Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Recombinant zoster vaccine (RZV) and Herpes Zoster Live-Attenuated Vaccine (ZVL)

Introduction

Since 2008, ZOSTAVAX®, a one-dose of herpes zoster live-attenuated vaccine (ZVL), has been recommended by the Advisory Committee for Immunization Practices (ACIP) for the prevention of herpes zoster in immunocompetent adults aged 60 years and older [1-2].

On October 20th 2017, SHINGRIX, a two-dose, adjuvanted, recombinant zoster vaccine (RZV) was approved by the FDA for the prevention of herpes zoster in immunocompetent adults aged 50 years and older. From 2015-2017, the ACIP reviewed evidence and considerations regarding the use of RZV (formerly referred to as herpes zoster subunit vaccine or HZ/su) in the United States to prevent herpes zoster and its complications. As part of ACIP's process, a systematic review and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) of the evidence for both herpes zoster vaccines was conducted and presented to ACIP. There were no conflicts of interest reported by CDC and ACIP Herpes Zoster Work Group members involved in the GRADE analysis.

The GRADE approach was adopted by ACIP in 2010 as the framework for evaluating the scientific evidence that informs recommendations for vaccine use. GRADE was used to evaluate both RZV and ZVL. Evidence of benefits and harms were reviewed based on the GRADE approach [3].

Separate GRADE analyses were conducted for each vaccine.

- **RZV:** GRADE was used to evaluate routine vaccination of healthy older adults with the recombinant zoster vaccine. The primary policy question was "Should a two-dose series of the recombinant zoster vaccine be given routinely to immunocompetent adults aged 50 years and older for the prevention of herpes zoster?"
- **ZVL:** GRADE was used to evaluate routine vaccination of healthy older adults with the live-attenuated herpes zoster vaccine (ZVL). The primary policy question was "Is one dose of ZVL safe and effective at preventing herpes zoster and postherpetic neuralgia PHN in the United States among immunocompetent adults aged 50 years and older?"

Methods for GRADE

GRADE of RZV studies

We conducted a systematic review of evidence on the efficacy and safety of a two dose regimen of recombinant zoster vaccine (RZV or SHINGRIX) to immunocompetent adults aged 50 years and older. We assessed outcomes and evaluated the quality of evidence using the GRADE approach.

We identified studies in Medline, Embase, CINAHL, Cochrane, Scopus and clinicaltrials.gov, without any language or date restrictions. Search terms are described in **Table 1**.

Articles were included if they provided data on vaccination with RZV and 1) involved human subjects; 2) reported primary data; 3) included immunocompetent adults aged 50 years or older; 4) included data relevant to the outcomes being measured; and 5) included data for the dosage and timing being recommended (50 µg gE/AS01B, 2 doses at 0 and 2 months). Efforts were also made to obtain unpublished and other relevant data by hand-searching reference lists, and consulting with vaccine manufacturers and subject matter experts. Title and abstracts were screened independently by two separate reviewers. After title and abstract screening, 22 studies were identified for in-depth review. Of these, 6 were still ongoing or had not yet reported results; 3 studies were done among immunocompromised participants; and 3 included co-administration of RZV with another vaccine as the intervention. This left 10 studies for the GRADE analysis [4-13]. Characteristics of these studies are presented in **Table 2**.

Beneficial and harmful outcomes for assessment were selected by the Work Group during work group calls and via online surveys where members were asked to rank the importance of relevant outcomes. The outcomes deemed critical by the work group were prevention of herpes zoster, prevention of PHN, and serious adverse events related to vaccination. Outcomes deemed important by the work group were duration of protection against herpes zoster and reactogenicity, specifically Grade 3 reactions (reactions that prevent normal activities) following vaccination.

The results of the GRADE analysis were presented to ACIP in February 2017.

Table 1. Evidence retrieval strategy, RZV

Database	**Search terms**
Medline (OVID) 1946-	(herpes zoster and subunit) OR (HZ ADJ5 subunit) OR HZ su OR GSK 1437173A
Embase (OVID) 1947-	(herpes zoster and subunit) OR (HZ ADJ5 subunit) OR HZ su OR GSK 1437173A
CINAHL (Ebsco) 1982-	(herpes zoster and subunit) OR (HZ ADJ5 subunit) OR HZ su OR GSK 1437173A
Cochrane Library	("herpes zoster" and subunit) OR (HZ NEAR/5 subunit) OR "HZ su" OR "GSK 1437173A"
Clinicaltrails.gov	herpes zoster subunit OR HZ subunit OR RZV OR GSK 1437173A
Scopus	TITLE-ABS-KEY(("herpes zoster" and subunit) OR (HZ NEAR/5 subunit) OR "HZ su" OR "GSK 1437173A") AND NOT INDEX(medline)

Abbreviations: RZV: Recombinant zoster vaccine

Table 2. Characteristics of Included Studies, RZV

Author, year	**Study design (N=total enrolled)**	**Population**	**VE [95% CI]**	**Safety**
Cunningham, 2016	RCT, 18 countries (N=14,816)	Immunocompetent adults ≥70 yrs	VE (HZ): 89.8% [84.2-93.7] VE (PHN): 88.8% [68.7-97.1]	**Serious adverse events (SAE)** Intervention: 0.2% [0.1-0.3] Placebo: 0.1% [0.0-0.2] **Reactogenicity**

			VE (HZ), by year post vaccination: 1y: 97.6% [90.9-99.8] 2y: 92.0% [82.8-96.9] 3y: 84.7% [69.0-93.4] 4y: 87.9% [73.3-95.4]	Any Grade 3 symptoms: Intervention: 11.9% [9.2-15.0] Placebo: 2.0% [1.0-3.6]
Lal, 2015	RCT, 18 countries (N=16,160)	Immunocompetent adults ≥50 yrs	VE (HZ): 97.2% [93.7-99.0]	**Serious adverse events** Intervention: 0.0% [0.0-0.1] Placebo: 0.0% [0.0-0.1] **Reactogenicity** Any Grade 3 symptoms: Intervention: 15.6% [14.5-16.7] Placebo: 1.9% [1.5-2.3]
Chlibek, 2013	RCT, 3 countries (N=410)	Immunocompetent adults ≥50 yrs	N/A	**Serious adverse events** No vaccine-related SAEs reported through month 14 **Reactogenicity** Any Grade 3 symptoms: Intervention: 9.3% Placebo: 5.3%
Chlibek, 2014 and Chilbek, 2016[+]	RCT, 4 countries (N=715)	Immunocompetent adults ≥60 yrs	N/A	**Serious adverse events** No vaccine related SAEs through month 72 **Reactogenicity:** Any Grade 3 symptoms: Not reported Specific Grade 3 symptoms: 1.2%-4.8% (myalgia most commonly reported symptom)
Lal, 2018[+]	RCT, 2 countries (N=119)	Immunocompetent adults ≥50 yrs	N/A	**Serious adverse events** No vaccine related SAEs through month 12 **Reactogenicity** Any solicited Grade 3 symptoms: Intervention: 15.1%
Leroux-Roels, 2012[+]	RCT, Belgium (N=135)	Immunocompetent adults 50-70 yrs	N/A	**Serious adverse events** No vaccine related SAEs through month 42 **Reactogenicity** Any Grade 3 symptoms: Not reported

				Specific Grade 3 symptoms: 0%-20% (redness most commonly reported symptom)
Vink, 2017[+]	RCT, Japan (N=60)	Immunocompetent adults ≥50 yrs	N/A	**Serious adverse events** No vaccine related SAEs through month 12 **Reactogenicity** Any Grade 3 symptoms: Not reported Specific Grade 3 symptoms: 0%-5% (redness most commonly reported symptom)
Godeaux, 2017[+]	Non-RCT, 2 countries (N=96)	Immunocompetent adults ≥50 yrs	N/A	**Serious adverse events** No vaccine related SAEs through month 12 **Reactogenicity** Any Grade 3 symptoms: Not reported Specific Grade 3 symptoms: 0%-10% (fatigue most commonly reported symptom)
Lal, 2013[+]	Non-RCT, Australia (N=10)	Immunocompetent adults 50-69 yrs	N/A	**Serious adverse events** No serious adverse events reported **Reactogenicity** Any Grade 3 symptoms: Intervention: 40%

Abbreviations: RZV: Recombinant zoster vaccine; VE: vaccine efficacy/effectiveness; 95% CI: 95% Confidence Interval; HZ: herpes zoster; PHN: post-herpetic neuralgia; SAE: Serious adverse events; RCT: randomized controlled trial; Non-RCT: non-randomized clinical trial;

[+] No comparison group: no participants received no vaccine or placebo.

GRADE of ZVL studies

We conducted a systematic review of evidence on the effectiveness and safety of a live attenuated herpes zoster vaccine (ZVL or ZOSTAVAX®) for immunocompetent adults aged 50 years and older. We assessed outcomes and evaluated the quality of evidence using the GRADE approach.

We identified studies in Medline, Embase, CINAHL, Cochrane, Scopus and clinicaltrials.gov, without any language or date restrictions. Search terms are described in **Table 3**.

Articles were included if they provided data on vaccination with one dose of ZVL and 1) involved human subjects; 2) reported primary data; 3) included immunocompetent adults aged 50 years or older; and 4) included data relevant to the outcomes being measured. Efforts were also made to obtain unpublished and other relevant data. Title and abstracts were screened independently by two separate reviewers. After title and abstract screening, 159 studies were identified for further review. Of these, 52 did not report outcomes of interest, 27 did not report data for ZVL, 23 had results reported in another study, 11 were still ongoing or had not yet reported results; and 7 were individual case reports. This left 40 studies for the GRADE analysis [14-53]. Characteristics of these studies are presented in **Table 4**.

The outcomes deemed critical by the work group were prevention of herpes zoster, prevention of PHN, and serious adverse events related to vaccination. Outcomes deemed important by the work group were duration of protection against herpes zoster (defined as 4 or more years post vaccination) and reactogenicity following vaccination.

The results of the GRADE analysis were presented to ACIP in June 2017.

Table 3. Evidence retrieval strategy, ZVL

Database	Strategy
Medline (OVID) 1946-	(zostavax OR (zoster AND (vaccine ADJ2 live*)) OR (zoster AND (attenuated ADJ2 live)) OR (zoster AND (vaccine ADJ2 attenuated)) OR ((zoster ADJ3 vaccin*) AND shingles))
Embase (OVID) 1947-	(zostavax OR (zoster AND (vaccine ADJ2 live)) OR (zoster AND (attenuated ADJ2 live)) OR (zoster AND (vaccine ADJ2 attenuated)) OR ((zoster ADJ3 vaccin*) AND shingles))
CINAHL (Ebsco) 1982-	(zostavax OR (zoster AND (vaccine N2 live*)) OR (zoster AND (attenuated N2 live)) OR (zoster AND (vaccine N2 attenuated)) OR ((zoster N3 vaccin*) AND shingles))
Cochrane Library	(zostavax OR (zoster AND (vaccine NEAR/2 live*)) OR (zoster AND (attenuated NEAR/2 live)) OR (zoster AND (vaccine NEAR/2 attenuated)) OR ((zoster NEAR/3 vaccin*) AND shingles))
Clinicaltrails.gov	Zostavax OR "zoster live vaccine" OR "zoster live attenuated" OR "zoster vaccine attenuated"
Scopus	TITLE-ABS-KEY(zostavax OR (zoster AND (vaccine W/2 live*)) OR (zoster AND (attenuated W/2 live)) OR (zoster AND (vaccine W/2 attenuated)) OR ((zoster NEAR/3 vaccin*) AND shingles)) AND NOT INDEX(medline)

Table 4. Characteristics of Included Studies, ZVL

Author, year	Study design (N=total enrolled)	Population	VE [95% CI]	Safety

Oxman, 2005 (SPS)	**RCT, USA (N=38,546)**	Immunocompetent adults ≥60y	VE (HZ): 51.3% [44.2-57.6] VE (PHN): 66.5% [47.5-79.2]	**Serious adverse events (SAE)** Intervention: 1.9% Placebo: 1.3%, p<0.05* **Reactogenicity** Any injection-site symptoms: Intervention: 48% Placebo: 17%, p<0.05
Schmader, 2012 (STPS)	**RCT w/limitations, USA (N=14,270)**	Immunocompetent adults ≥60y	VE (HZ), by year post vaccination: 4y*: 44.6% [20.5-61.8] 5y*: 43.1% [5.1-66.5] 6y: 30.6% [-6.0-54.6] **HZ events and person-years follow-up pooled for SPS and STPS* VE (PHN), 3 to 7 years post vaccination: 60% [-10-87%]	**Serious adverse events** No serious adverse events related to the vaccination reported.
Morrison, 2015 (LTPS)	**RCT w/limitations, USA (N=6,867)**	Immunocompetent adults ≥60y	VE (HZ), by year post vaccination: 7y*: 46.0% [28.4–60.2] 8y*: 31.1% [11.2–47.6] 9y: 6.8% [−16.5-26.4] 10y: 14.1% [−11.3-34.9] 11y: −1.7% [−57.1-37.9] **HZ events and person-years follow-up pooled for STPS and LTPS* VE (PHN), 7 to 11 years post vaccination: 35% [9-56]	**Serious adverse events** No serious adverse events related to the vaccination reported.
Schmader, 2012 (ZEST)	**RCT, North America and Europe (N=22,439)**	Immunocompetent adults 50-59y	VE (HZ): 69.8% [54.1-80.6]	**Serious adverse events** Intervention: 0.6% Placebo: 0.5%, p>0.05 **Reactogenicity** Any injection-site symptoms: Intervention: 64% Placebo: 14%, p<0.05
Langan, 2013	**Cohort, USA (N=766,330)**	Medicare enrollees, adults ≥65y	VE (HZ): 48% [39-56] VE (PHN): 59% [21-79]	Did not report safety results.

Tseng, 2014	**Cohort, USA (N=21,476)**	KPSC members, adults ≥60y who later undergo chemotherapy	Hazard ratio (HZ, vaccinated vs unvaccinated): 0.58 [0.46-0.73]	Did not report safety results.
Tseng, 2016b	**Cohort, USA (N=3,492)**	KPSC members, adults ≥60y with end-state renal disease	Hazard ratio (HZ, vaccinated vs unvaccinated): 0.49 [0.29-0.85]	Did not report safety results.
Tseng, 2015	**Cohort, USA (N=2,310)**	KPSC members, adults ≥60y	Risk ratio (PHN, vaccinated vs unvaccinated): 0.59 [0.41-0.85]	Did not report safety results.
Baxter, 2017	**Cohort, USA (N=1.3 million)**	KPNC members, adults ≥50y	VE (HZ): 49.1% [47.5-50.6]	Did not report safety results.
Marin, 2015	**Case control, USA (N=628)**	Adults aged ≥60y	VE (HZ): 54.2% [32.0-69.2] VE (PHN): 55.2% [0.0-91.6]	Did not report safety results.
Baxter, 2016a	**Cohort, USA (N=1.3 million)**	KPNC members, adults ≥50y	VE (PHN) = 68.7% [64.6-72.3]	Did not report safety results.
Tseng, 2016a	**Cohort, USA (N=706,312)**	KPSC members, adults ≥60y	VE (HZ), by year post vaccination: • 1y: 68.7% [66.3-70.9] • 2y: 49.5% [45.7-53.1] • 3y: 39.1% [33.8-43.9] • 4y: 35.2% [28.3-41.4] • 5y: 37.1% [29.1-44.2] • 6y: 32.9% [23.1-41.5] • 7y: 16.5% [1.4-29.3] • 8y: 4.2% [-24.0-25.9]	Did not report safety results.
Izurieta, 2017	**Cohort, USA (N=1,891,984)**	Medicare enrollees, adults ≥65y	VE (HZ), by year post vaccination • ≤3y: 33% [32-35] • ≥4y: 19% [17-22]	Did not report safety results.
Murray, 2011	**RCT, Canada, Germany, Spain, UK, US (N=11,999)**	Immunocompetent adults ≥60y	Did not report VE.	Estimated risk of SAEs within 42 days was 1.41% for vaccine recipients versus 1.12% for placebo, with a relative-risk of 1.26 [0.91-1.73]
MacIntyre, 2010	**RCT, Australia, Canada, Germany, Italy, Spain, UK (N=475)**	Immunocompetent adults ≥60y	Did not report VE.	**Serious adverse events** No SAE related to vaccine reported within 28 days **Reactogenicity** Any injection-site symptoms: Intervention: 36%

				Placebo: 11%
Mills, 2010	**RCT, USA (N=101)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAE related to vaccine reported within 28 days **Reactogenicity** Any injection-site symptoms: Intervention: 46% Placebo: 4%
Beals, 2016	**RCT, USA (N=224)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAE related to vaccine reported within 42 days **Reactogenicity** Any injection-site symptoms: Intervention: 52% Placebo: 13%
Hata, 2016	**RCT, Japan (N=62)**	KPNC members, adults ≥60y	Did not report VE.	**Serious adverse events** No SAE related to vaccine reported within 42 days **Reactogenicity** Any injection-site symptoms: Intervention: 8% Placebo: 11%
Macaladad, 2007	**RCT, Brazil, Costa Rica, Colombia, Mexico, Peru, Venezuela, Phillipines (N=21)**	Immunocompetent adults ≥30y	Did not report VE.	**Serious adverse events** No SAE related to vaccine reported within 42 days **Reactogenicity** Any injection-site symptoms: Intervention: 11% Placebo: 0%
Zoran, 2016	**RCT, USA (N=28,785)**	Immunocompetent adults ≥60y	Did not report VE.	**Reactogenicity** Any Grade 3 symptoms: Not reported Specific Grade 3 symptoms: 0.4%-0.9% (erythema most commonly reported symptom)
Baxter, 2012	**Cohort, USA (N≈29,000)**	KPNC members, adults ≥60y	Did not report VE.	Compared rates of adverse events in a 42-day risk time period immediately following vaccination with rates in the same cohort in a subsequent comparison time period. Found increased relative risks

				for coronary atherosclerosis and other heart disease, percutaneous transluminal coronary angioplasty, systemic lupus erythematosus and connective tissue disorders. But after medical chart review found no safety concerns within 42 days of vaccination.
Tseng, 2012	**Cohort, USA (N= 193,083)**	Adults ≥50y	Did not report VE.	Compared rates of adverse events using a case-centered and self-controlled case series design and found no increased risk for cerebrovascular events; cardiovascular events; meningitis; encephalitis; and encephalopathy; and Ramsay-Hunt syndrome and Bell's palsy. The risk of allergic reaction was significantly increased within 1-7 days of vaccination [relative risk = 2.13, 95% confidence interval (CI): 1.87-2.40 by case-centred method and relative rate = 2.32, 95% CI: 1.85-2.91 by SCCS]
Berger, 1998[+]	**RCT**[§]	Immunocompetent adults ≥55y	Did not report VE.	**Reactogenicity** Any injection-site symptoms: Intervention: 26.5%
Kerzner, 2007[+]	**RCT, USA and Europe (N=762)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity** Any injection-site symptoms: Intervention: 35%
Tyring, 2007[+]	**RCT, USA, Canada, UK, Germany, Belgium (N=698)**	Immunocompetent adults ≥55y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 42 days. **Reactogenicity** Any injection-site symptoms: Intervention: 62%
Gilderman, 2008[+]	**RCT, USA (N=367)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity**

				Any injection-site symptoms: Intervention: 46%
Leroux-Roels, 2012[+]	**RCT, Belgium (n=155)**	Immunocompetent adults 50-70y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 12 months. **Reactogenicity** Redness at injection-site: Intervention: 62% (4% were considered grade 3).
Vesikari, 2013[+]	**RCT, Finland, Germany, Italy, Spain, Netherlands (N=759)**	Immunocompetent adults ≥70y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity** Any injection-site symptoms: Intervention: 46%
Diez-Domingo, 2015[+]	**RCT, Germany and Spain (N=354)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity** Intramuscular administration resulted in significantly fewer injection-site reactions compared to subcutaneous administration [47.2% vs 69.5%, respectively]
Arnou, 2011[+]	**Non-RCT, France (n=96)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity** Any injection-site symptoms: Intervention: 52% (2 individuals reported severe injection-site reactions)
Hata, 2013[+]	**Non-RCT, Japan (N=20)**	Immunocompetent adults 60-70y with diabetes mellitus	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 1 year. **Reactogenicity** Intervention: 10%
Morrison, 2013[+]	**Non-RCT, USA (N=13,681)**	Immunocompetent adults ≥64y with documented herpes zoster	Did not report VE.	**Serious adverse events** Rates of SAEs not significantly different among those with or without prior zoster (0.95%

				and 0.66%, respectively; p= .37)
Stanford, 2014[+]	**Non-RCT, USA (N=54)**	Immunocompetent adults ≥50y	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 35 days. **Reactogenicity** Any injection-site symptoms: Intervention: 64%
Yao, 2015[+]	**Non-RCT, Taiwan (N=150)**	Adults ≥50y with any underlying chronic illness in stable condition	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 28 days. **Reactogenicity** Any injection-site symptoms: Intervention: 36%
Choi, 2016[+]	**Non-RCT, Korea (N=180)**	Adults ≥50y with any underlying chronic illness in stable condition	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 42 days. **Reactogenicity** Any injection-site symptoms: Intervention: 53%
Levin, 2003[+]	**Non-RCT, USA (N=196)**	Immunocompetent adults ≥60y previously received VZV vaccine	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 42 days. **Reactogenicity** Pain at injection-site: Intervention: 48%
Lelic, 2016[+]	**Non-RCT, Canada (N=240)**	Nursing home residents, adults ≥80y	Did not report VE.	No adverse events related to vaccine reported within 42 days.
Levin, 2016[+]	**Non-RCT, USA (N=600)**	Adults ≥60y with any underlying chronic illness in stable condition, including adults ≥70y who previously received ZVL	Did not report VE.	**Serious adverse events** No SAEs related to vaccine reported within 1 year. **Reactogenicity** Any injection-site symptoms: Intervention: 44%
Baxter, 2016b[+]	**Non-RCT, USA (N=376,531)**	KPNC members who received ZVL	Did not report VE.	No association found between sudden sensorineural hearing loss and ZVL, OR=0.424 (95% CI: 0.08-1.53)

Willis, 2016+	**Non-RCT, global**	Merck Adverse Event Reporting System worldwide postmarketing adverse event database	Did not report VE.	Merck's 10 year post-marketing analysis reviewed 23,556 reports with a total of 45,898 adverse events. The majority of reported adverse events were non-serious (93%). Most commonly reported adverse events were injection-site reactions and herpes zoster. There were some reports of PCR-confirmed VZV rash caused by Oka/Merck vaccine strain.

Abbreviations: ZVL: Live-attenuated zoster vaccine; VE: vaccine efficacy/effectiveness; 95% CI: 95% Confidence Interval; HZ: herpes zoster; PHN: post-herpetic neuralgia; SAE: Serious adverse events; RCT: randomized controlled trial; Non-RCT: non-randomized clinical trial; SPS: Shingles Prevention Study; STPS: Short-term Persistence Study; LTPS: Long-term Persistence Study; VZV: varicella zoster virus; KPNC: Kaiser Permanente Northern California; KPSC: Kaiser Permanente Southern California; OR: Odds ratio

*In the Shingles Prevention Study, adverse event substudy, significantly more subjects in the vaccine group had serious adverse events than in the placebo group (1.9% vs. 1.3%, respectively; P=0.03); A post hoc, subject-by-subject review found no clinically meaningful differences between the groups in the pathophysiology, nature, timing, intensity, or outcome of these events. (Oxman, NEJM, 2005)

** Ad-hoc analysis of reactogenicity among participants of the Shingles Prevention Study (Oxman, NEJM, 2005)

+ No comparison group: no participants received no vaccine or placebo.

§ Did not report number of subjects who received ZVL

Results

GRADE of RZV studies

Table 5. Included data, by outcome, RZV

Outcome	**Number of subjects (number of studies)**	**Comparison groups**	**Findings**
Prevention of herpes zoster	50-59y: 7,017 (1) 60-69y: 4,307 (1) ≥70y: 16,596 (1)	2 dose RZV vs placebo	VE [95% CI] • 50-59y: 96.6% [89.6-99.3] • 60-69y: 97.4% [90.1-99.7] • ≥70y: 91.3% [86.8-94.5]
Prevention of post-herpetic neuralgia	≥50y: 27,916 (1) ≥70y: 16,596 (1)	2 dose RZV vs placebo	VE [95% CI] • ≥50y: 91.2% [75.9-97.7] • ≥70y: 88.8% [68.7-97.1]
Duration of protection against herpes zoster (up	14,693 (1)	2 dose RZV vs placebo	VE remained about 85% in the first 4 years following vaccination

to 4 years post vaccination)			
Serious adverse events	29,965 (8)	2 dose RZV vs placebo	No differences in serious adverse events between vaccinated and placebo groups. No serious adverse events related to vaccination found.
Reactogenicity (Grade 3 reaction)	10,590[+] (8)	2 dose RZV vs placebo	Grade 3 reactions more commonly reported in vaccinated populations compared to placebo. In phase III clinical trials (n=9,936): • 16.5% of vaccine recipients reported any Grade 3 reaction compared to 3.1% of placebo recipients. • 9.4% of vaccine recipients reported Grade 3 injection-site reactions, compared to 0.3% of placebo recipients. • 10.8% of vaccine recipients reported Grade 3 systemic reactions, compared to 2.4% of placebo recipients. Safety and immunogenicity studies reported similar reactogenicity rates among participants receiving RZV

Abbreviations: y: years-old; RZV: recombinant zoster vaccine; VE: vaccine efficacy/effectiveness; 95% CI: 95% Confidence Interval

[+]In the ZOE 50/70 Phase III clinical trials, reactogenicity data was only collected from a randomly selected sub-set of participants (n=9,936)

Table 6. Summary of the evidence for select outcomes with use of RZV in immunocompetent adults aged 50 years and older

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Others	Evidence type	Outcome evidence type	Overall Evidence Type
Benefits										
Prevent herpes zoster	1 RCT	1	Not Serious	Not Serious	Not Serious	Not Serious	None	1	1	1
Prevent post-herpetic neuralgia	1 RCT	1	Not Serious	Not Serious	Not Serious	Not Serious	None	1	1	

Duration of protection against herpes zoster (up to 4 years post vaccination)	1 RCT	1	Not Serious	Not Serious	Not Serious	Not Serious	None	1	1	
Harms										
Serious adverse events (after any dose)	2 RCT	1	Not serious	Not serious	Not Serious	Not Serious	None	1	1	1
	4 RCT with no placebo	1	Serious*(-1)	Not Serious	Serious‡(-1)	Not Serious	None	3		
	2 Non-RCT	2	Serious*(-1)	Not Serious	Serious‡(-1)	Not Serious	None	4		
Reactogenicity (Grade 3 reaction)	2 RCT	1	Not serious	Not serious	Not Serious	Not Serious	None	1	1	
	4 RCT with no placebo	1	Serious*(-1)	Not Serious	Serious‡(-1)	Not Serious	None	3		
	2 Non-RCT	2	Serious*(-1)	Not Serious	Serious‡(-1)	Not Serious	None	4		

Abbreviations: RZV: recombinant zoster vaccine; RCT: randomized controlled trial; Non-RCT: non-randomized clinical trial
*Studies were non-blinded, open-label trials
‡No placebo comparison group. Did not directly meet our policy question of comparing outcomes between vaccine and placebo recipients

GRADE of ZVL studies

Table 7. Included data, by outcome, ZVL

Outcome	**Number of subjects (number of studies)**	**Comparison groups**	**Findings**
Prevention of herpes zoster	50-59y: 22,439 (1) ≥60y: ~4.7 million (8)	One dose ZVL vs placebo or no vaccine	Vaccine efficacy against herpes zoster, clinical trial data: VE [95% CI] – 50-59y: 70% [54-81] – 60-69y: 64% [56-71] – 70-79y: 41% [28-52] – ≥80y: 18% [-29-48] VE from observational studies in adults ≥60y ranged from 33% to 51% (within 4 years post vaccination)
Prevention of post-herpetic neuralgia	≥60y: ~4 million (8)	One dose ZVL vs placebo or no vaccine	Vaccine efficacy against herpes zoster, clinical trial data: VE [95% CI] – 60-69y: 65.7% [20.4-86.7] – ≥70y: 66.8% [43.3-81.3]

			VE from observational studies in adults ≥60y ranged from 41% to 69% (within 4 years post vaccination)
Duration of protection against herpes zoster (up to 4 years post vaccination)	≥60y: ~3.9 million (5)	One dose ZVL vs placebo or no vaccine	RCT (SPS, STPS, LTPS) VE, ≥60y, by year post vaccination: • 1y: 62.0 [49.6–71.6] • 2y: 48.9 [34.7–60.1] • 3y: 46.8 [31.1–59.2] • 4y: 44.6 [20.5–61.8] • 5y: 43.1 [5.1–66.5] • 6y: 30.6 [−6.0 to 54.6] • 7y: 46.0 [28.4–60.2] • 8y: 31.1 [11.2–47.6] • 9y: 6.8 [−16.5 to 26.4] • 10y: 14.1 [−11.3 to 34.9] • 11y: −1.7 [−57.1 to 37.9] Observational studies: ZVL wanes year by year. Beyond 4 years, all studies estimates VE ≤40% after 4 years post vaccination
Serious adverse events	≥50y: ~712,000 (28)	One dose ZVL vs placebo or no vaccine	No differences in serious adverse events between vaccinated and placebo groups in RCTs. Overall found no serious adverse events associated with ZVL In clinical trials 2 subjects with varicella-like rashes and zoster like rashes had PCR confirmed Oka/Merck strain varicella [54].
Reactogenicity	≥50y: ~310,000 (25)	One dose ZVL vs placebo	Injection-site reactions were the most common adverse reaction related to vaccination 4 studies reported moderate/severe (grade 3) injection-site reactions that ranged between 0%-4% of vaccine recipients

Abbreviations: y: years-old; ZVL: Live-attenuated zoster vaccine; VE: vaccine efficacy/effectiveness; 95% CI: 95% Confidence Interval; RCT: randomized controlled trial; SPS: Shingles Prevention Study; STPS: Short-term Persistence Study; LTPS: Long-term Persistence Study

Table 8. Summary of the evidence for select outcomes with use of ZVL in immunocompetent adults aged 50 years and older

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Others	Evidence type	Outcome evidence type	Overall Evidence Type
Benefits										
Prevent herpes zoster	2 RCT	1	Not Serious	Not Serious	Not Serious	Not Serious	None	1	1	1
	7 Obs	3	Serious*(-1)	Not Serious	Not Serious	Not Serious	None	4		
Prevent post-herpetic neuralgia	1 RCT	1	Not Serious	N/A	Not Serious	Not Serious	None	1	1	
	2 RCT with limitations†	2	Not Serious	Not Serious	Not Serious	Serious(-1)	None	3		
	5 Obs	3	Serious**(-1)	Not Serious	Not Serious	Not Serious	None	4		
Duration of protection against herpes zoster (4 or more years post vaccination)	2 RCT with limitations†	2	Not Serious	Not Serious	Not Serious	Not Serious	None	2	2	
	3 Obs	3	Serious*(-1)	Not Serious	Not Serious	Not Serious	None	4		
Harms										
Serious adverse events (after any dose)	8 RCT	1	Not serious	Not serious	Not Serious	Not Serious	None	1	1	1
	13 RCT with limitations‡	2	Serious‡(-1)	Not Serious	Not Serious	Not Serious	None	3		
	7 Obs	3	Serious*(-1)	Not Serious	Not Serious	Not Serious	None	4		
Reactogenicity	15 RCT	1	Not serious	Not serious	Not Serious	Not Serious	None	1	1	
	5 Non-RCT	2	Serious‡(-1)	Not Serious	Not Serious	Not Serious	None	3		
	5 Obs	3	Serious*(-1)	Not Serious	Not Serious	Not Serious	None	4		

Abbreviations: ZVL: Live-attenuated zoster vaccine; RCT: randomized controlled trial; Non-RCT: non-randomized clinical trial; Obs: observational study

*Outcome assessors were likely aware of intervention received by participants.

**Outcome assessors were likely aware of intervention received by participants. PHN may have been underreported - PHN diagnosis based on healthcare encounters not self-report.

†Limitations due to comparison groups. During the STPS, placebo participants could receive ZVL and censoring due to vaccination may have introduced bias that increased incidence of HZ among remaining placebo recipients. During the LTPS, there were no unvaccinated controls so comparison group was modeled.

‡Studies were non-blinded, open-label trials with no comparison group.

Summary

The evidence type for use of herpes zoster recombinant vaccine in immunocompetent adults aged 50 years and older was determined to be type 1 (high level of evidence). The evidence type for use of the live attenuated herpes zoster vaccine in immunocompetent adults aged 50 years and older was determined to be type 1 (high level of evidence). The Advisory Committee on Immunization Practices reviewed the results of both GRADE analysis as well as other data demonstrating high burden of herpes zoster and PHN among the target population, cost effectiveness and implementation analysis.

In October 2017, ACIP recommended:

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

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

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

These recommendations serve as a supplement to the 2008 Prevention of Herpes Zoster Recommendations of ACIP, for the use of ZVL in adults age 60 years and older (1,55,56).The Policy Note detailing the 2017 ACIP recommendations for use of herpes zoster vaccine in adults aged 50 years and older are available on the ACIP website.

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