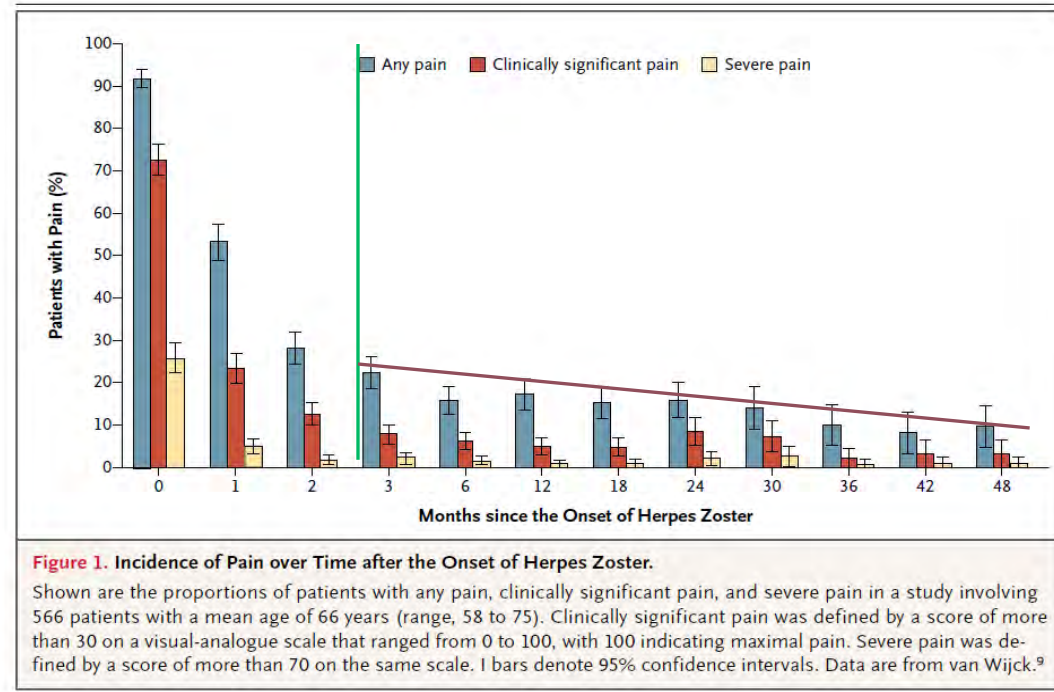
- Advancing age
- Prodromal pain
- Greater severity of acute pain
- Greater rash severity
- Greater degree of sensory impairment in the affected dermatome
- No clear evidence for gender, immune compromise, or dermatome affected
- No evidence of higher PHN with depression or cancer

Up to 20% of adults may develop postherpetic neuralgia (PHN)<sup>3</sup>

1. Thomas and Hall Lancet Infect Dis. 2004 Jan;4(1):26-33.
2. Forbes et al. Pain 2015;157 : 30–54

# POSTHERPETIC NEURALGIA (PHN)<sup>1-3</sup>

- 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
- PHN patients report experiencing pain in the area of their shingles rash for an average of 3.5 years<sup>3</sup>



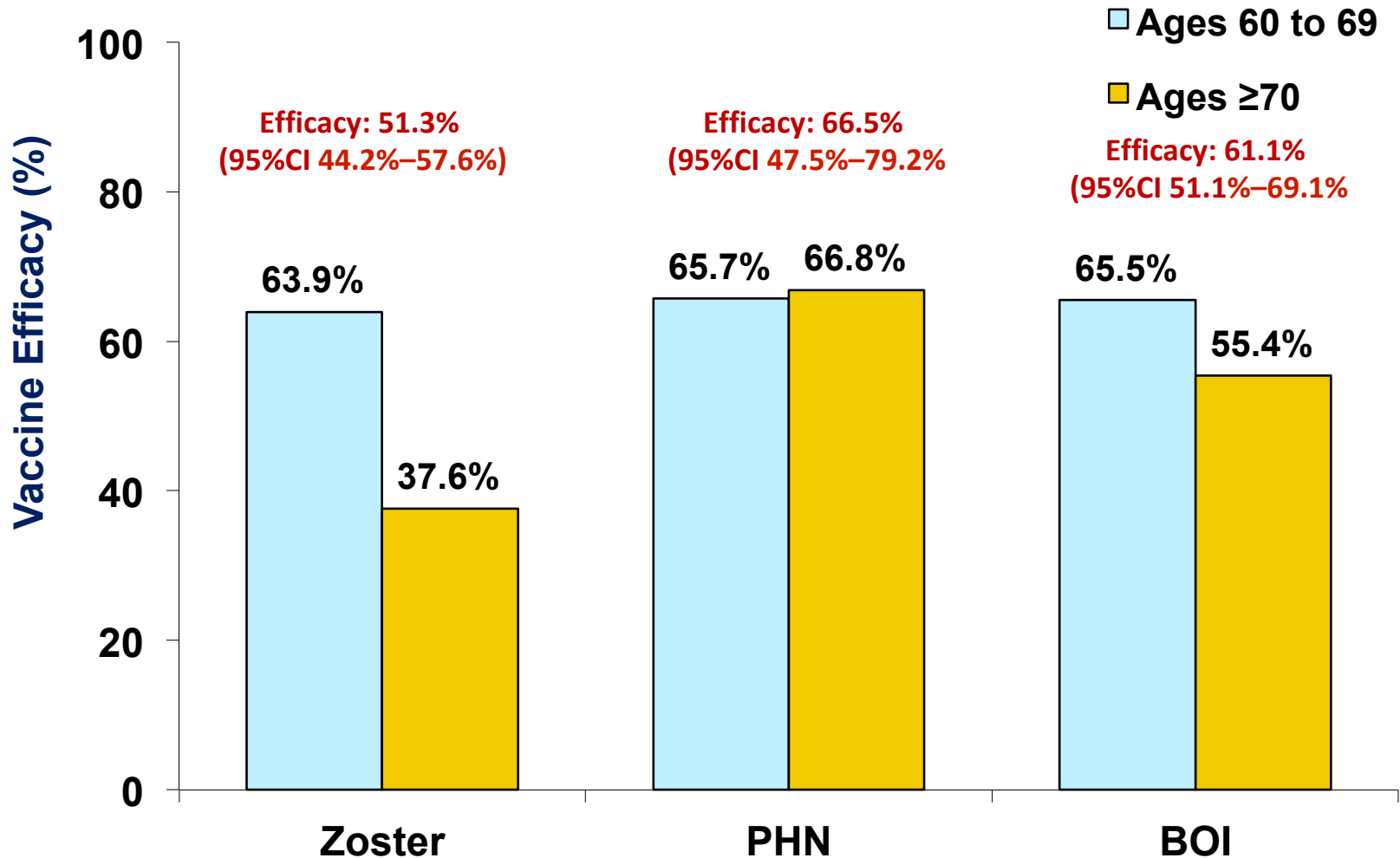
1. Johnson et al NEJM 2014; 371(16):1526-33

2. Schmader CID 2001; 32(10):1481-6

3. Chen May Clin Proc 2004; 79 (12):1533.. Serpell M et al. Health Qual Life Outcomes 2014; 12: 9

Prevention

# Summary: SPS Efficacy of the Zoster Vaccine by Age Stratum

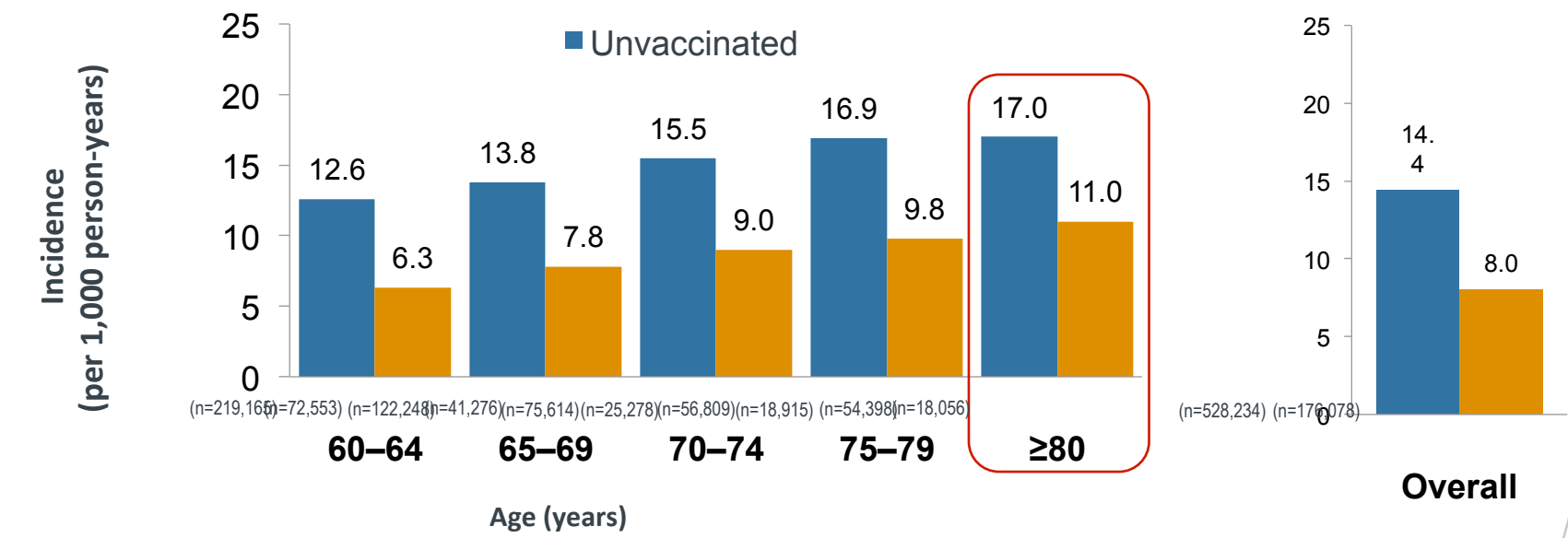




# Effectiveness of ZOSTAVAX<sup>®</sup> in Adults Aged ≥60 Years (2007-2015)

**Incidence of HZ in a large US retrospective cohort study<sup>1</sup>**

Effectiveness*	<b>56%</b>	<b>48%</b>	<b>47%</b>	<b>47%</b>	<b>42%</b>	<b>49%</b>
(95% CI)	(53%–59%)	(44%–52%)	(43%–51%)	(42%–52%)	(36%–47%)	(48%–51%)



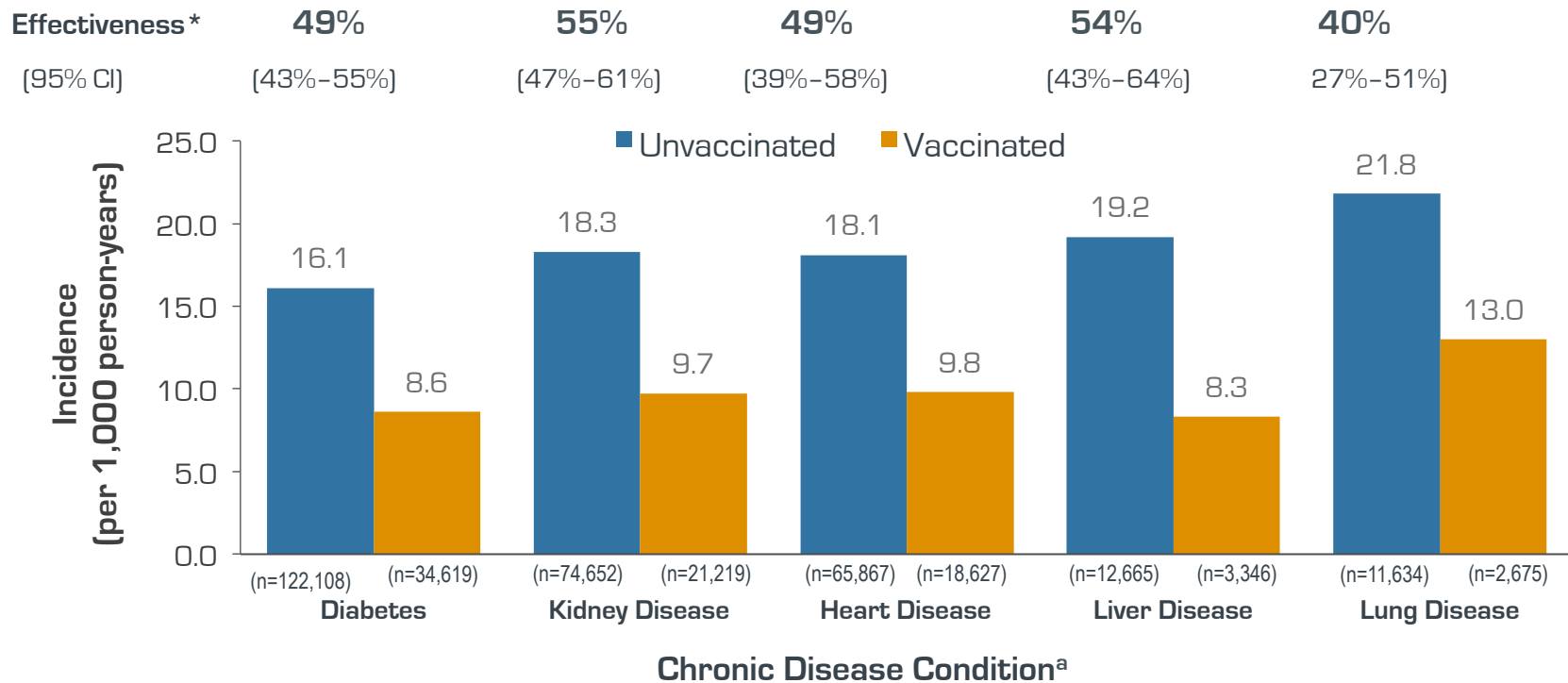
Survey of the electronic records of 176 078 vaccinated and 528 234 unvaccinated members of Kaiser Permanente Southern California (KPSC). The vaccinated cohort had been vaccinated against HZ between 1 January 2007 and 31 December 2014 at the age of ≥60 years. Unvaccinated cohort consisted of randomly sampled members who were matched at a ratio of 3:1 to the vaccinated cohort. Electronic medical records were used to identify episodes of HZ.

\*Calculated vaccine effectiveness is adjusted for age, sex, race/ethnicity, healthcare utilization, length of membership prior to index date, and chronic disease. CI=confidence interval; HZ=herpes zoster.

1. Tseng HF et al. *J Infect Dis*. First published online February 9, 2016. doi:10.1093/infdis/jiw047.

# Effectiveness of ZOSTAVAX<sup>®</sup> in Adults Aged ≥60 Years with Chronic Disease Conditions. KPSC (2007-2015)

## Incidence of HZ in a chronic conditions cohort<sup>1</sup>



Survey of the electronic records of 176 078 vaccinated and 528 234 unvaccinated members of Kaiser Permanente Southern California (KPSC). The vaccinated cohort had been vaccinated against HZ between 1 January 2007 and 31 December 2014 at the age of ≥60 years. Unvaccinated cohort consisted of randomly sampled members who were matched at a ratio of 3:1 to the vaccinated cohort. Electronic medical records were used to identify episodes of HZ.

\*Calculated vaccine effectiveness is adjusted for age, sex, race/ethnicity, healthcare utilization, length of membership prior to index date, and chronic disease.

<sup>a</sup>Patients could have more than 1 co-morbid chronic disease.

CI=confidence interval; HZ=herpes zoster.<sup>1</sup> Tseng HF et al. *J Infect Dis*. First published online February 9, 2016. doi:10.1093/infdis/jjw047.

# ZOSTAVAX is contraindicated in patients with:

- History of hypersensitivity to any component of the vaccine.
- History of anaphylactic/anaphylactoid reaction to neomycin
- Primary and acquired immunodeficiency states  
e.g. leukemia, lymphoma, conditions affecting the bone marrow or lymphatic system, immunosuppression due to HIV/AIDS, cellular immune deficiencies
- Immunosuppressive therapy (including high-dose corticosteroids)
- Active untreated tuberculosis
- Pregnancy

# Persons significantly immunocompromised should not receive ZOSTAVAX

Unless a contraindication or precaution exists, ZOSTAVAX may be given to patients receiving

- topical/inhaled corticosteroids,
  - low-dose systemic corticosteroids or
  - corticosteroids as replacement therapy, e.g. for adrenal insufficiency
- Contraindicated in those with a disease that suppresses immunity
    - One death in Australia from Zostavax in such a case
  - HCWs should seek Specialist advice for immunocompromised patients

Anti-TNF	Etanercept Infliximab	NONE	Vaccinate 1 month before treatment initiation <b>OR</b> 12 months after treatment cessation
IL-1 inhibition	Anakinra		
Costimulation blockade	Abatacept		
B-cell depletion/ inhibition	Rituximab		
Immunomodulators (antimetabolites)	Azathioprine 6-mercaptopurine Methotrexate	$\leq 3.0$ mg/kg/day $\leq 1.5$ mg/kg/day $\leq 0.4$ mg/kg/week	If on higher dose, vaccinate 1 month before treatment initiation <b>OR</b> 3 months after treatment cessation
Corticosteroids	Prednisone	<20 mg/day	If $\geq 20$ mg/day for <14 days, vaccinate 1 month before treatment initiation <b>OR</b> any time after treatment cessation  If $\geq 20$ mg/day for $\geq 14$ days, vaccinate 1 month before treatment initiation <b>OR</b> 1 month after treatment cessation
T-cell activation/ inhibition	Tacrolimus Cyclosporine	NONE	Vaccinate 1 month before treatment initiation <b>OR</b> 3 months after treatment cessation
Others	Cyclophosphamide Mycophenolate		

\* NOTE: This is not a complete list of all licensed biologics, or medications within each class, but serves as a guide only.

\*\* Refer to The Australian Immunisation Handbook 10th edition, Chapters 3.3.3 and 4.24.

1. NCIRS Fact Sheet. Zoster vaccine – Frequently Asked Questions Dec 2017. Available at: <http://ncirs.edu.au/provider-resources/ncirs-fact-sheets/> Accessed February 2018.

Immunosuppressive condition or agent	Examples*	Safe dose**	Comments
Sulfasalazine		ANY DOSE	Provided patient is not taking other immunosuppressives or has no immunosuppressive condition
HIV infection	CD4 T cells < 350/ $\mu$ L or CD4 T cells <15% of total lymphocytes*	NONE	Serologic confirmation of previous varicella-zoster viral infection must be obtained prior to vaccination.
Chemotherapy/ Radiotherapy		NONE	At least six months after the end of treatment AND after patients are demonstrated to be in remission.
Chronic lymphocytic leukaemia	Alkylating agents e.g. chlorambucil, cyclophosphamide; monoclonal antibodies e.g. rituximab, ofatumumab, obinutuzumab	NONE	Haematological malignancy is an absolute contraindication to live vaccination, regardless of therapy (even if no therapy is given).

Table prepared from information available in NCIRS Factsheet, Zoster Vaccine FAQ, 2017 and adapted from Litt et al. 2017.<sup>1,2</sup>

\*The safety of administering the Herpes zoster vaccine should always be considered on a case-by-case basis. If there is uncertainty about the degree of immunocompromise and when vaccine administration may be safe, vaccination should be withheld and expert advice sought from the treating physician and/or an immunisation specialist.

\*\* Refer to The Australian Immunisation Handbook 10th edition, Chapters 3.3.3 and 4.24.

1. NCIRS Fact Sheet. Zoster vaccine – Frequently Asked Questions (FAQ), Updated Dec 2017. Available at: <http://ncirs.edu.au/provider-resources/ncirs-fact-sheets/Accessed February 2018>. 2. Litt JCB, Cunningham, T, Van Buynder, P, et al. Update on Herpes Zoster. Health Ed 2017.

# ZOSTAVAX is generally well tolerated

- In clinical trials, ZOSTAVAX has been evaluated for safety in more than 32,000 adults 50 years of age and older
- Injection site reactions are the most common side effect
  - Erythema, pain/tenderness, swelling and pruritus have been reported very commonly in clinical trials
- Headache and fatigue are the most frequent systemic side effects
- Over 33 million doses of ZOSTAVAX have been distributed worldwide since 2006
- Results from “real world” postmarketing safety studies support the safety profile seen in clinical trials

# FREQUENTLY ASKED QUESTIONS

- What other vaccines can be administered at the same time as Zostavax?
  - Influenza vaccine <sup>1</sup>                      yes
  - ADT (tetanus)                              no data but Immunisation handbook says yes
  - Pneumococcal vaccine<sup>2</sup>                  unclear: Sequris PI says no; Immunisation handbook says yes; consider separating by 4 weeks.

1. Kerzner et al J Am Geriatr Soc 2007;55(10):1499-1507.

2. MacIntyre et al Hum Vac 2010; 6(11):894-902. Tseng et al Vaccine 2011;29(20):3628-32



# ZOSTAVAX dosage and administration

- Individuals 50 years of age and older should receive a single dose (0.65mL) of the vaccine subcutaneously
- Reconstitute immediately after removal from the fridge
- Administer the vaccine immediately after reconstitution (discard if not used within 30 minutes)

Refer to product information for further information



# FREQUENTLY ASKED QUESTIONS

- Is giving Zostavax to a person with a previous history of shingles associated with a higher local adverse event rate?<sup>1</sup>
- No
  - SPS placebo group offered Zostavax at the end of the SPS study
  - The proportion of vaccinated SPS placebo recipients with prior HZ who developed  $\geq 1$  SAE (0.95%) was not significantly different from that of vaccinated SPS placebo recipients with no prior history of HZ (0.66%),
  - The distribution of SAEs in the 2 groups was comparable

# FREQUENTLY ASKED QUESTIONS

Is zoster associated with an increased risk of cancer?

- Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis
- 46 eligible studies, 10 of which considered all cancer types combined.
- The 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 hematological cancer
- The absolute risk of any cancer at one year after presentation with zoster was 0.7-1.8%.
- Conclusion: *low absolute risk of cancer limits the clinical implications.*
- ['Herpes zoster could thus be a marker of impaired immunologic surveillance in the host, resulting also in the development of cancer']

# FREQUENTLY ASKED QUESTIONS

- Is there evidence of Zostavax effectiveness in subjects 50-59yrs?
- YES
  - ZEST RCT:
    - Randomized (1:1), multicenter, double-blind, placebo-controlled study
    - 22,439 varicella history-positive, HZ history-negative, 50 to 59 years of age

## FREQUENTLY ASKED QUESTIONS

What is the real-world impact of Zostavax?

### Herpes Zoster Vaccine in Older Adults and the Risk of Subsequent Herpes Zoster Disease

**Table 2.** Comparison of Herpes Zoster Incidence in Study Cohorts by Herpes Zoster Vaccination Status

Characteristic	Vaccinated (n = 75 761)				Unvaccinated (n = 227 283)				Rate Ratio (95% CI)	P Value
	No. of Participants	No. of Cases	Total No. of Person-years	Incidence/1000 Person-years (95% CI)	No. of Participants	No. of Cases	Total No. of Person-years	Incidence/1000 Person-years (95% CI)		
Age of participants, y										
60-64	23 195	204	38 405	5.3 (4.6-6.1)	69 585	1027	105 700	9.7 (9.1-10.3)	0.55 (0.47-0.64)	<.001
65-69	20 166	197	34 975	5.6 (4.9-6.5)	60 498	1206	94 835	12.7 (12.0-13.5)	0.44 (0.38-0.52)	<.001
70-74	15 426	202	27 635	7.3 (6.3-8.4)	46 278	1090	74 532	14.6 (13.8-15.5)	0.50 (0.43-0.58)	<.001
75-79	10 978	146	19 894	7.3 (6.2-8.6)	32 934	824	54 074	15.2 (14.2-16.3)	0.48 (0.40-0.58)	<.001
≥80	5996	79	9506	8.3 (6.6-10.4)	17 988	459	26 518	17.3 (15.8-19.0)	0.48 (0.38-0.61)	<.001

increased with age  
(80 years vs 60-64years:HR,1.45;95%CI,1.30-1.63)

Overall	75 761	828	130 415	6.4 (5.9-6.8)	227 283	4606	355 659	13.0 (12.6-13.3)	0.49 (0.46-0.53)	<.001
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Hazard Ratio (95% Confidence Interval)

Unadjusted

0.49 (0.46-0.53)

Adjusted<sup>a</sup>

0.45 (0.42-0.48)

Tseng et al. *JAMA* 2011;305(2):160-166

**VE: 55%**

# HZ/su Vaccine

- Herpes zoster subunit vaccine (HZ/su) - SHINGRIX<sup>1</sup>
  - Contains AS01<sub>B</sub> adjuvant designed to increase vaccine immunogenicity
- IM injection given as 2 doses 2 months apart (no efficacy data published for single dose)
- Efficacy and safety tested in two large phase 3 trials (ZOE-50 and ZOE-70)<sup>1,2</sup> which showed an overall vaccine efficacy of:
  - **97.2% (95% CI, 93.7 to 99.0; P<0.001 vs placebo)** in age group ≥50 years<sup>1</sup>
  - **89.8% (95% CI, 84.2 to 93.7; P<0.001 vs placebo)** in age group ≥70 years<sup>2</sup>
  - **91.3% (95% CI, 86.8 to 94.5; P<0.001 vs placebo)** in age group ≥70 years (pooled results from ZOE-50 and ZOE-70)<sup>2</sup>

1. Lal et al NEJM 2015; 372: 2087-96. 2. Cunningham et al NEJM 2016; 375: 1019-12. 3. US Food and Drug Administration. Shingrix BLA Approval letter. Available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581750.pdf>

# HZ/su Vaccine

- Duration of protection
  - 2 doses of HZ/su induced robust humoral and cellular immune responses in all age groups (especially people  $\geq 70$  years) that remained substantially above baseline 3 years after vaccination<sup>1</sup>
- Safety
  - No safety concerns related to vaccination were identified<sup>2,3</sup>
- Adverse reactions
  - HZ/su vaccine was more reactogenic\*<sup>1</sup> than placebo with a high local and systemic reaction rate
  - Solicited injection site reactions (81.5% vs 11.9%)
  - 1 in 8 stating it was severe enough to prevent normal activities
  - Likely due to the adjuvant & may affect acceptance of second dose
- Systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) (53% vs 25%) HZ/su group vs placebo

\*Most common reactions were pain at injection site and myalgia<sup>1</sup>

1.. Cunningham et al J Infect Dis. 2018 May 5;217(11):1750-1760 .2. Lal et al NEJM 2015; 372: 2087-96. 3. Cunningham et al NEJM 2016; 375: 1019-12.

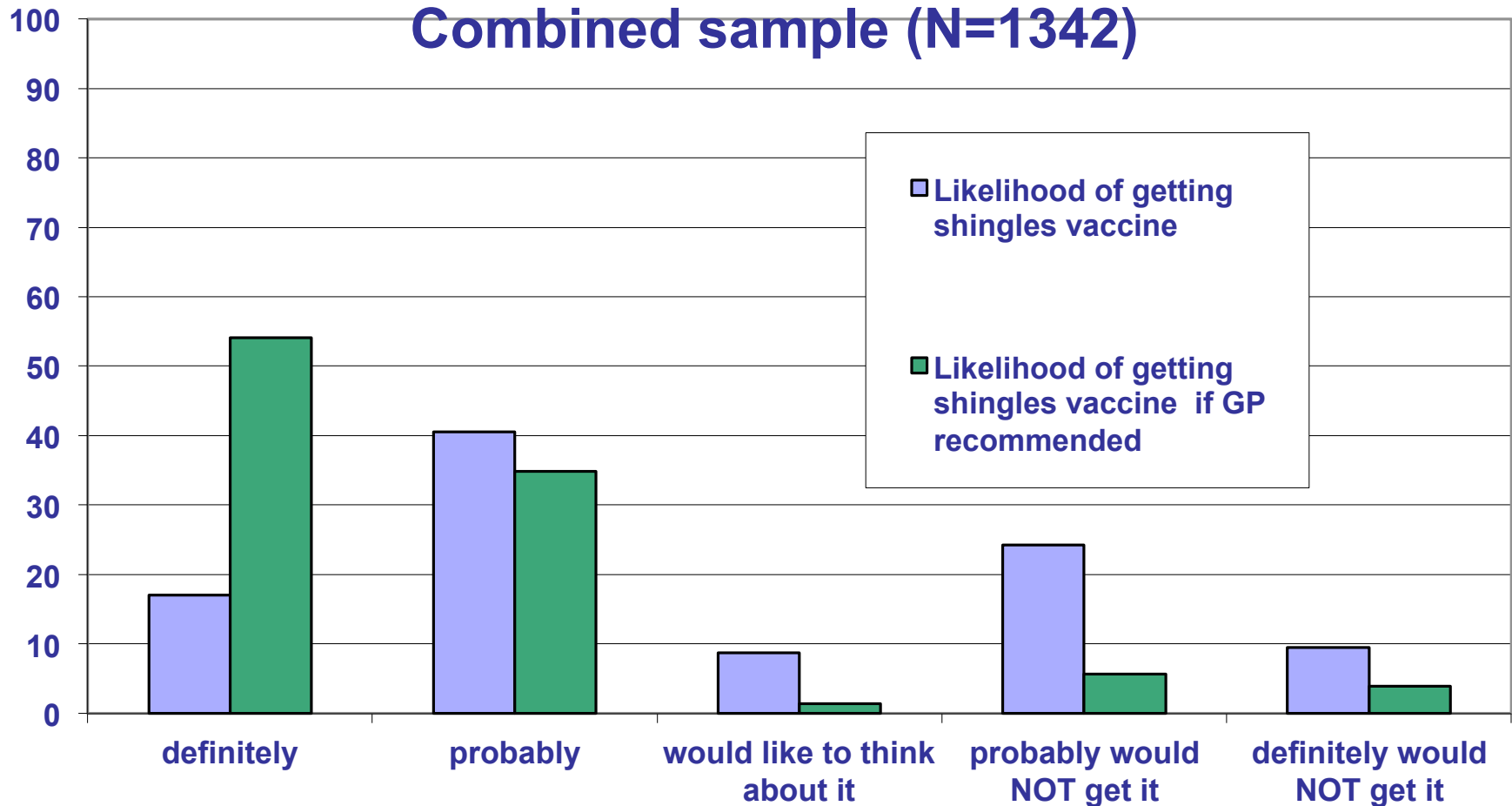
# Strategies to Implement vaccination programs in practice



# Zostavax in the cohort 70-79 years: a good news story

- By May 2017 66% of the nearly 1,200,000 doses of Zostavax needed to immunize 70-79 year olds were distributed to the states and territories
  - 55% of those doses either in GP and other vaccination centre fridges or administered
- Australia leads the way in shingles vaccination coverage in this age group
- How can we achieve similar results with other adult vaccines?

# IMPACT OF GP RECOMMENDATION ON VAX INTENTION



Litt JCB, et al. *Int J Infect Diseases* 2014; 21:436-7

# Factors increasing zoster vaccine uptake

Increase zoster vaccine uptake			Reference
Demographic	Age	older	(18-23)
	Gender	female	(19-22)
	Level of education	higher	(18-23)
Health knowledge and behaviour	Other vaccines	Regularly get influenza or pneumococcal vaccines	(19, 20, 22, 24)
	Awareness about shingles and the zoster vaccine	Higher awareness	(20-27)
Beliefs about shingles	Belief zoster can be a severe condition	Agree	(20, 25)
Health care provider	Has a usual GP	Yes	(24)
	GP recommendation to get the zoster vaccine	Strong recommendation	(20-25, 28)
Other	Family or friends	Have previously been affected with Shingles or PHN	(20, 24, 26)
	Availability of the zoster vaccine	Available	(21)

# Factors decreasing zoster vaccine uptake

## Reduce Zoster vaccine uptake

<b>Beliefs about shingles or immunity</b>	Risk of getting shingles	Low perceived risk	(20-23, 25)
	Vaccine not needed rarely get sick	Agree	(21, 22, 25)
	Immunity to shingles	Believe that they already have good immunity	(20-22, 25)
	Natural immunity is better/ Vaccines weaken the immune system	Agree	(20, 25)
<b>Beliefs about the Zoster vaccine</b>	Concerned about the effectiveness of the zoster vaccine	Agree	(22, 23, 25, 29)
	Concerned about adverse effects from the zoster vaccine	Agree	(20, 22, 24, 25)
	Concerned about a possible allergic reaction to the vaccine	Agree	(20)
	Believe that the Zoster vaccine can cause shingle	Agree	(25)
<b>Health care provider</b>	GP did not discuss the need for the zoster vaccine	Yes	(22, 24, 25)
	Difficulty getting to see their GP	Yes	(18, 19)

# AZoS predictors of intention to get the zoster vaccine (n=1342)

Factor	%	OR	95% CI
-I would get the zoster vaccine if my doctor recommended it	10.6	6.3 – 18.0	82.0
Positive attitudes towards the zoster vaccine	3.6	2.6 – 5.1	
- zoster vaccine is effective			50.7
- zoster vaccine will prevent/reduce likelihood of PHN			49.3
- likely to get shingles in the near future			24.6
Patient had the flu vaccine in the last 3 years	1.8	1.2 – 2.8	85.1
Agree that chances of getting chronic pain (PHN) increases with age	1.7	1.2 – 2.3	60.4

# Practice-based strategies to increase Zostavax uptake

- Educate at risk groups about:
  - Risk of zoster & its burden of illness
  - Vaccine effectiveness and safety
  - Nature of zoster immunity and value of boosting
  - **Zostavax is the only currently available strategy that can prevent zoster and PHN**
- Consider practice-wide strategies
  - PN vax clinics
  - Opportunistic:
    - Flag' target group + maximise 'opportunistic' patient visits
    - Offer concomitantly with fluvax
  - Practice champion
  - Practice newsletter
  - Use of Immunisation registers including AIR
  - ? Invitation letters to target sub-groups eg infrequent attenders

# SUMMARY

- Incidence of zoster
  - Increases with age, especially >50 years
  - Lifetime risk 15-30%
- PHN
  - Incidence rises significantly in older subjects
  - Considerable morbidity and impact on QOL
  - Difficult to treat
  - Zoster vaccine is main option to prevent occurrence
- Zoster vaccine is both safe and effective
  - In clinical trials, ZOSTAVAX reduced the incidence, severity, and complications of herpes zoster.
  - ZOSTAVAX is generally well tolerated, with adverse events largely limited to injection-site reactions.
- Implementation
  - GP recommendation is a major factor
  - NIP uptake in 70-79 yr old a success story
- Unresolved issues
  - Protection for immunocompromised patients
  - Duration of immunity

# Resources

NCIRS Zoster Vaccine: FAQ

[http://www.ncirs.edu.au/assets/provider\\_resources/fact-sheets/zoster-vaccine-FAQ.pdf](http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-FAQ.pdf)

[www.communityimmunity.com.au](http://www.communityimmunity.com.au)

- Recall resources
- Vaccine management resources

[www.shingles.com.au](http://www.shingles.com.au)

- Download patient education information about shingles

Litt, JCB. Cunningham, T. Van Buynder, P. Update on Zoster, HealthEd, December 2017.

<https://www.healthed.com.au/monographs/update-herpes-zoster/>

The Australian Immunisation Handbook 10th Edition

ZOSTAVAX patient recall kit

