



Considerations for the use of herpes zoster vaccines

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Herpes Zoster (HZ) and Post Herpetic 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}
- For adults 50 years and older with HZ, 10-18% will go on to develop PHN. Similar to HZ, the incidence increases with age³

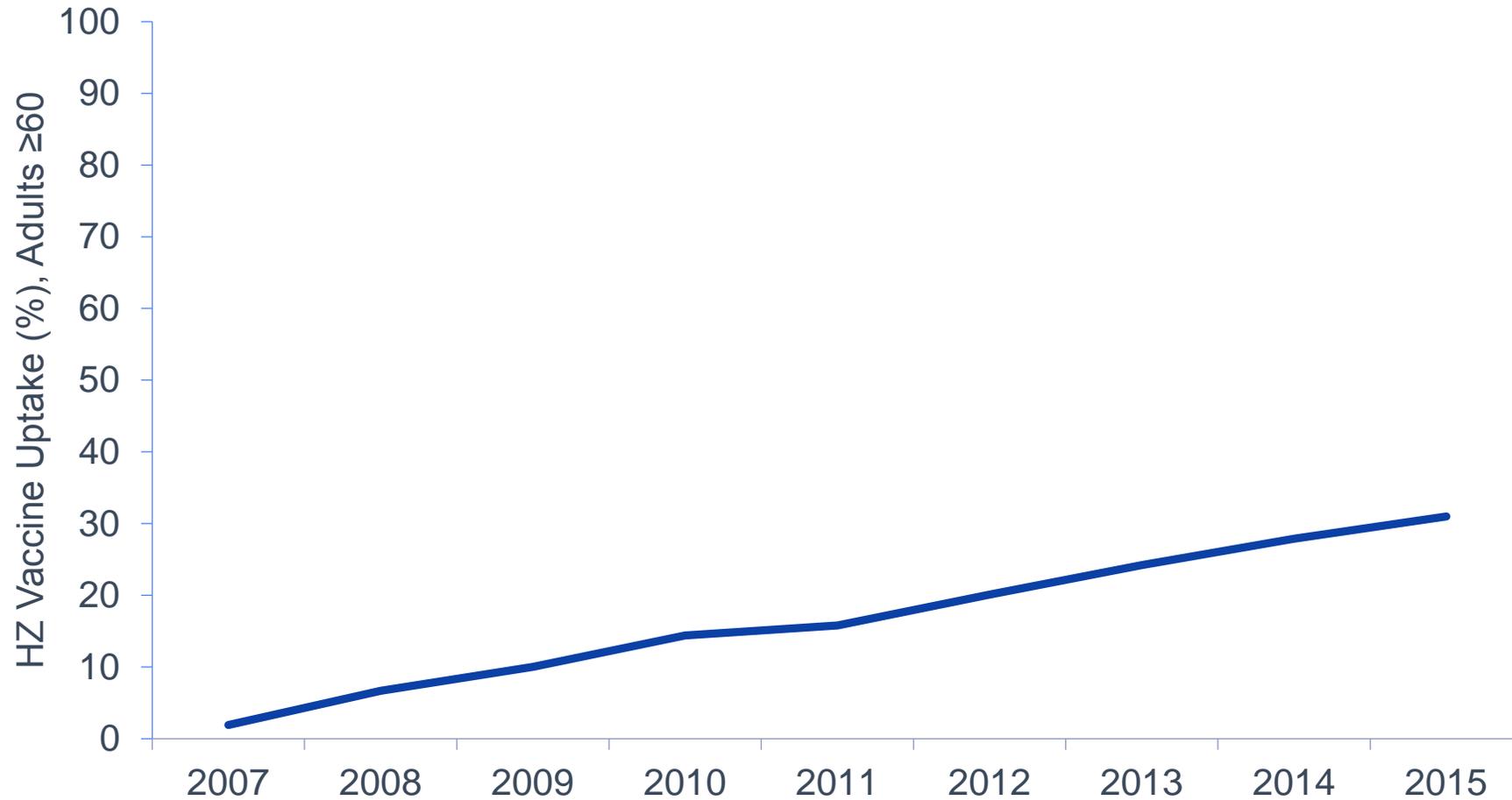
1. Jumaan et al., JID, 2005, 191:2002-7

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

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

4. Hapaz et al, IDWeek 2015

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)

GRADE of Herpes Zoster subunit (HZ/su): Summary

Outcome	Interpretation	Estimate of Effect	Evidence type
HZ	Significantly efficacious	50-69y: 97% 70+ y: 91%	1
PHN	Significantly efficacious	50+ y: 91% 70+ y: 89%	1
Duration of protection (HZ)	Significantly efficacious 4 years post last vaccination	≥85% for all 4 years	1
Severe adverse events	No differences detected between vaccinated and comparison populations for serious adverse events	Vaccine: 12.6% Placebo: 13.0%	1
Reactogenicity (Grade 3 rxn)	Grade 3 reactions more commonly reported in vaccinated groups compared to placebo	Vaccine: 16.5% Placebo: 3.1%	1

Herpes Zoster Vaccines: Policy Questions

- Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults?
(Category A vs Category B)**
- Q2. At what age should HZ/su age-based recommendations start?
(50 yrs vs. 60 yrs)**
- Q3a. Should ACIP recommend a preference for HZ/su over ZVL?**
- Q3b. Should ACIP recommend that individuals previously vaccinated with ZVL
receive HZ/su?**

Herpes Zoster Vaccines: Policy Questions

- Work Group interpretation of the data
- Work Group deliberations
- Work Group Perspective
 - Work Group is awaiting a final price for HZ/su in order to complete final cost effectiveness analyses, as well as strategies to achieve high 2 dose adherence for HZ/su. Therefore, the interim work group perspective will be expressed here.

Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults? (Category A vs Category B)

WG interpretation of the data:

- ❑ **Based on 1 large Phase III RCT, HZ/su demonstrated the following benefits:**
 - High vaccine efficacy against HZ (97% and 91% for 50-69 year olds and ≥ 70 year olds, respectively)
 - High vaccine efficacy against PHN (91% for >50 year olds)
 - Maintained efficacy above 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%)

Health outcomes comparing HZ/su to no vaccine, in a cohort of 10,000 60 year olds, over 4 years

Assumptions:

- VE stable over 4 yrs [97% (HZ) & 93% (PHN)]
- Disease incidence stable over 4 yrs (HZ= 8:1,000, PHN= 0.9:1,000)
- All vaccinees completed 2 doses of HZ/su

Outcome	No Vaccine	HZ/su	Cases Averted
HZ cases expected	320	10	310
PHN cases expected	36	3	33

Number needed to vaccinate to prevent 1 case of HZ in 4 yrs: **32**

Number needed to vaccinate to prevent 1 case of PHN in 4 yrs: **303**

Health outcomes comparing HZ/su to no vaccine, in a cohort of 10,000 60 year olds, over the lifespan

- Key assumptions include: 2 dose adherence and 1 dose effectiveness of HZ/su, rates of waning
- Estimates derived from Merck and GSK CEA analysis

Outcome	No Vaccine	HZ/su	Cases Averted
HZ cases expected			
Merck analysis	2020	1240	780
GSK analysis	1961	925	1036
PHN cases expected			
Merck analysis	200	130	70
GSK analysis	226	114	112

Number needed to vaccinate to prevent 1 case of HZ: 10-13

Number needed to vaccinate to prevent 1 case of PHN: 89-143

Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults? (Category A vs Category B)

WG deliberations:

- ❑ Based on review and GRADE assessment of the evidence for critical and important outcomes, the Work Group is confident that the vaccine is safe, efficacious and maintains high protection against HZ four years following vaccination.
- ❑ WG members acknowledged the importance of clear ACIP recommendations
- ❑ Under most assumptions, HZ/su demonstrates NNV and cost effectiveness similar to or more favorable than other adult vaccines

WG perspective:

WG is favorable to vaccinating immunocompetent adults with HZ/su (Category A).

Q2. At what age should HZ/su age-based recommendations start? (50 yrs vs. 60 yrs)

WG interpretation of the data

- HZ/su efficacy is very high in the 50-59 yr old group: 97% (95% CI 90%-99%).
- There is minimal waning in the first 4 years (VE>93% in yr 4).
 - Waning beyond 4 years is unknown
- In a small phase II study (participants ≥60yrs), immunogenicity data at year 4, 6 and 9 years following HZ/su vaccination shows similar CD4+ T cell response with a >3 fold rise above baseline (*presented to ACIP Feb 2017*)
 - However, there is no established correlate of protection.

Q2. At what age should HZ/su age-based recommendations start? (50 yrs vs. 60 yrs)

WG deliberations

- ❑ HZ and PHN incidence increases with age
- ❑ In 2011, ACIP did not recommend ZVL for 50-59 year olds because there was evidence of waning in the first 4 years and beyond.
- ❑ HZ/su VE is very high in this age group (97%) with minimal waning in the first 4 years
- ❑ The degree of waning beyond 4 years is uncertain. However, durability has been demonstrated for immunological outcomes at 6 and 9 years.
- ❑ There are ~42 million 50-59 yr olds and ~21% of all HZ episodes occur in this age group annually.

Work Group Perspective:

- ❑ The Work Group is favorable towards a proposal for age based recommendations to start at age 50 yrs.
- ❑ The Work Group is awaiting a final price for HZ/su and accompanying cost effectiveness analyses

Q3a. Should ACIP recommend a preference for HZ/su over ZVL?

WG interpretation of data (NB: These vaccines have not been studied in a head to head efficacy trial):

Efficacy

- ❑ HZ/su estimates of efficacy are higher than ZVL estimates across all age groups
- ❑ HZ/su appears to wane at a slower rate than ZVL over the first 4 yrs

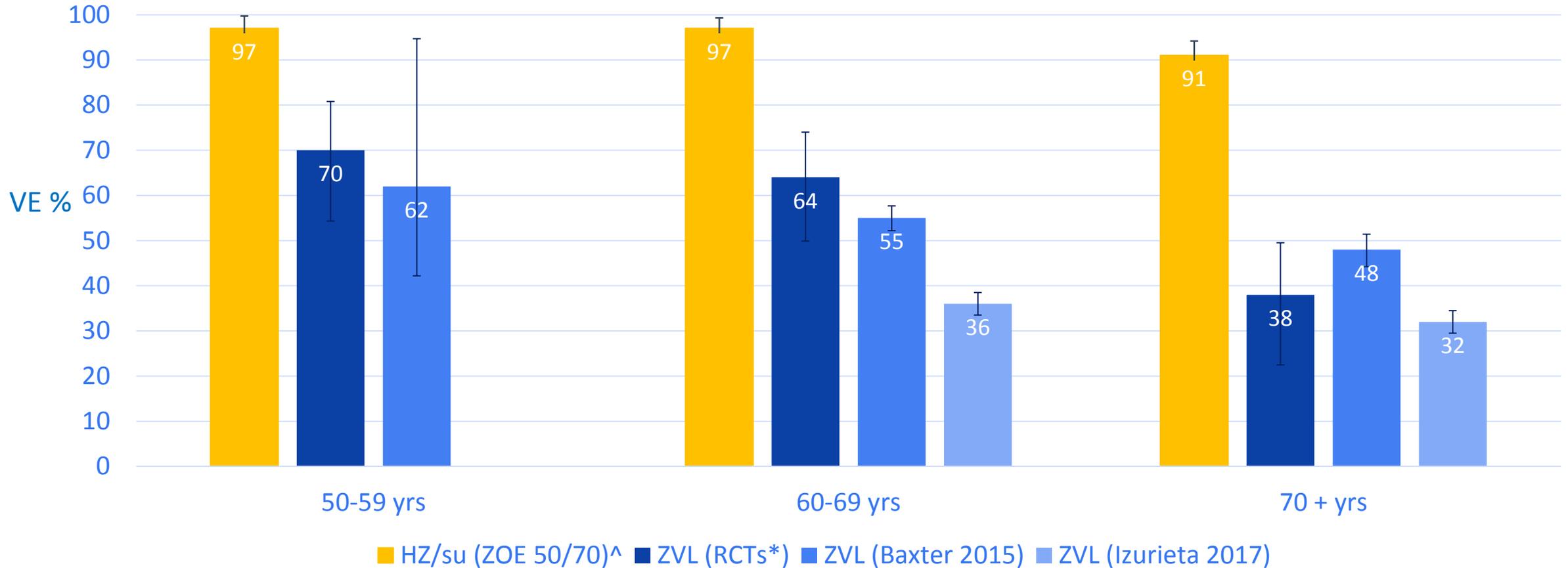
Safety

- ❑ Neither vaccine is associated with serious adverse events in immunocompetent persons
- ❑ HZ/su is more reactogenic than ZVL
- ❑ ZVL is a live attenuated virus which can cause herpes zoster in rare circumstances

Economics

- ❑ HZ/su is more cost effective than ZVL under most assumptions

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



^ ZOE 50= 50-69yr: Lal 2015, 70+yr: Cunningham 2016

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

Health outcomes comparing no vaccine, ZVL and HZ/su, in a cohort of 10,000 60 year olds, over 4 yrs

Assumptions:

- VE stable over 4 yrs (HZ/su=97% & 93%, ZVL=64% & 67%)
- Disease incidence stable over 4 yrs (HZ= 8:1,000, PHN= 0.9:1,000)
- HZ/su recipients completed 2 doses

Outcome	No Vaccine	HZ/su	ZVL	Δ (ZVL- HZ/su)
HZ cases expected	320	10	115	105
PHN cases expected	36	3	12	9

Health outcomes comparing no vaccine to HZ/su to ZVL, in a cohort of 10,000 60 year olds, over the lifespan

- Key assumptions include: 2 dose adherence and 1 dose effectiveness of HZ/su, rates of waning
- Estimates derived from Merck and GSK CEA analysis

Outcome	No Vaccine	HZ/su	ZVL	Δ (ZVL- HZ/su)
HZ cases expected				
Merck analysis	2020	1240	1600	360
GSK analysis	1961	925	1640	715
PHN cases expected				
Merck analysis	200	130	140	10
GSK analysis	226	114	177	63

Policy Option	PRO	CON	Unknowns
Preference for HZ/su	<ul style="list-style-type: none"> -Substantially more prevention of HZ, PHN and other complications -HZ/su more cost-effective than ZVL under most assumptions (*price) -HZ/su is refrigerator stable (↓ provider barriers) 	<ul style="list-style-type: none"> -Reversal of preference may be needed if unexpected safety signal or poor VE is observed with HZ/su. -Will lead to more grade 3 reactions following vaccination -Requires 2 doses (↑ program barriers) 	<ul style="list-style-type: none"> -Possibility for rare safety events with HZ/su (new adjuvant) -VE of HZ/su beyond 4 yrs -2 dose adherence HZ/su -VE and durability of 1 dose HZ/su
No Preference	<ul style="list-style-type: none"> -Supports competition -2 manufacturers safeguard stable vaccine supply 	<ul style="list-style-type: none"> -Large difference in VE will result in thousands of preventable HZ cases and hundreds of PHN cases -Some insurers/Healthcare delivery systems may choose to cover only the less expensive vaccine if no preference is stated -Onus on providers to compare safety and efficacy 	<ul style="list-style-type: none"> -Price -Insurance coverage details -Healthcare seeking among vaccinees with reactions

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No Preference	<ul style="list-style-type: none"> -Supports competition -2 manufacturers safeguard stable vaccine supply 	<ul style="list-style-type: none"> -Large difference in VE will result in thousands of preventable HZ cases and hundreds of PHN cases -Some insurers/healthcare delivery systems may choose to carry only the less expensive vaccine if no preference is stated -Onus on providers to compare safety and efficacy 	<ul style="list-style-type: none"> -Care seeking among vaccinees with reactions

Q3a. Should ACIP recommend a preference for HZ/su over ZVL?

□ How long would it take to answer the unknowns?

- ~3-4 M people are vaccinated for HZ each year.
- **Real-world safety data:** 1-2 year period may be sufficient for surveillance for rare adverse events
- **2 dose adherence of HZ/su:** 1-2 year period, adherence will likely change as the program matures and providers become familiar with HZ/su reactogenicity profile
- **VE of HZ/su beyond 4 years:** 4-8 year period beyond licensure would be necessary to study and report on long-term effectiveness
- **VE of 1 dose HZ/su:** 2-3 year period needed for an observational study in a large HMO (e.g. 1M unvaccinated adults) to accumulate sufficient 1 dose HZ/su recipients. 4yrs+ required for age-specific estimates and duration of protection.

Q3a. Should ACIP recommend a preference for HZ/su over ZVL?

WG deliberations:

- ❑ HZ/su can prevent significantly more HZ and PHN than ZVL
- ❑ HZ/su is more cost effective than ZVL under most assumptions
- ❑ A preference would safeguard insurance/healthcare system delivery coverage for the more efficacious vaccine whereas insurers may choose to carry only the less expensive vaccine if no preference is stated
- ❑ An equivalent recommendation puts the onus on clinicians to review the literature on both vaccines to compare safety and efficacy
- ❑ Key unknowns: 2 dose adherence, VE of 1 dose, long term waning, and the possibility of an unexpected safety signal

Work Group Perspective:

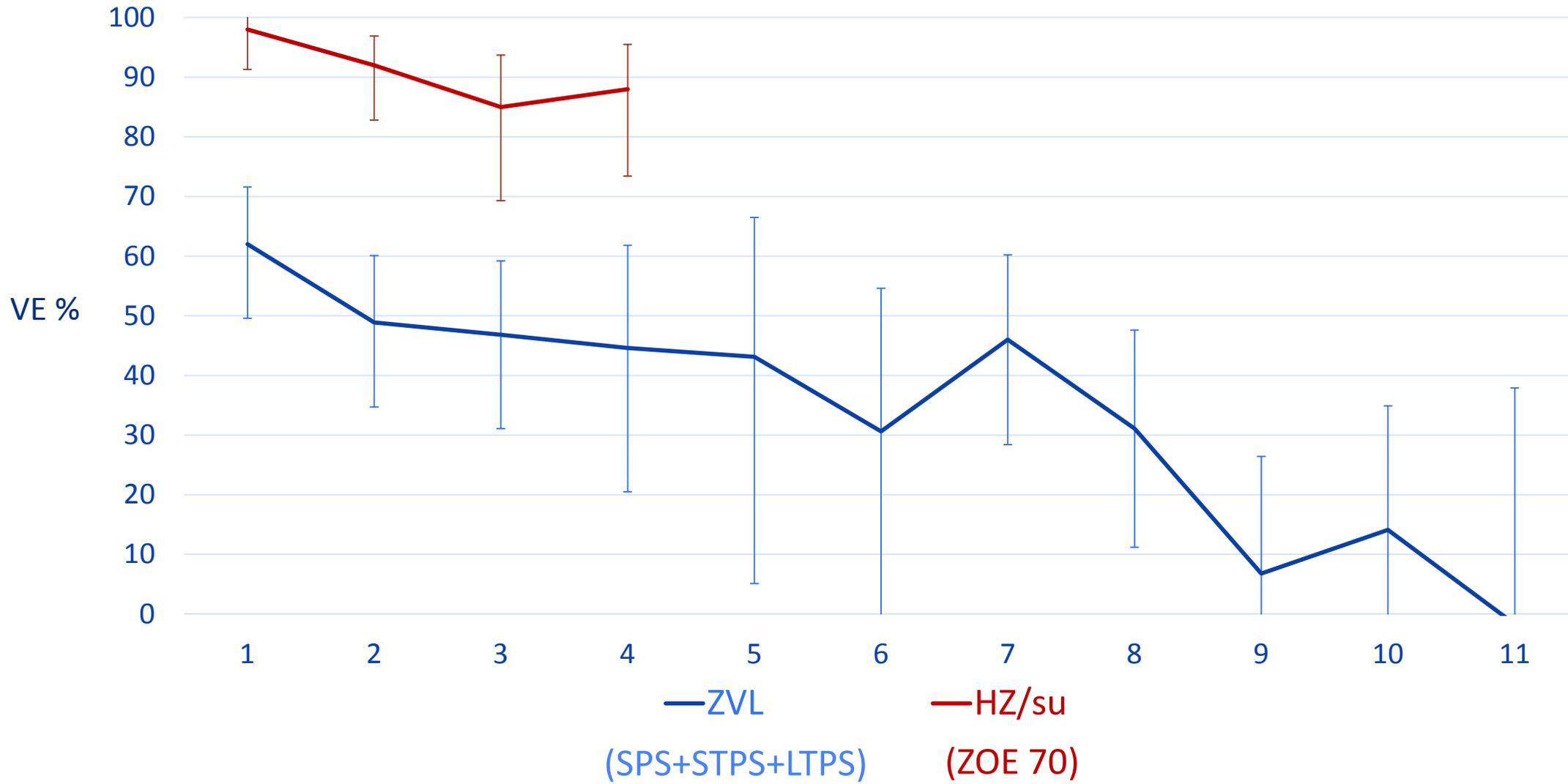
- ❑ WG majority: a preference be stated for HZ/su over ZVL
- ❑ WG minority: no preference be stated at this time
- ❑ WG is awaiting a final price for HZ/su and accompanying cost effectiveness analyses

Q3b. Should individuals previously vaccinated with ZVL received HZ/su?

WG interpretation of the data:

- ❑ HZ/su is more efficacious than ZVL in all age categories.
- ❑ 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 above 85% in 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 in a randomized control trial over time.

Q3b. Should individuals previously vaccinated with ZVL receive HZ/su?

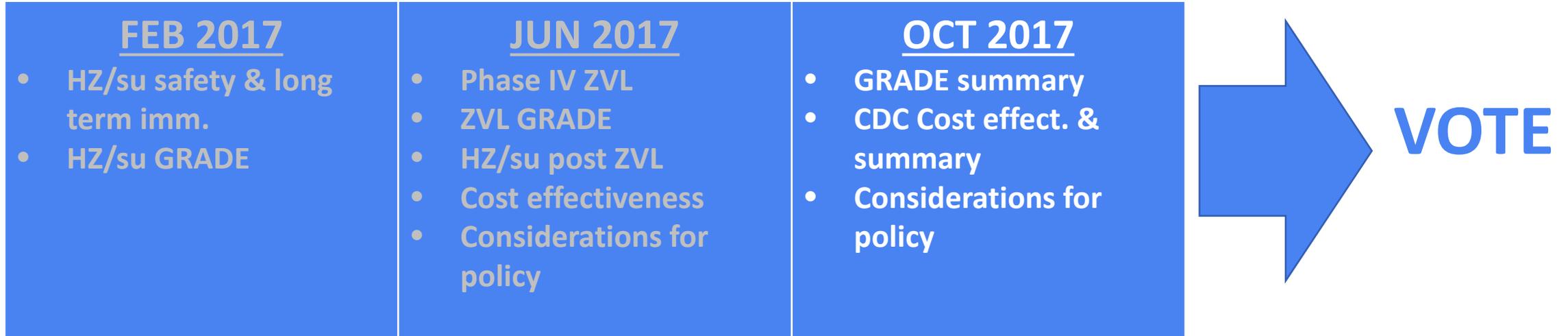
HZ Work Group deliberations:

- Prior ZVL receipt should **not** be a contraindication to receiving HZ/su
- For prior ZVL recipients, HZ/su is a new vaccine
- A substantial amount of HZ and PHN could be prevented by vaccinating this population with HZ/su
- Prior ZVL did not alter the safety or immunogenicity of HZ/su
- 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

Work Group Perspective:

- HZ/su should be considered for people who have already received ZVL
- WG is awaiting a final price for HZ/su and accompanying cost effectiveness analyses

Discussion



Are there additional data that would help ACIP develop policy for the use of herpes zoster vaccines in adults?