



Considerations for the use of herpes zoster vaccines

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Current Issues in Immunization

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The information that follows pertains to ACIP presentations, discussion and votes. Resolutions passed by the ACIP must be signed by the CDC Director and published in the MMWR to become official CDC policy.

Herpes Zoster (HZ) and Postherpetic Neuralgia (PHN) epidemiology, United States

- Annual rate ~4 HZ cases per 1000 population --1 million cases annually^{1,2}
- Incidence increases with age, ranging from <1 case/1000 children to >15 cases/1000 population 80 years and older^{2,3,4}
- For adults 50 years and older with HZ, 10-18% will go on to develop PHN. Similar to HZ, the incidence increases with age³
- Zoster Vaccine Live (ZVL, Zostavax™) has been licensed in the U.S. since 2006-- 31% of individuals 60 years and older report receipt.⁵

1. Jumaan et al., JID, 2005, 191:2002-7

2. Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9

3. Insinga et al., J Gen Intern Med. 2005, 20:748-53

4. Harpaz et al, IDWeek 2015

5. Williams et al, MMWR 2017, 66:1-28

Herpes Zoster (HZ): Clinical Manifestations



Courtesy of NIAID



Courtesy of CDC



Courtesy of CDC/Robert Sumpter

Herpes Zoster & PHN: Clinical Manifestations

Herpes Zoster

- About 90% of HZ episodes associated with pain
- Treatment: antivirals reduce duration of rash and pain¹

PHN

- Pain at least 90 days following resolution of rash
- Treatment: minimal or no efficacy. Side effects, especially in elderly²

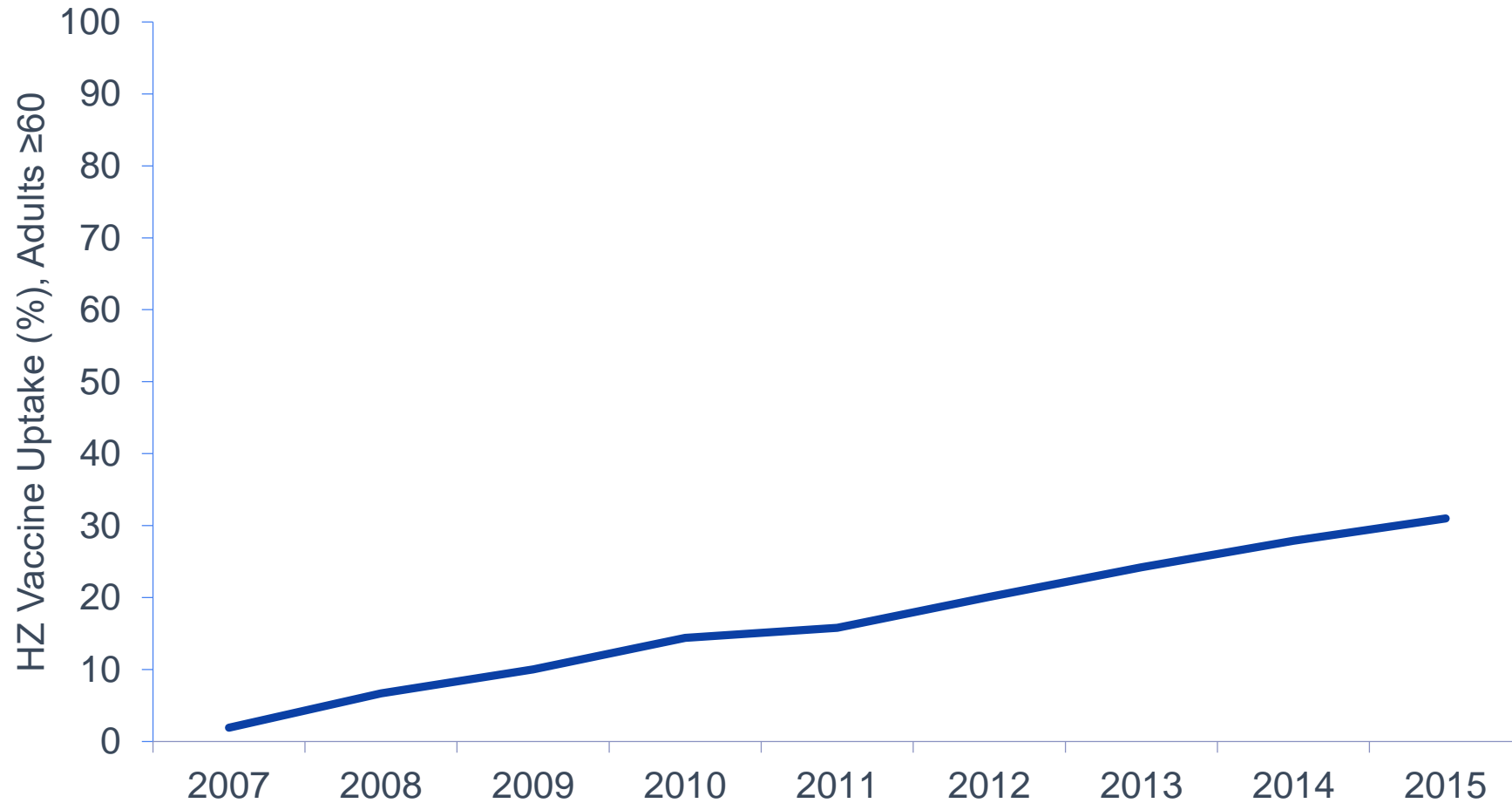


Courtesy Courtesy of M. Oxman, M.D.

**“My PHN is worse than my cancer and chemotherapy...
[it] has made me depressed and suicidal in the past”**

1. Cohen et al, NEJM 2013, 2. Johnson et al, NEJM 2014

Vaccination Coverage of Zoster Vaccine Live (ZVL), among adults ≥ 60 yrs, United States, 2007-2015



* 2007: National immunization Survey (Lu et al, Vaccine 27:882-7); 2008-13: NHIS (Am J Prev Med 40:e1-6 & MMWR February 5, 2016 / 65(1);1-36)

Shingrix™- Herpes Zoster subunit vaccine (HZ/su)

- ❑ **An adjuvanted recombinant protein subunit vaccine**
- ❑ **2 components**
 - Adjuvant AS01B
 - Glycoprotein E
- ❑ **Refrigerator stable, required reconstitution prior to injection**
 - adjuvant solution + lyophilized protein
- ❑ **2 doses, IM at 0, 2 months (max interval=6 months)**
- ❑ **Tested in Phase III clinical trials in ~38,000 people (ZOE 50/ZOE 70)**
- ❑ **>17,000 people have received at least 1 dose of HZ/su in safety studies**
- ❑ **Licensed by the FDA on Oct 20, 2017**

Herpes Zoster Vaccines: Policy Questions

Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults, 50 years and older?

Q2. Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?

Q3. Should ACIP recommend HZ/su be preferred over ZVL?

Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults 50 years and older?

- **Based on 1 large Phase III RCT, HZ/su demonstrated the following benefits:**
 - High vaccine efficacy against HZ
 - **97%** (50-69 yrs)
 - **91%** (≥ 70 yrs)
 - High vaccine efficacy against PHN (**91%** for >50 year olds)
 - Maintained efficacy \geq **85%** for 4 years following vaccination in ≥ 70 year olds

- **Based on 1 large Phase III RCT and additional small studies, HZ/su demonstrated the following:**
 - No differences detected between vaccinated and comparison populations for serious adverse events
 - Grade 3 reactions more commonly reported in vaccinated groups (17%) compared to placebo (3%)

Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults 50 years and older?

- In a small phase II study with subjects ≥ 60 yrs, immunogenicity data at 4, 6 and 9 years post HZ/su (*presented to ACIP Feb 2017*):
 - CD4+ T cell response maintained from 4 years through 9 years at >3 times baseline
 - Immune response maintained in the oldest age group (>70 yrs)
 - However, there is no established correlate of protection

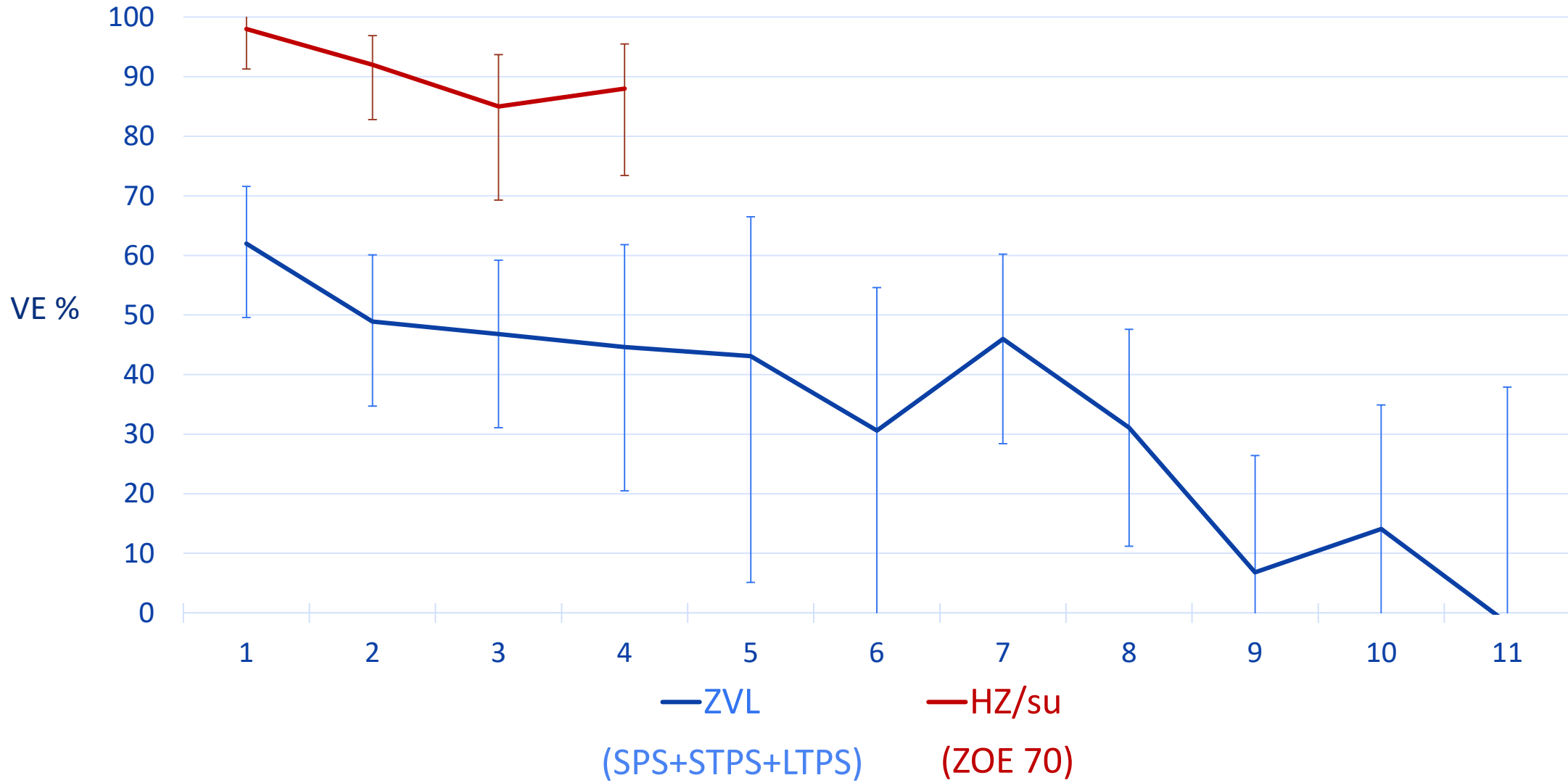
- Number needed to vaccinate to prevent 1 case:
 - HZ: 11 – 17
 - PHN: 70 – 187

- Incremental cost-effectiveness ratios
 - \$9,700/QALY (80-89 yo)- \$47,000/QALY (50-59 yo)

Q2. Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?

- ❑ HZ/su is more efficacious than ZVL in all age categories; differences are larger at older ages
- ❑ Experimental and observational studies indicate significant waning of protection from ZVL:
 - VE drops the first year after receipt (15-25%)
 - By 6 yrs post vaccination, VE <35%
 - Negligible protection by 10 years
- ❑ HZ/su is significantly more efficacious over 4 years, with VE > 97% in the first year which is maintained ≥85% during the first 4 years for all ages
- ❑ In a small study, vaccination with HZ/su 5 yrs following ZVL did not alter the safety or immunogenicity of HZ/su.

Vaccine efficacy against HZ for ZVL and HZ/su, by year following vaccination



Note: The Shingles Prevention Study, Short-term Persistence Study, and Long-term Persistence Study followed the same study population over time.

Q2. Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?

- ~20 million people have been vaccinated with ZVL and potentially eligible for HZ/su¹
- Incremental cost-effectiveness ratio (societal perspective) of revaccination at a minimal interval (8 weeks* post ZVL) is similar to or lower than other adult vaccines:
 - \$15,000 /QALY (80-89 yrs) to \$117,000 /QALY (50-59 yrs)

1. Source: IMS

* Revaccination at 8 weeks was approximated in the CEA model by revaccination immediately following ZVL

Q3. Should ACIP recommend a preference for HZ/su over ZVL?

These vaccines have not been studied in a head to head efficacy trial

Efficacy

- ❑ HZ/su estimates of efficacy are significantly higher than ZVL estimates across all age groups:
 - 60-69 years: 97% vs 64%
 - 70-79 years: 91% vs 41%
 - >80 years 91% vs 18%
- ❑ HZ/su appears to wane at a slower rate than ZVL over the first 4 yrs
- ❑ The expected cases of HZ and PHN averted are far greater with HZ/su compared to ZVL

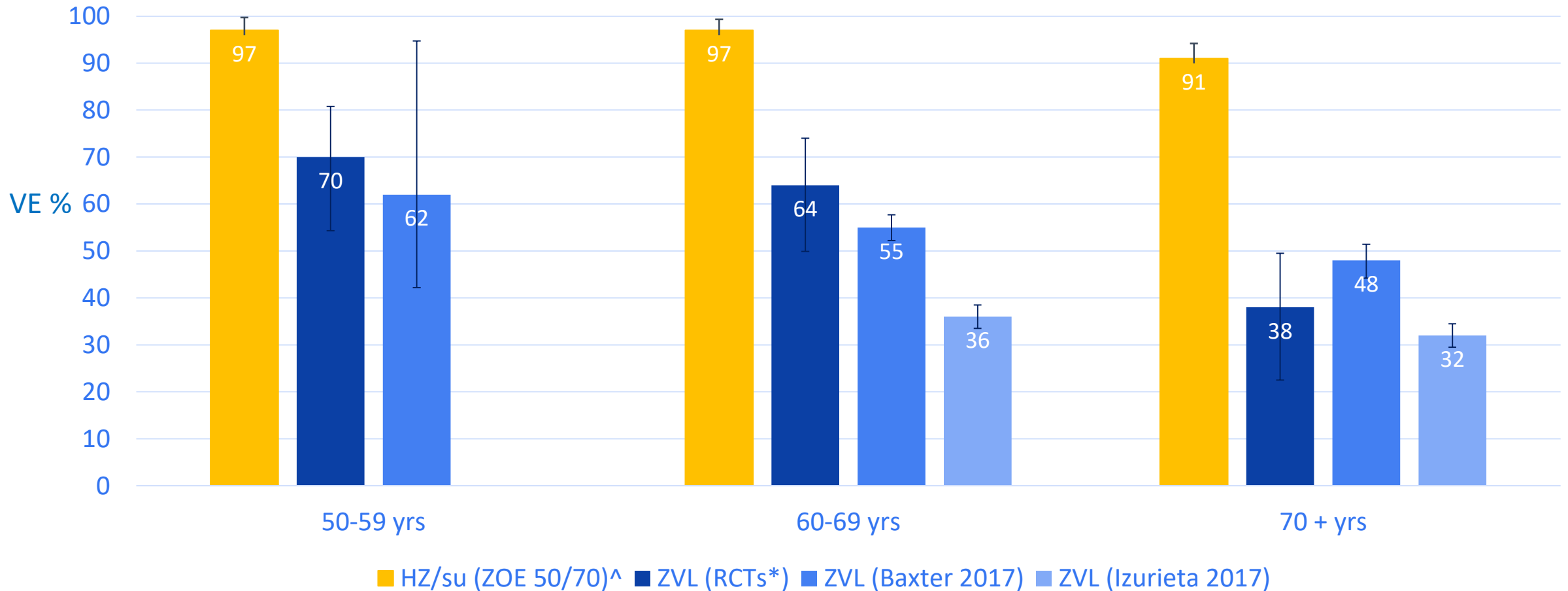
Adverse Effects

- ❑ Neither vaccine is associated with serious adverse events in immunocompetent persons
- ❑ HZ/su is more reactogenic than ZVL

Economics

- ❑ HZ/su leads to more disease prevention and decreased overall costs (vaccine + expected disease costs)

Vaccine efficacy and effectiveness against HZ for HZ/su and ZVL, by age group, during the first 4[‡] years following vaccination

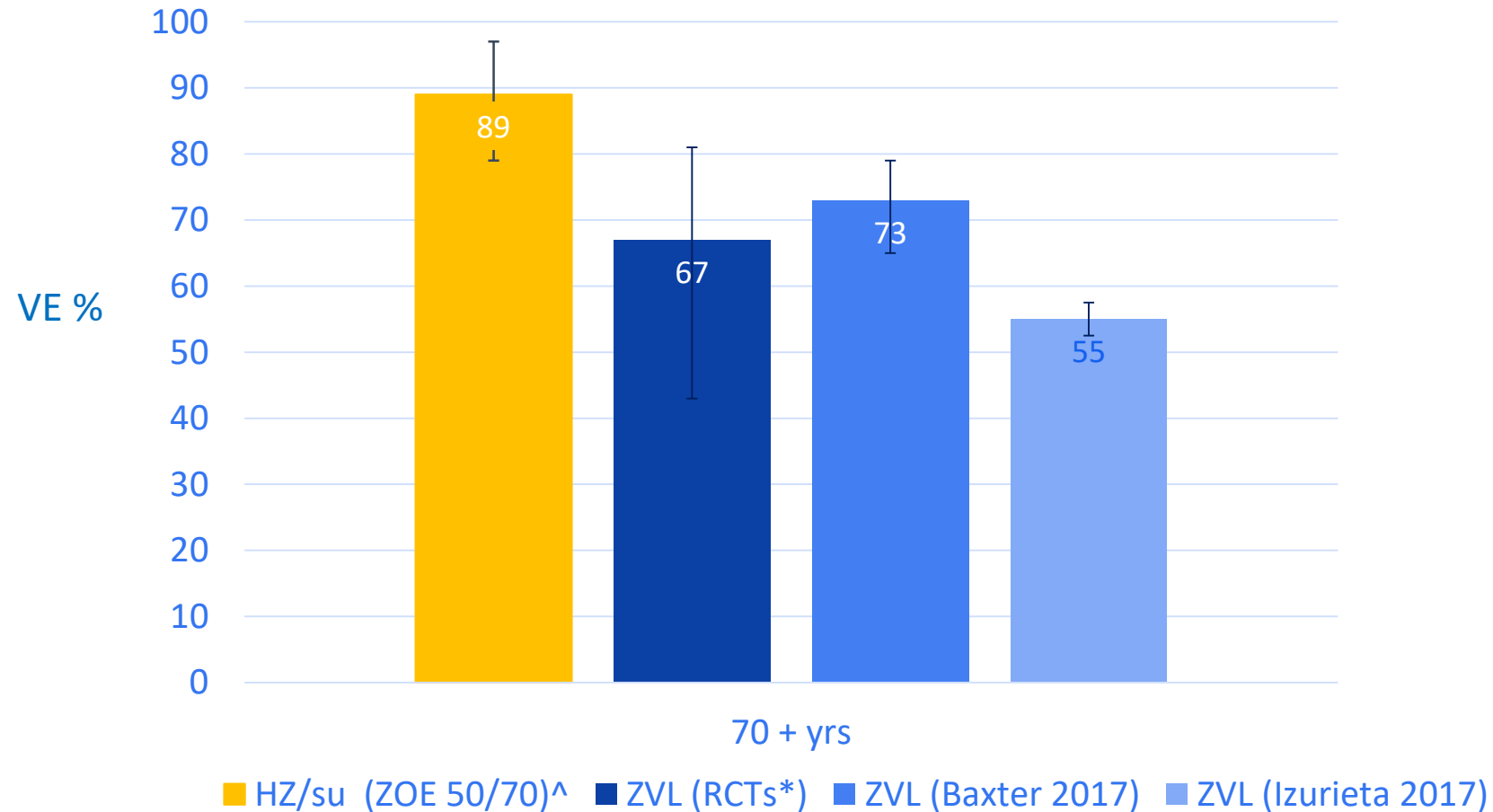


[‡] Median follow up may be less than 3 yrs: Schmader 2012= 1.3 yrs

[^] ZOE 50/70= 50-59 & 60-69yr: Lal 2015, 70+yrs: Cunningham 2016

* RCTs= 50-59 yrs: Schmader 2012, 60-69 and 70+ yrs: Oxman 2005,

Vaccine efficacy and effectiveness against PHN for HZ/su and ZVL, in adults 70 years and older during the first 4 years following vaccination



^ Pooled ZOE 50/70: Cunningham 2016

* Shingles Prevention Study: Oxman 2005,

Cost Effectiveness Analysis

100% 2-dose completion, \$/QALY (95% CI)

Age	HZ/su vs No vaccination	ZVL vs No vaccination
50-59 y	\$46,824 (CS*- 133,244)	\$85,026 (65,441 - 118,116)
60-69 y	\$25,683 (CS - 74,875)	\$54,920 (39,090 - 78,879)
70-79 y	\$11,561 (CS - 39,954)	\$58,703 (44,556 - 81,773)
80-89 y	\$9,739 (CS - 29,570)	\$137,631 (110,262 - 184,955)
90-99 y	\$27,310 (14,718 - 43,534)	\$364,224 (285,501 - 494,097)

*Cost saving

Policy Option	PRO	CON	Unknowns
Preference for HZ/su	<ul style="list-style-type: none"> -Substantially more prevention of HZ, PHN and complications, especially in the elderly -HZ/su more cost-effective than ZVL under almost all assumptions -Promote patient access to the more efficacious vaccine -HZ/su is refrigerator stable (↓ implementation barriers) 	<ul style="list-style-type: none"> -HZ/su may be pulled from the market if unexpected safety problem is observed. -If effectiveness or long term protection are substantially less than expected, ACIP will need to reverse the preferential recommendation. -More grade 3 reactions following vaccination -Requires 2 doses (↑ implementation barriers) 	
No Preference			

Policy Option	PRO	CON	Unknowns
Preference for HZ/su			
No Preference	<p>-2 manufacturers safeguard stable vaccine supply</p>	<p>-Large difference in VE will result in 1000s of preventable cases of HZ & PHN over the lifespan</p> <p>-Onus is on providers to compare the evidence and determine vaccine choice</p>	

Policy Option	PRO	CON	Unknowns
Preference for HZ/su	<ul style="list-style-type: none"> -Substantially more prevention of HZ, PHN and complications, especially in the elderly -HZ/su more cost-effective than ZVL under almost all assumptions -Promote patient access to the more efficacious vaccine -HZ/su is refrigerator stable (↓ implementation barriers) 	<ul style="list-style-type: none"> -HZ/su may be pulled from the market if unexpected safety problem is observed. -If effectiveness or long term protection are substantially less than expected, ACIP will need to reverse the preferential recommendation. -More grade 3 reactions following vaccination -Requires 2 doses (↑ implementation barriers) 	<p><u>Vaccine characteristics</u></p> <ul style="list-style-type: none"> -Possibility for rare safety events with HZ/su (new adjuvant) -VE of HZ/su beyond 4 yrs -VE and durability of 1 dose HZ/su <hr/> <p><u>Program implementation</u></p>
No Preference	<ul style="list-style-type: none"> -2 manufacturers safeguard stable vaccine supply 	<ul style="list-style-type: none"> -Large difference in VE will result in 1000s of preventable cases of HZ & PHN over the lifespan -Onus is on providers to compare the evidence and determine vaccine choice 	<ul style="list-style-type: none"> -2 dose adherence HZ/su --Healthcare seeking among recipients with reactions (physician and pharmacist administered)

Herpes Zoster Vaccines: Policy Questions

Policy Question	ACIP Vote
Should ACIP recommend HZ/su for vaccination of immunocompetent adults, 50 years and older?	Yes (14Y, 1=N)
Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL	Yes (12=Y, 3=N)
Should ACIP recommend that HZ/su be preferred over ZVL?	Yes (8=Y, 7=N)

What does this mean for you?

- ❑ When do these recommendations come into effect?
- ❑ When will the new vaccine (Shingrix) be available?
- ❑ How much will Shingrix cost?
- ❑ How will Shingrix be covered?
- ❑ Will immunocompromised people be able to get Shingrix?
- ❑ Can Zostavax still be used?
- ❑ What are the contraindications for Shingrix?
- ❑ What are the precautions for Shingrix?