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"Recommendations for the Use of Herpes Zoster Vaccines"

Clinician Outreach and Communication Activity (COCA)

Webinar

May 10, 2018

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At the conclusion of the session, participants will be able to accomplish the following:

- List CDC's recommendations on herpes zoster vaccines, in particular, new guidelines for Shingrix.
- Explain who should receive Shingrix and how to administer it.
- Describe the benefits and side effects of Shingrix.

Today's Presenter

Kathleen Dooling, MD, MPH

Medical Officer
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Centers for Disease Control and Prevention

ACIP Recommendations for the use of herpes zoster vaccines

Dr. Kathleen Dooling, MD, MPH

Medical Officer, Division of Viral Diseases

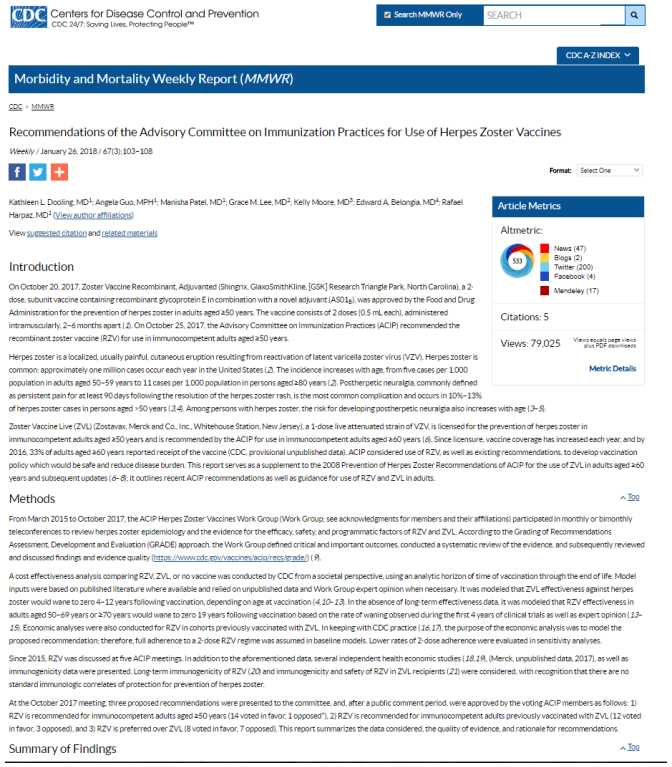
COCA call

May 10, 2018

Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

PUBLISHED ONLINE January 25, 2018

https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm?s_cid=mm6703a5_w



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Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

Weekly / January 26, 2018 / 67(3);103–108

Format: Select One

Kathleen L. Dooling, MD[1]; Angela Guo, MPH[1]; Manisha Patel, MD[1]; Grace M. Lee, MD[2]; Kelly Moore, MD[3]; Edward A. Belongia, MD[4]; Rafael Harpaz, MD[1] (View author affiliations)

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Introduction

On October 20, 2017, Zoster Vaccine Recombinant, Adjuvanted (Shingrix, GlaxoSmithKline, [GSK] Research Triangle Park, North Carolina), a 2-dose, subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant (AS01$_B$), was approved by the Food and Drug Administration for the prevention of herpes zoster in adults aged ≥50 years. The vaccine consists of 2 doses (0.5 mL each), administered intramuscularly, 2–6 months apart (*1*). On October 25, 2017, the Advisory Committee on Immunization Practices (ACIP) recommended the recombinant zoster vaccine (RZV) for use in immunocompetent adults aged ≥50 years.

Herpes zoster is a localized, usually painful, cutaneous eruption resulting from reactivation of latent varicella zoster virus (VZV). Herpes zoster is common: approximately one million cases occur each year in the United States (*2*). The incidence increases with age, from five cases per 1,000 population in adults aged 50–59 years to 11 cases per 1,000 population in persons aged ≥80 years (*2*). Postherpetic neuralgia, commonly defined as persistent pain for at least 90 days following the resolution of the herpes zoster rash, is the most common complication and occurs in 10%–13% of herpes zoster cases in persons aged >50 years (*3,4*). Among persons with herpes zoster, the risk for developing postherpetic neuralgia also increases with age (*3–5*).

Zoster Vaccine Live (ZVL) (Zostavax, Merck and Co., Inc., Whitehouse Station, New Jersey), a 1-dose live attenuated strain of VZV, is licensed for the prevention of herpes zoster in immunocompetent adults aged ≥50 years and is recommended by the ACIP for use in immunocompetent adults aged ≥60 years (*6*). Since licensure, vaccine coverage has increased each year, and by 2016, 33% of adults aged ≥60 years reported receipt of the vaccine (CDC, provisional unpublished data). ACIP considered use of RZV, as well as existing recommendations, to develop vaccination policy which would be safe and reduce disease burden. This report serves as a supplement to the 2008 Prevention of Herpes Zoster Recommendations of ACIP for the use of ZVL in adults aged ≥60 years and subsequent updates (*6–8*); it outlines recent ACIP recommendations as well as guidance for use of RZV and ZVL in adults.

Methods

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From March 2015 to October 2017, the ACIP Herpes Zoster Vaccines Work Group (Work Group; see acknowledgments for members and their affiliations) participated in monthly or bimonthly teleconferences to review herpes zoster epidemiology and the evidence for the efficacy, safety, and programmatic factors of RZV and ZVL. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the Work Group defined critical and important outcomes, conducted a systematic review of the evidence, and subsequently reviewed and discussed findings and evidence quality (https://www.cdc.gov/vaccines/acip/recs/grade.html) (*9*).

A cost effectiveness analysis comparing RZV, ZVL, or no vaccine was conducted by CDC from a societal perspective, using an analytic horizon of time of vaccination through the end of life. Model inputs were based on published literature where available and relied on unpublished data and Work Group expert opinion when necessary. It was modeled that ZVL effectiveness against herpes zoster would wane to zero 4–12 years following vaccination, depending on age at vaccination (*4,10–13*). In the absence of long-term effectiveness data, it was modeled that RZV effectiveness in adults aged 50–69 years or ≥70 years would wane to zero 19 years following vaccination based on the rate of waning observed during the first 4 years of clinical trials as well as expert opinion (*13–15*). Economic analyses were also conducted for RZV in cohorts previously vaccinated with ZVL. In keeping with CDC practice (*16,17*), the purpose of the economic analysis was to model the proposed recommendation; therefore, full adherence to a 2-dose RZV regime was assumed in baseline models. Lower rates of 2-dose adherence were evaluated in sensitivity analyses.

Since 2015, RZV was discussed at five ACIP meetings. In addition to the aforementioned data, several independent health economic studies (*18,19*), (Merck, unpublished data, 2017), as well as immunogenicity data were presented. Long-term immunogenicity of RZV (*20*) and immunogenicity and safety of RZV in ZVL recipients (*21*) were considered, with recognition that there are no standard immunologic correlates of protection for prevention of herpes zoster.

At the October 2017 meeting, three proposed recommendations were presented to the committee, and, after a public comment period, were approved by the voting ACIP members as follows: 1) RZV is recommended for immunocompetent adults aged ≥50 years (14 voted in favor, 1 opposed"), 2) RZV is recommended for immunocompetent adults previously vaccinated with ZVL (12 voted in favor, 3 opposed), and 3) RZV is preferred over ZVL (8 voted in favor, 7 opposed). This report summarizes the data considered, the quality of evidence, and rationale for recommendations.

Summary of Findings

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In October 2017, the ACIP made the following recommendations:

1) Recombinant zoster vaccine (RZV) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years.

2) RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL).

3) RZV is preferred over ZVL for the prevention of herpes zoster and related complications.

CDC 2018 Herpes Zoster Policy Note recommendations serve as a supplement to the existing recommendations for the use of ZVL in immunocompetent adults aged ≥60 years.

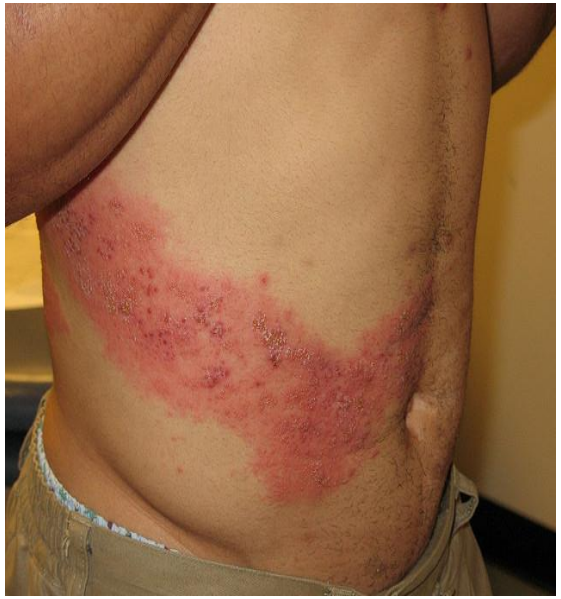
Dooling et al. **MMWR Jan 26, 2018**

Outline

- Background
  - Herpes zoster disease, epidemiology and vaccination
- ACIP Recommendations for Herpes Zoster Vaccines
  - Rationale
- Clinical guidance for Recombinant Zoster Vaccine (RZV, Shingrix)
  - Who
  - When
  - What
  - How

Background

Herpes Zoster (HZ): Clinical Manifestations



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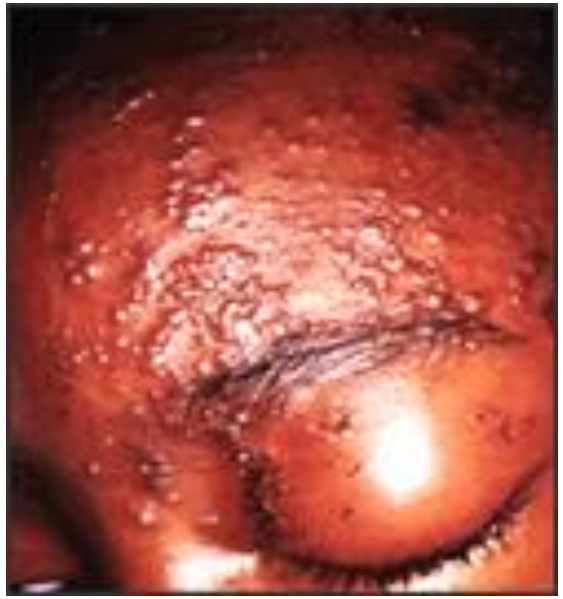

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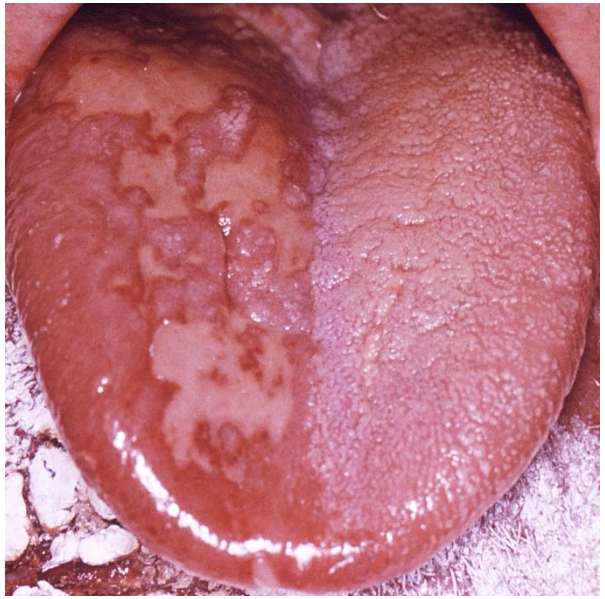


Courtesy of CDC/Robert Sumpter

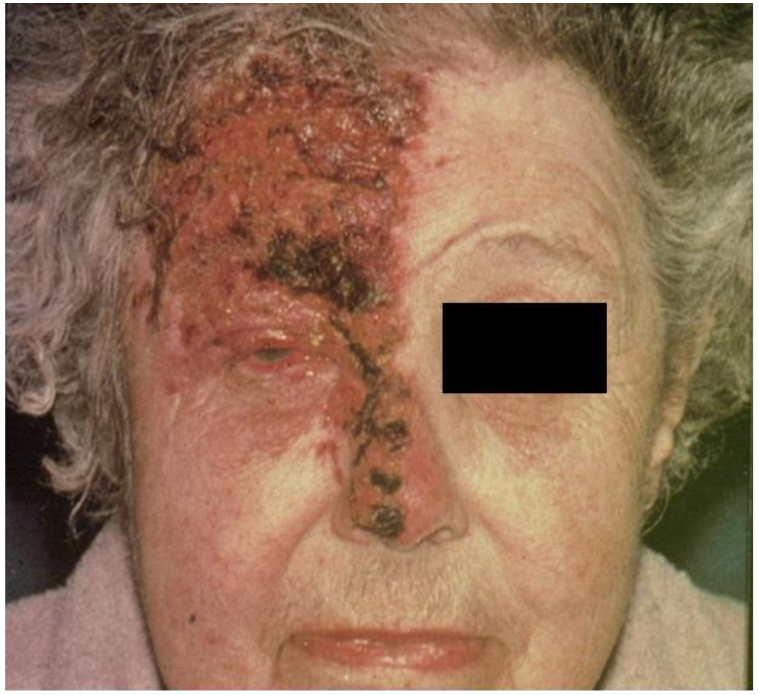
Herpes Zoster & PHN: Clinical Manifestations

Herpes Zoster

- About 90% of HZ episodes associated with pain
- Treatment: antivirals reduce duration of rash and pain[1]

PHN

- Pain at least 90 days following resolution of rash
- Treatment: minimal or no efficacy. Side effects, especially in elderly[2]



Courtesy of M. Oxman

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

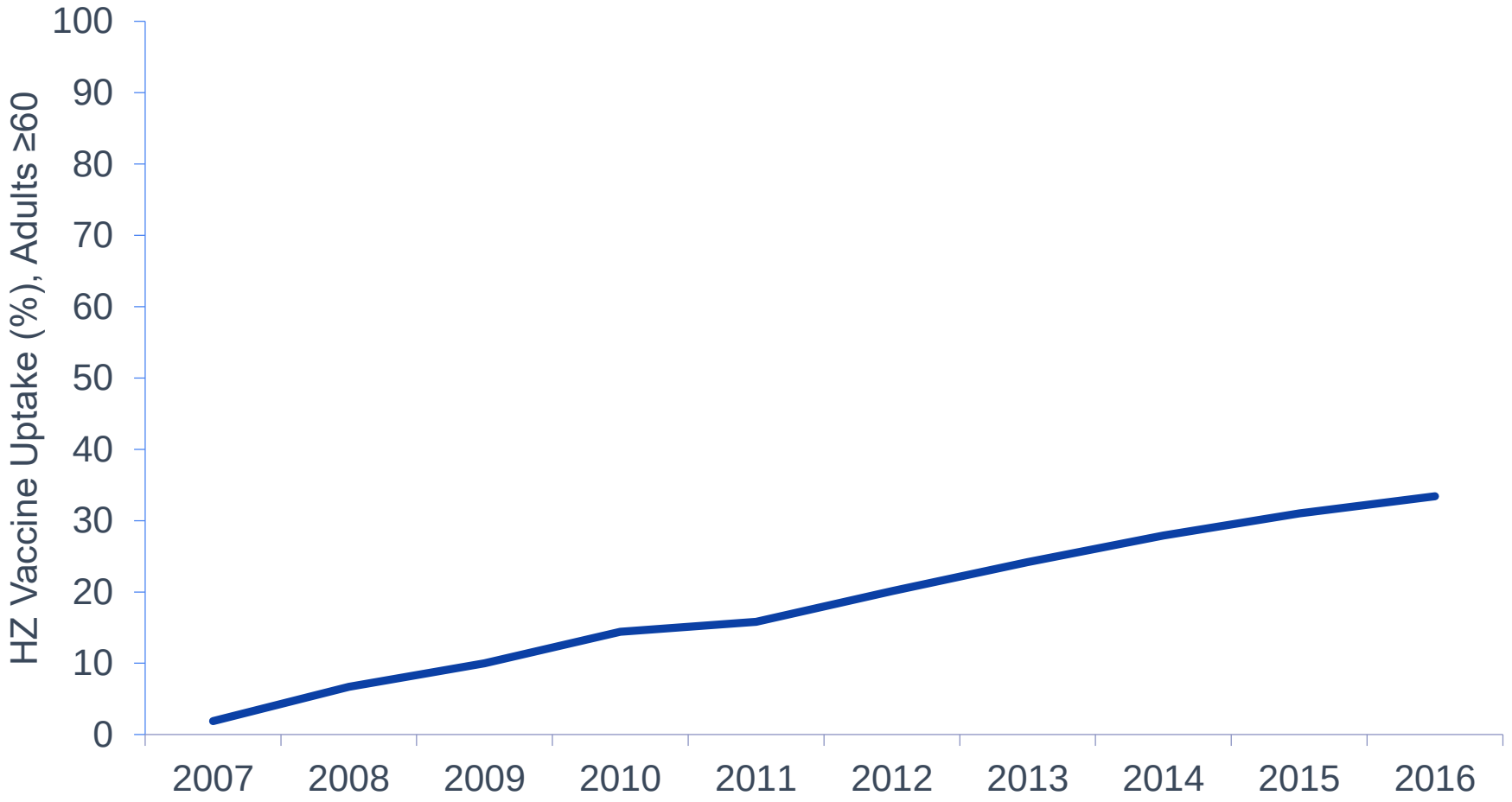
1. Cohen et al, NEJM 2013, 2. Johnson et al, NEJM 2014

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

- ~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 age[3]
- Zoster Vaccine Live (ZVL, ZOSTAVAX™) has been licensed in the U.S. since 2006-- 33% 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. CDC, provisional unpublished data from NHIS

Vaccination Coverage of Zoster Vaccine Live (ZVL), among adults ≥60 yrs, United States, 2007-2016



* 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), 2016 CDC, unpublished

2018 ACIP Recommendations

Shingrix- Recombinant Zoster Vaccine (RZV)

- **An adjuvanted recombinant protein subunit vaccine (previously referred to as HZ/su)**
- **2 components**
  - Glycoprotein E
  - Adjuvant $ASO1_B$
- **Efficacy & safety evaluated in a 2-part, phase III RCT, >30,000 subjects**
  - ZOE 50 (50+ yrs)
  - ZOE 70 (70+ yrs)
- **Licensed by the FDA on Oct 20, 2017**
  - https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm581491.htm

1) RZV is recommended for immunocompetent adults aged ≥50 years.

- **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 ≥ **85%** for 4 years following vaccination in ≥ 70 year olds

- **Harms:**
  - 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%)

1) RZV is recommended for immunocompetent adults aged ≥50 years.

- Long-term immunogenicity:
  - 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

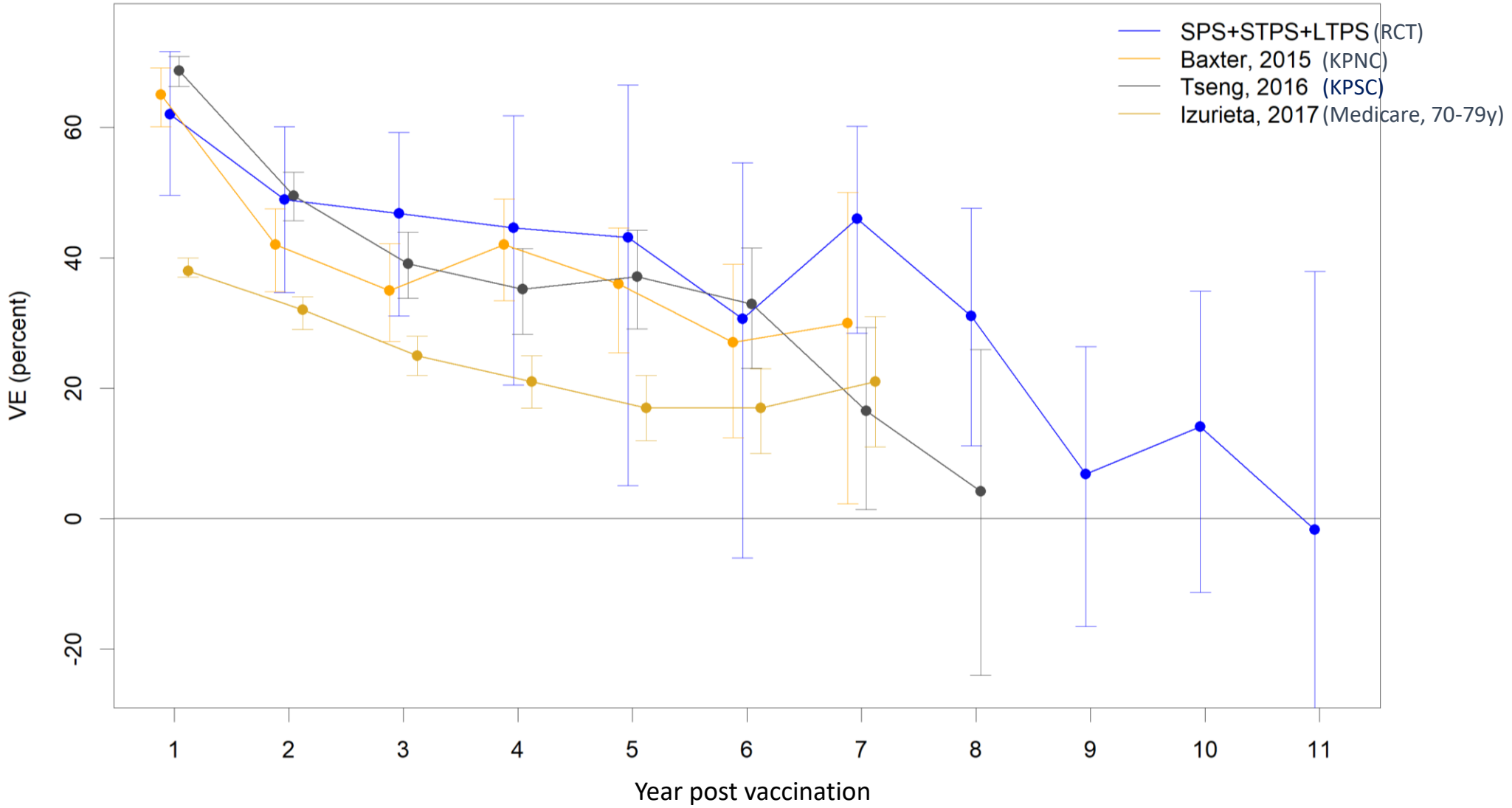
- Number needed to vaccinate to prevent 1 case:
  - HZ: 11 – 17
  - PHN: 70 – 187

- Cost-effectiveness:
  - $31,000/QALY (average 50 yrs+)
    - $9,700/QALY (80-89 yo)- $47,000/QALY (50-59 yo)

2) RZV is recommended for immunocompetent adults who previously received zoster vaccine live (ZVL)

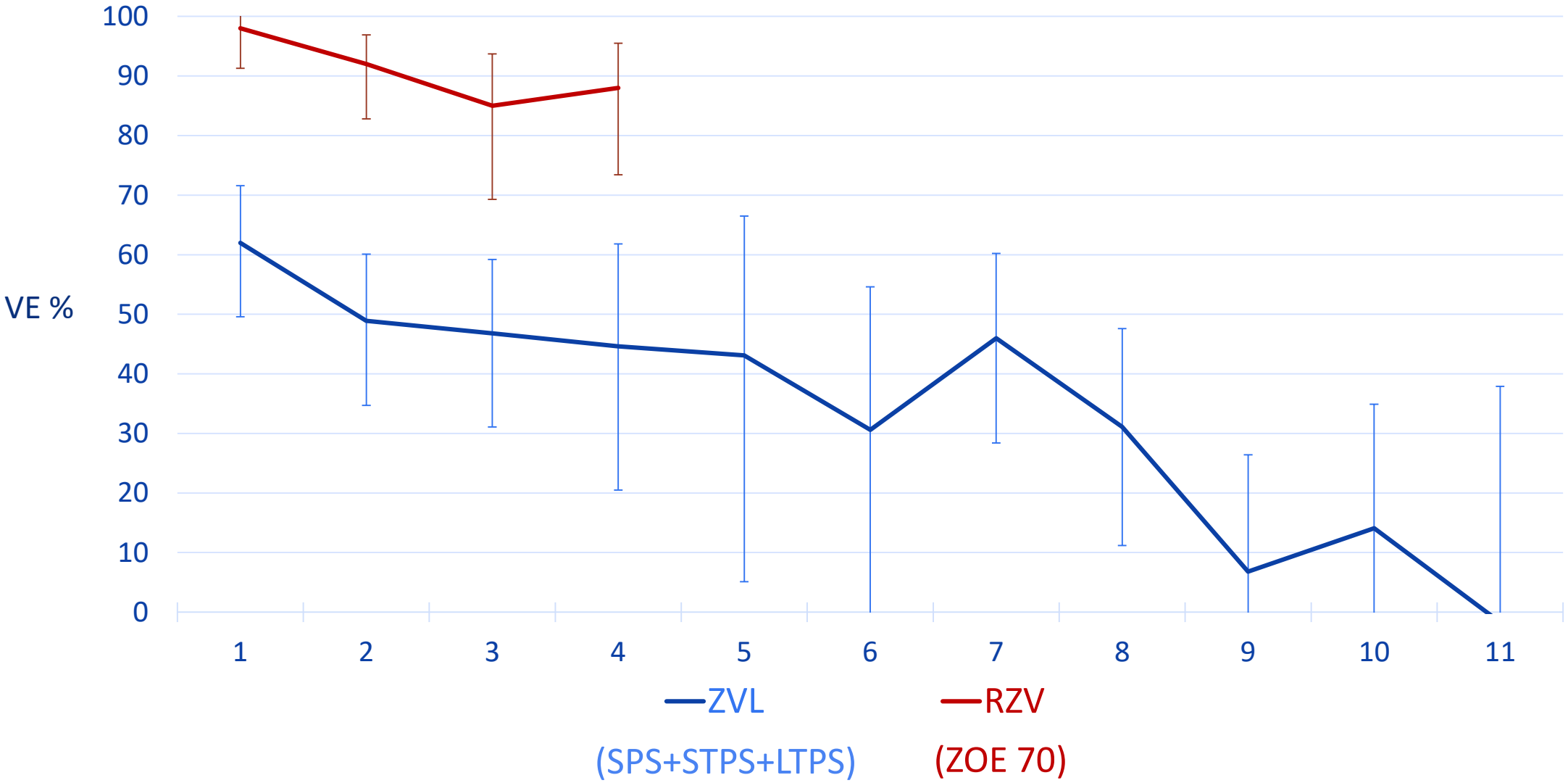
- RZV is more efficacious than ZVL in all age categories; differences are larger at older ages
- Experimental and observational studies indicate significant waning of protection from ZVL:
  - VE drops the first year after receipt (15-25%)
  - By 6 yrs post vaccination, VE <35%
  - Negligible protection by 10 years
- RZV 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

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 RZV, 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.

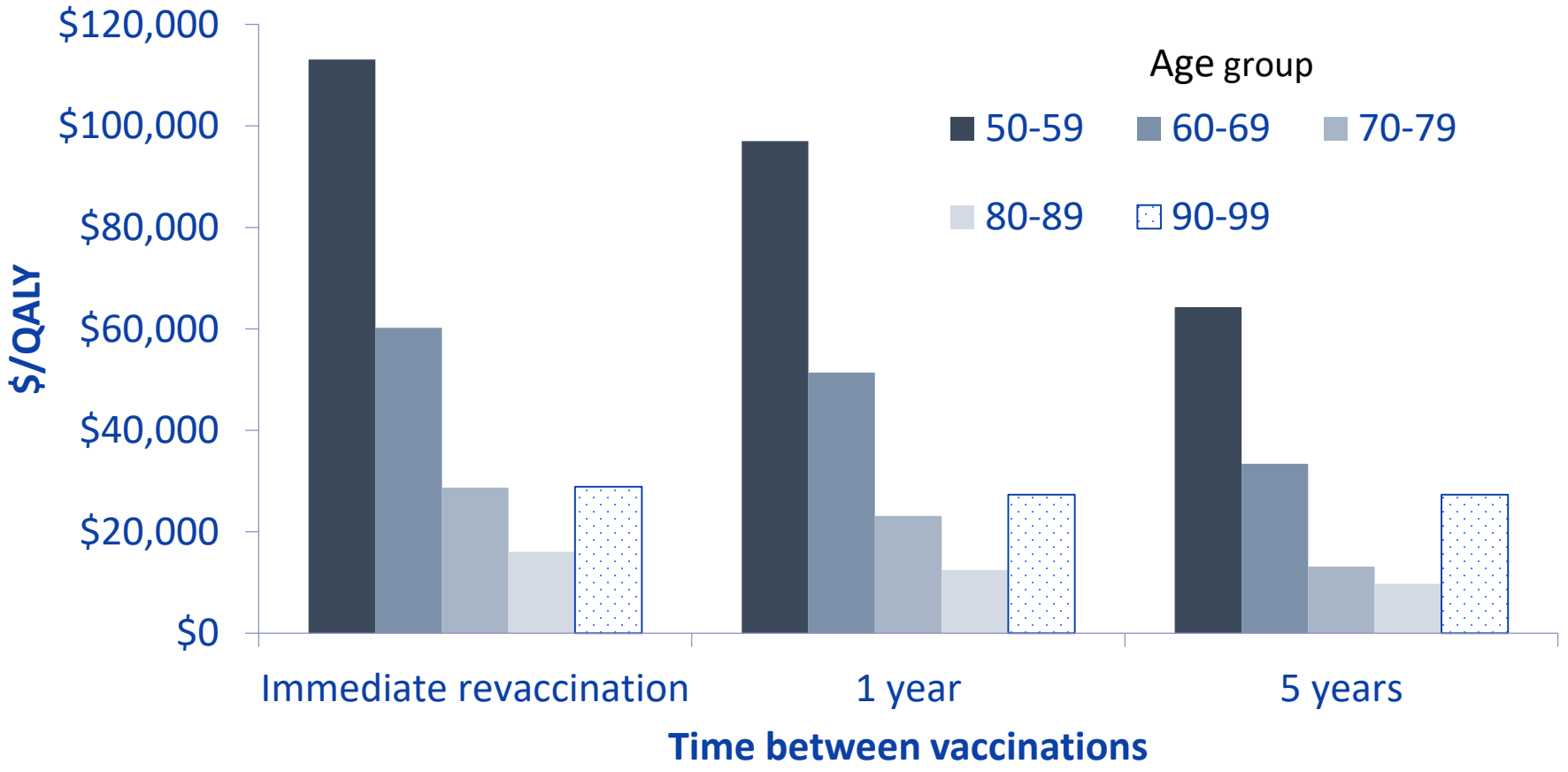
2) RZV is recommended for immunocompetent adults who previously received zoster vaccine live (ZVL)

- In a small study, vaccination with RZV 5 yrs following ZVL did not alter the safety or immunogenicity of RZV.
- 20 million people have been vaccinated with ZVL and potentially eligible for RZV[1]
- Cost-effectiveness ratios for revaccination were calculated for all ages, for the following intervals:
  - 8 weeks (approximated by t=0 in the model)
  - 1 yr
  - 5 yrs

1. Source: IMS

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

Cost effectiveness of RZV following ZVL receipt



Adapted from Prosser, ACIP Oct 2017

3) RZV is preferred over ZVL

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

Efficacy

- RZV 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

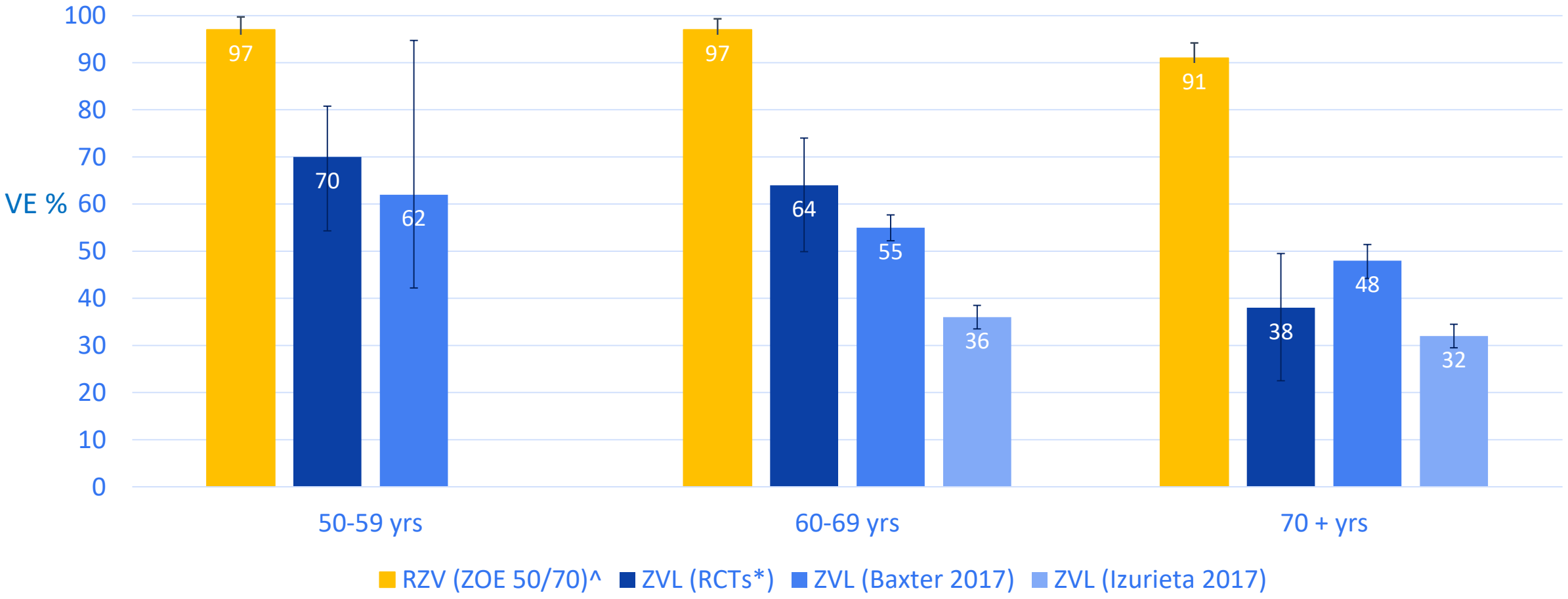
Adverse Effects

- Neither vaccine is associated with serious adverse events in immunocompetent persons
- RZV is more reactogenic than ZVL

Economics

- RZV leads to more disease prevention and decreased overall costs (vaccine + expected disease costs)

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

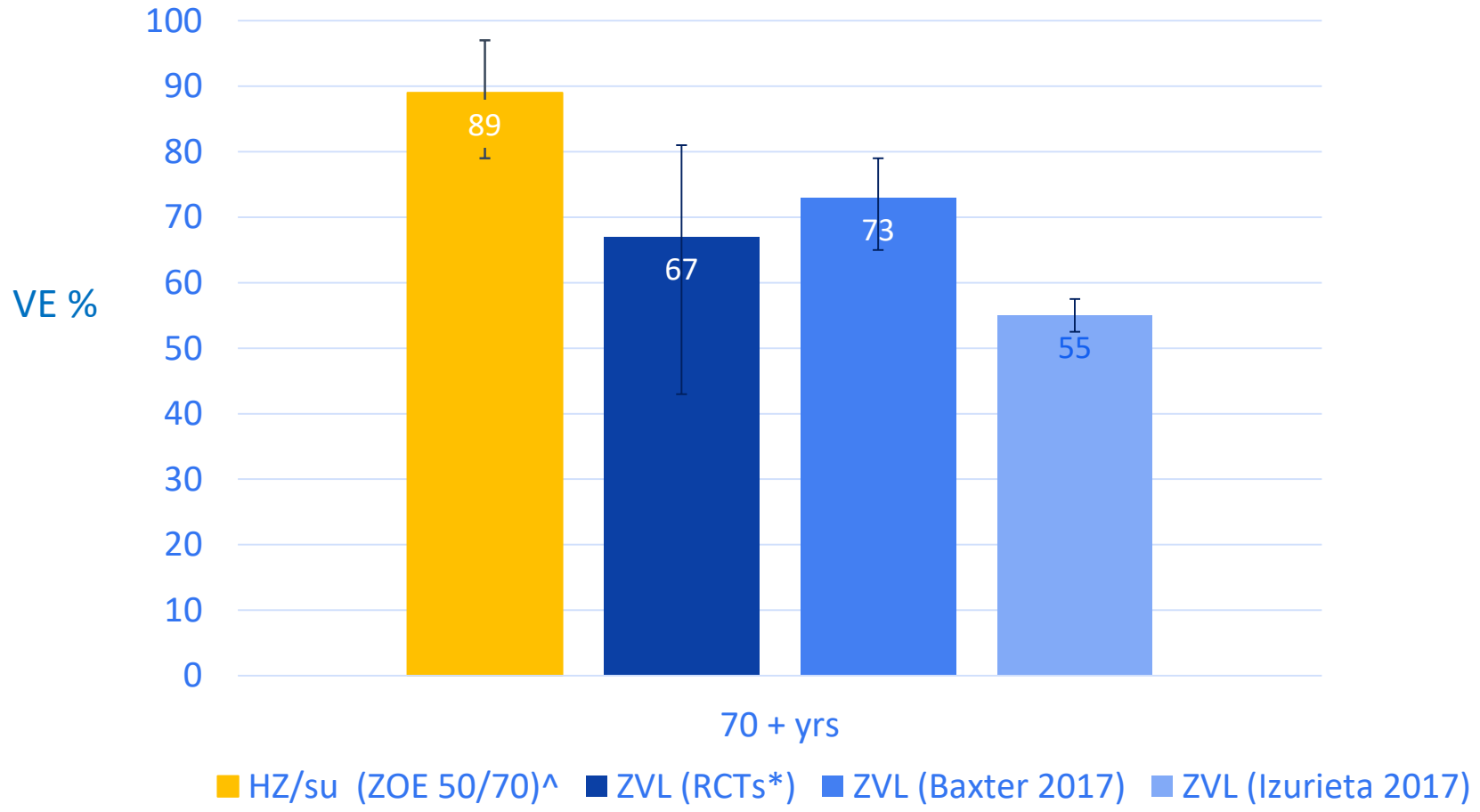


‡ Median follow up may be less than 3 yrs: Schmader 2012= 1.3 yrs

^ 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 RZV 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,

Projected cases (per 1000): No vaccine, ZVL and RZV

	No vaccine	ZVL	RZV
Herpes Zoster			
50-59 years	265	231	186
60-69 years	204	170	117
70-79 years	138	119	61
80-89 years	81	77	23
90-99 years	42	42	7
Total	**730**	**639**	**394**
Postherpetic neuralgia			
50-59 years	32	29	27
60-69 years	31	25	21
70-79 years	27	20	13
80-89 years	21	17	6
90-99 years	14	12	2
Total	**125**	**103**	**69**

Adapted from Prosser, ACIP Oct 20017

Clinical Guidance

Who, When, What, How

Clinical Guidance– Who?

Recommended for immunocompetent adults ≥50 years old, including:

- Adults with chronic medical conditions
- Adults taking low-dose immunosuppressive therapy, anticipating or have recovered from immunosuppression
- Adults with prior receipt of varicella vaccine, ZVL, or herpes zoster episode

HZ vaccines do not require screening for a history of chickenpox (varicella)

Immunocompromised persons were excluded from ZOE Phase III efficacy studies, thus, ACIP is awaiting studies of RZV in these patients.

Clinical Guidance- Who?

CONTRAINDICATION:

- Allergy: RZV should not be administered to persons with a history of severe allergic reaction, such as anaphylaxis, to any component of this vaccine.

PRECAUTIONS:

- Current herpes zoster infection
- Pregnancy and breastfeeding

Clinical Guidance- When?

2 doses necessary for protection

- 2-6 months apart
- The series need not be restarted if >6 months elapse (*expert opinion*)

For adults who previously received ZVL:

- No interference or safety problems when RZV vaccination administered ≥5 years after ZVL
- Consider a shorter interval
  - Eg. if individual is ≥70yrs, protection from ZVL is 38% over ~3yrs
- Minimal interval of 8 weeks between ZVL and RZV (*expert opinion*)

Clinical Guidance- What/How?

- **Store between 36-46ºF (2-8ºC)**
- **Reconstitute 2 components**
  - Lyophilized Glycoprotein E
  - Adjuvant ASO1$_B$

  } 0.5ml
- **Administer intramuscularly in the deltoid**
- **RZV may be co-administered with other vaccines**

Source: GSK

https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm581491.htm

Clinical Guidance

Common errors to avoid:

1) **Storage**: Refrigerate between **36-46°F** ⇨ Do NOT freeze

1) **Reconstitution**: Mix antigen and **adjuvant provided** ⇨ Do NOT use sterile water/other

1) **Administration**: Administer **I.M. in DELTOID** ⇨ Do NOT administer S.Q.

Clinical Guidance: Patient Counseling

Know the benefits and side effects of Shingrix so you're prepared to talk with your patients before administering the vaccine.

- **You may tell patients:**
  - You can protect yourself against shingles. Shingles is a very painful disease, and your risk of getting it increases as you age.
  - Also, you are more likely to have severe, long-term pain if you get shingles when you are older.
  - About 1 out of every 3 people in the United States will develop shingles in their lifetime.
  - Shingrix provides strong protection against shingles and long-term pain from the disease. Two doses of Shingrix are more than 90% effective at preventing shingles. So it's very important that you get this vaccine.

Clinical Guidance: Counseling for Reactogenicity

Before vaccination, counsel about expected systemic and local reactogenicity

- pain (78%)
- myalgia (45%)
- fatigue (45%)

- **1 in 6 recipients had reactions that prevented regular activities (grade 3 rxn)**
  - Suggest patients plan to avoid strenuous activities, such as yardwork or swimming, for a few days after vaccination. Remind them that the pain from shingles can last a lifetime, and these side effects should only last 2-3 days.
- **Reactions to the first dose did not strongly predict reactions to the second dose**
- **Vaccine recipients should be encouraged to complete the series even if they experienced a grade 1–3 reaction to the first dose.**
  - You may suggest patients take over-the-counter pain medicine such as ibuprofen or acetaminophen to ease the pain from side effects.

Recombinant Zoster Vaccine (Shingrix)- Supply

- Due to high levels of demand for GSK's Shingrix vaccine, providers should anticipate ordering limits and intermittent shipping delays for Shingrix between now and the end of June 2018, whether vaccine is ordered directly from GSK or through wholesalers and distributors. GSK is currently working to make more doses available in the near term for the US market in order to meet the demand for this vaccine. (https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html)

- While Shingrix should be administered to adults age 50 years and older as a two-dose series, 2 to 6 months apart, if more than 6 months have elapsed since the first dose of Shingrix, you should administer the second dose as soon as possible. However, you do not need to restart the vaccine series. CDC does not recommend substituting another shingles vaccine for the second dose if Shingrix is not available.)

- For more information on the Shingrix shipping delays, please contact GSK.

QUESTIONS?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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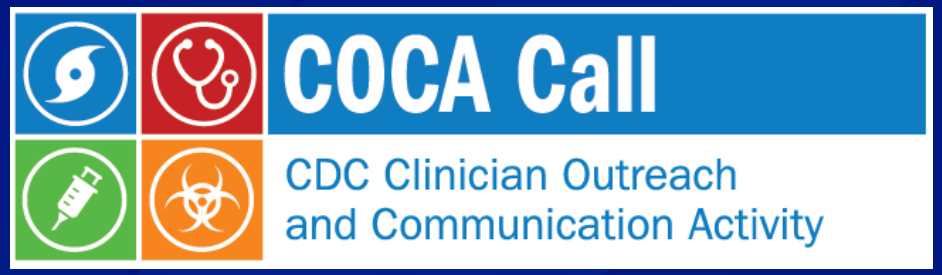

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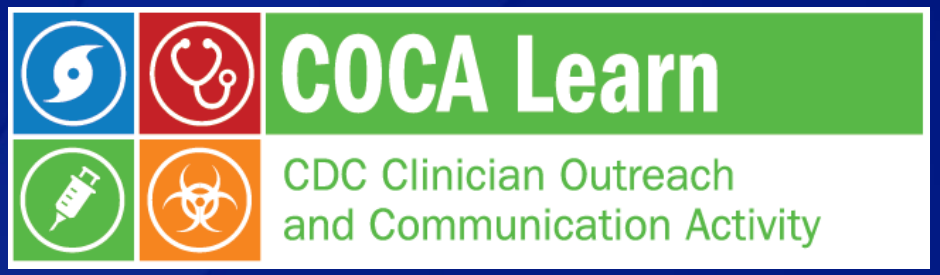

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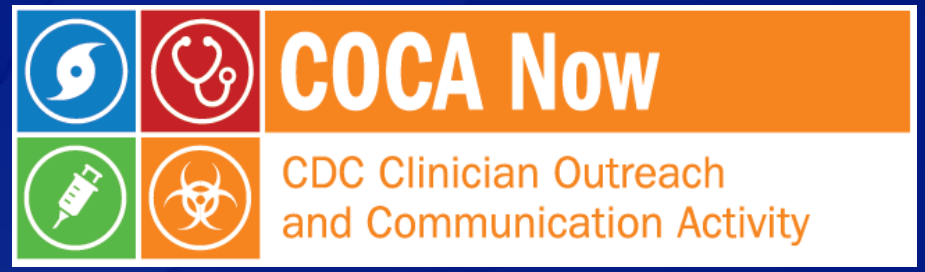
COCA Products & Services

Monthly email that provides new CDC & COCA resources for clinicians from the past month and additional information important during public health emergencies and disasters.



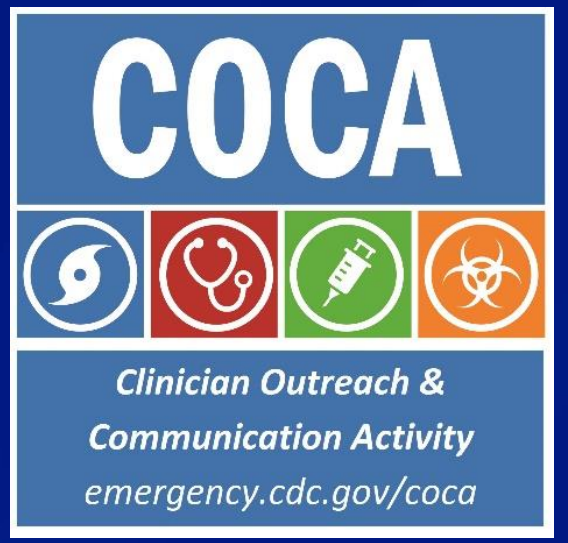
Informs clinicians of new CDC resources and guidance related to emergency preparedness and response. This email is sent as soon as possible after CDC publishes new content.

CDC's primary method of sharing cleared information about urgent public health incidents with public information officers; federal, state, territorial, and local public health practitioners; clinicians; and public health laboratories.

Join COCA's Mailing List!

Receive information about:

- Upcoming COCA Calls
- Health Alert Network notices
- CDC public health activations
- Emerging health threats
- Emergency preparedness and response conferences and training opportunities



http://emergency.cdc.gov/coca

CDC Clinician Outreach and Communication Activity - COCA

@CDCClinicianOutreachAndCommunicationActivity

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1600 Clifton Rd NE
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Posts

CDC Clinician Outreach and Communication Activity - COCA shared their event.

October 31 at 1:18pm

Clinicians, you can earn FREE CE with this COCA Call! Join us for this COCA Call November 7, 2017 at 2:00PM.

Thank you for joining!

Centers for Disease Control and Prevention
Atlanta, Georgia
http://emergency.cdc.gov/coca