

Considerations for the use of herpes zoster vaccines

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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 of M. Oxman VAMC.

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

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?**

Herpes Zoster Vaccines: Policy Questions

- ❑ Work Group interpretation of the data
- ❑ Work Group deliberations
- ❑ Work Group perspective

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

WG interpretation of the data:

- ❑ 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?

WG interpretation of the data:

- ❑ 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 (societal perspective, comparison to no vaccine):
 - \$9,700/QALY (80-89 yo)- \$47,000/QALY (50-59 yo)

Health outcomes comparing HZ/su to no vaccine

Assumptions:

- Cohorts of 1 million vaccinated (50-59 & 60-69 year olds)
- Health outcomes measured over the lifespan
- Vaccine recipients completed 2 doses of HZ/su and effectiveness wanes to 0% over ~19 yrs.

	Cases Expected		Cases Averted	Number Needed to Vaccinate*
Outcome	No Vaccine	HZ/su	No Vacc- HZ/su	
HZ cases				
50-59 yo	265,000	186,000	80,000	13
60-69 yo	204,000	117,000	87,000	11
PHN cases				
50-59 yo	32,000	27,000	5,000	187
60-69 yo	31,000	21,000	10,000	100

* NNV modelled cohort= # vaccinated/ # cases averted

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

WG deliberations:

- ❑ Based on review and GRADE assessment of the evidence for critical and important outcomes, the HZ Work Group found strong evidence that the vaccine is efficacious and durable and found no evidence that it is unsafe.
- ❑ There is minimal waning in the first 4 years— effectiveness beyond 4 years is uncertain. However, durability has been demonstrated for immunological outcomes at 6 and 9 years.
- ❑ The vaccine is reactogenic, resulting in a ~13% excess of grade 3 reactions in vaccines.
- ❑ There are ~42 million 50-59 yr olds and ~21% of all HZ episodes occur in this age group annually.
- ❑ Under almost all assumptions, HZ/su demonstrates NNV and cost effectiveness similar to or more favorable than other adult vaccines, for all age groups, including 50-59 years of age.

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

WG perspective:

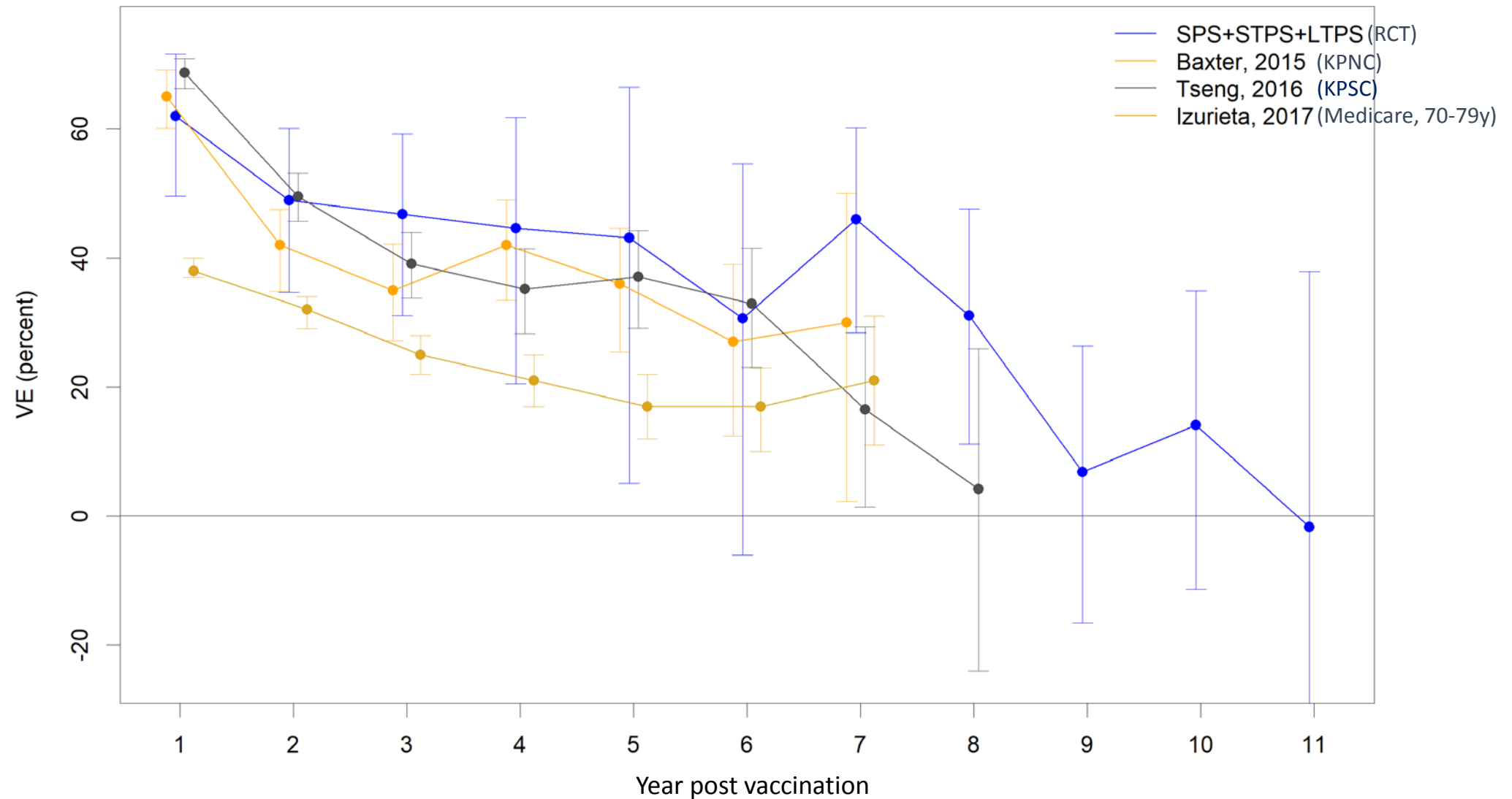
The majority of WG members favor a policy which recommends HZ/su vaccine for immunocompetent adults 50 years and older.

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

WG interpretation of the data

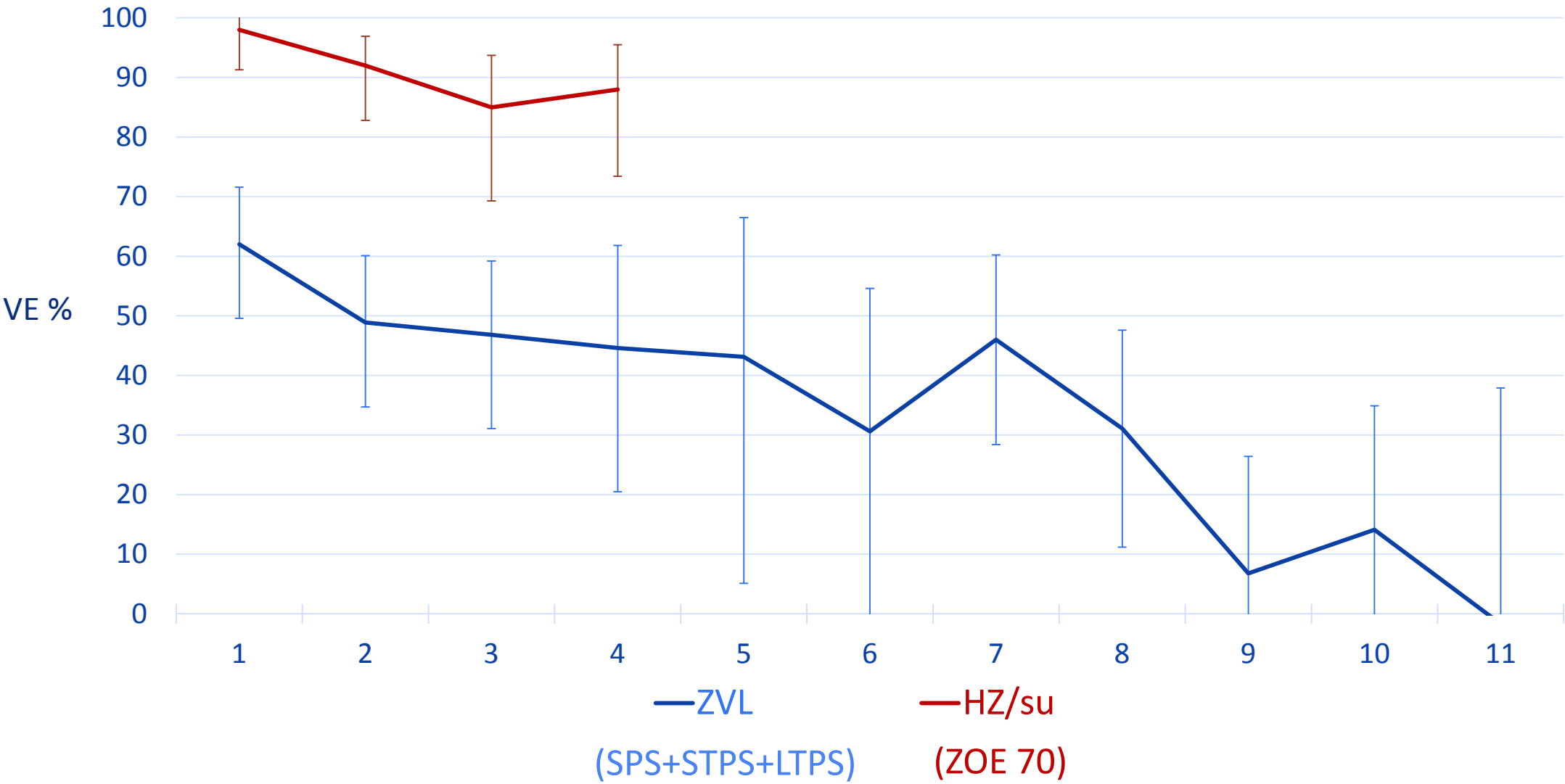
- ❑ HZ/su is more efficacious than ZVL in all age categories; differences are larger at older ages
- ❑ Experimental and observational studies indicate significant waning of protection from ZVL:
 - VE drops the first year after receipt (15-25%)
 - By 6 yrs post vaccination, VE <35%
 - Negligible protection 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.

Duration of protection of ZVL against herpes zoster by year



Note: The Shingles Prevention Study, Short-term Persistence Study, and Long-term Persistence Study followed the same study population in a randomized control trial over time. Baxter (2015), Tseng (2016), and Izurieta (2017) are observational studies. Studies were done in different time periods and among different study populations that had different age structures.

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?

WG interpretation of the data

- ~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

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

HZ Work Group deliberations:

- Prior ZVL receipt should **not** be a contraindication to receiving HZ/su
- For prior ZVL recipients, HZ/su should be viewed as a new vaccine to prevent HZ
- Substantial burden of HZ and PHN could be prevented by vaccinating this population with HZ/su, in particular among the elderly
- Prior ZVL did not alter the safety or immunogenicity of HZ/su (5 year interval)
 - We do not have efficacy data in this population and there are no established correlates of protection
 - We do not have data on other intervals
- 31% of the US population 60 yrs and older followed ACIP recommendations and received ZVL
 - A significant fraction of ZVL recipients now have very low vaccine protection for HZ and PHN
- Vaccination with HZ/su is a cost effective strategy for individuals who have previously received ZVL

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

Work Group Perspective:

The majority of WG members favor a policy recommending HZ/su for individuals previously vaccinated with ZVL

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

WG interpretation of data:

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

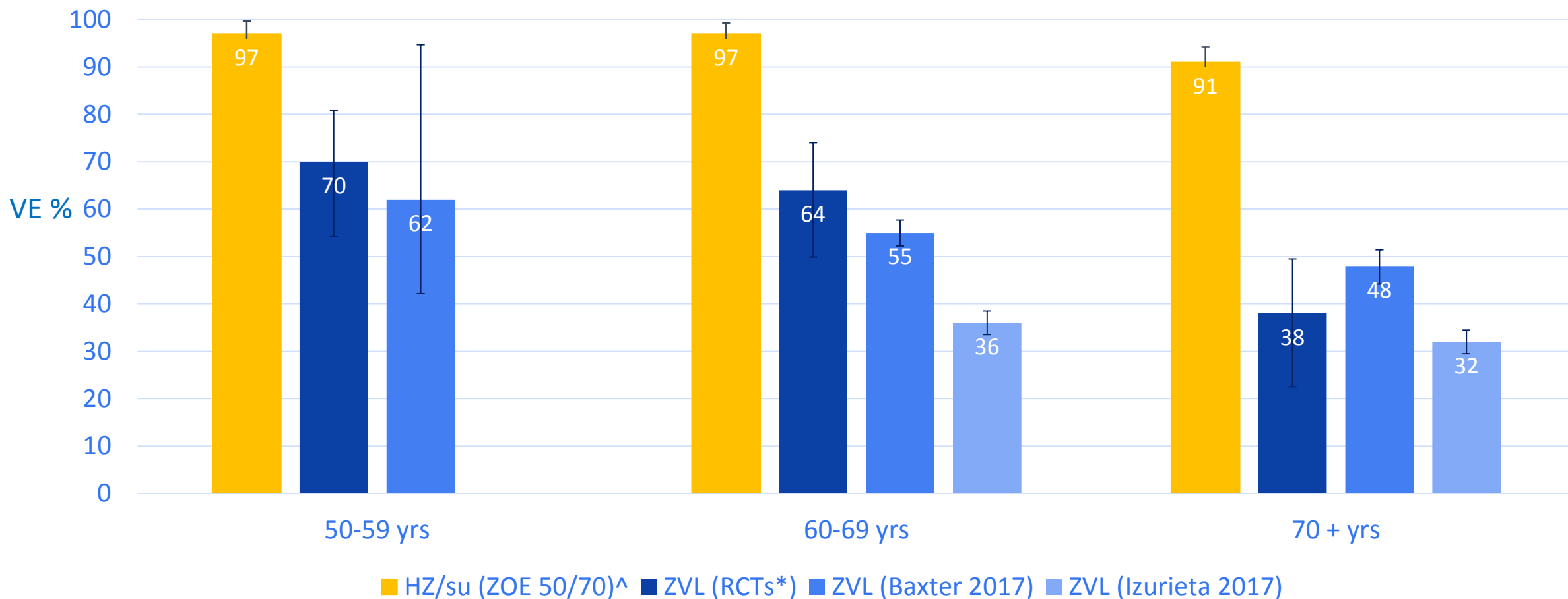
Adverse Effects

- ❑ 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

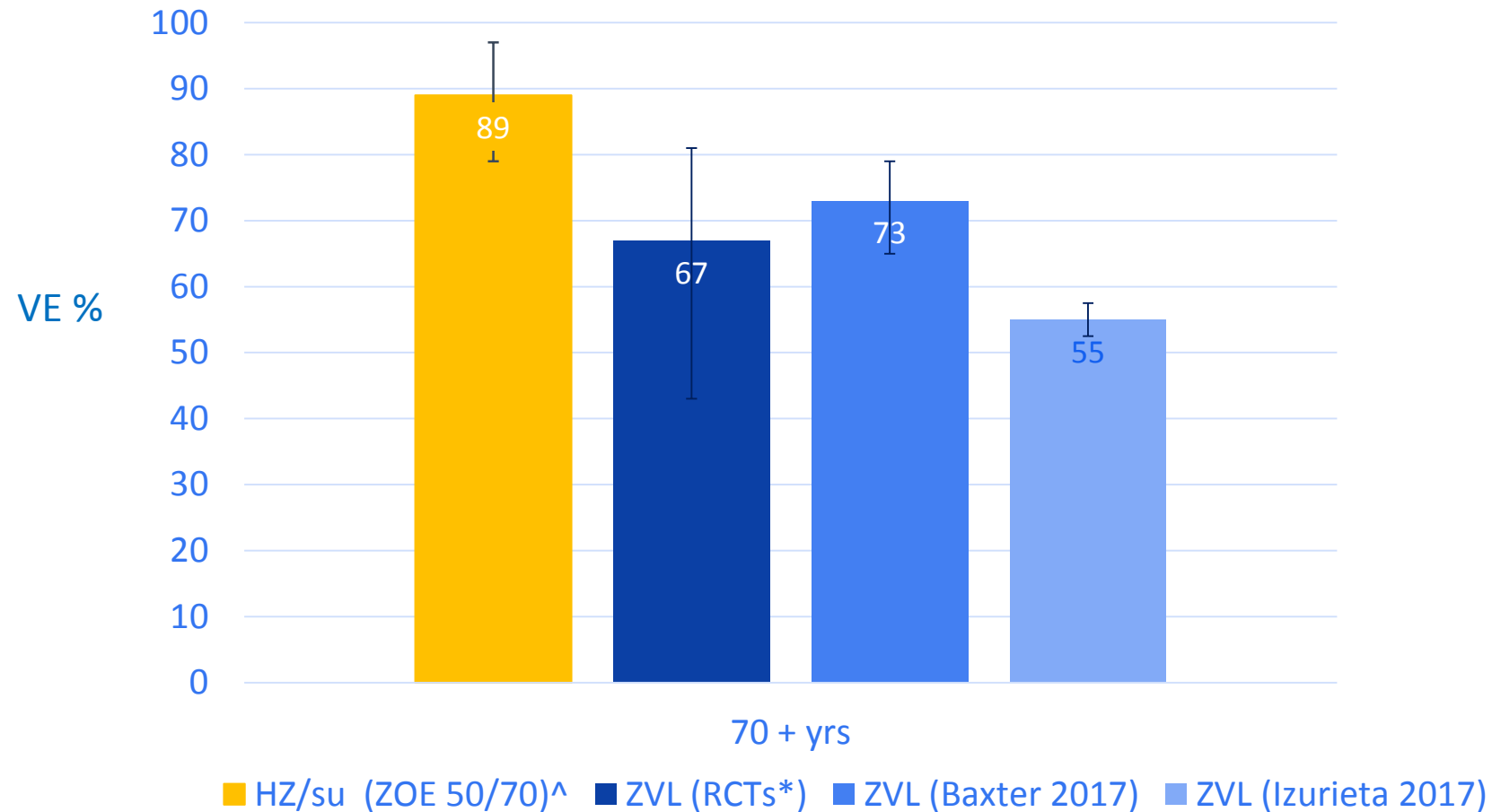


[‡] Median follow up may be less than 3 yrs: Schmader 2012= 1.3 yrs

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

Health outcomes comparing no vaccine, ZVL and HZ/su

Assumptions:

- Cohort 1 million vaccines (60-69 year olds)
- Health outcomes measured over the lifespan
- HZ/su recipients completed 2 doses VE HZ/su wanes to 0% over ~19 yrs
- ZVL wanes to 0% over ~10 yrs

	Cases Expected			Cases Averted HZ/su vs. ZVL
Outcome	No Vaccine	ZVL	HZ/su	Δ (ZVL- HZ/su)
HZ cases	204,000	170,000	117,000	53,000
PHN cases	31,000	25,000	21,000	4,000

Expected cases of HZ and PHN averted under varying examples of vaccine uptake:

Assumptions:

- Cohort 1 million vaccines (60-69 year olds)
- Health outcomes measured over the lifespan
- HZ/su recipients completed 2 doses VE HZ/su wanes to 0% over ~19 yrs
- ZVL wanes to 0% over ~10 yrs

	Cases Expected			Cases Averted
	Baseline	Example #1	Example #2	
Outcome	100% ZVL	50% : 50% ZVL : HZ/su	10% : 90% ZVL : HZ/su	Δ (Eg #1- Eg #2)
HZ cases	170,000	143,500	122,300	21,200
PHN cases	25,000	23,000	21,400	1,600

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	-2 manufacturers safeguard stable vaccine supply	-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	

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) 	<u>Vaccine characteristics</u> <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/> <u>Program implementation</u>
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)

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

WG deliberations:

□ Key unknowns:

- Effectiveness and the possibility of an unexpected safety signal:
 - Most HZ Work Group members thought that adequate surveillance, pharmacovigilance and long-term testing is in place to detect unexpected occurrences. ACIP will re-evaluate the benefit: harm ratio if steep waning or serious adverse events occur.
- 2 dose adherence and 1-dose VE
 - Provider and patient education regarding expected reactogenicity may positively impact adherence
 - Observational studies will be required to estimate 1-dose VE

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

WG deliberations:

- ❑ Preferential recommendation for HZ/su is likely to prevent significantly more disease compared to a non-preferential recommendation
- ❑ HZ/su is more cost effective than ZVL under almost all assumptions
- ❑ A non-preferential recommendation puts the onus on clinicians to compare safety and efficacy literature to select a vaccine
- ❑ A preference would promote access to the more efficacious vaccine whereas health systems or providers may choose to stock only the less expensive vaccine if no preference is stated
- ❑ Preferential votes are uncommon for new vaccines but warranted when ACIP believes there is sufficient evidence of superior benefit to harm ratio of one vaccine compared to another

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

Work Group Perspective:

- ❑ The majority of WG members favor a policy recommending a preference for HZ/su over ZVL**

Vote

Vote #1

Herpes Zoster subunit vaccine is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged 50 years and older.

Vote #2

Herpes Zoster subunit vaccine is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received Zoster Vaccine Live (Zostavax).

Vote #3

Herpes Zoster subunit vaccine is preferred over Zoster Vaccine Live (Zostavax) for the prevention of herpes zoster and related complications.