Grading of Recommendations Assessment, Development and Evaluation (GRADE): live attenuated herpes zoster vaccine (ZVL)

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GRADE Process

- **Develop policy questions**
- **Consider critical outcomes**
- **Review and summarize evidence of benefits and harms**
- **Evaluate quality of evidence**
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

Policy Question: Is the live attenuated herpes zoster vaccine (ZVL) safe and effective at preventing herpes zoster?

Population	Immunocompetent adults aged 50 years or older
Intervention	One dose live attenuated zoster vaccine (ZVL, PFU≥19,400)
Comparison	Placebo or no vaccine
Outcomes	• Herpes zoster (HZ) • Post herpetic neuralgia (PHN) • Duration of protection against herpes zoster (4+ years post vaccination) • Severe adverse events • Reactogenicity (injection-site or systemic reactions)

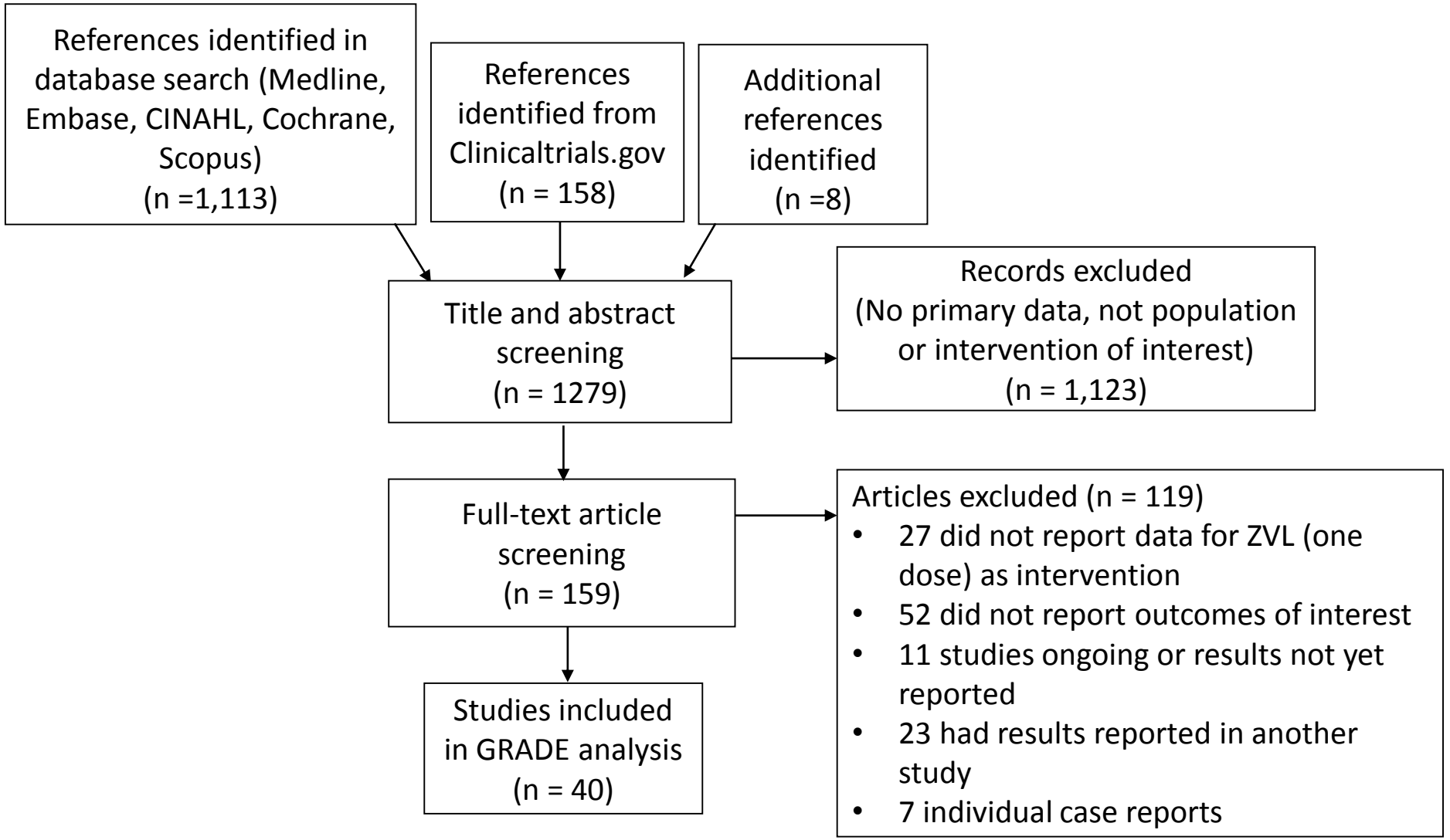
Outcome measures included in evidence profile

OUTCOME	IMPORTANCE
Benefits	
Prevent herpes zoster	Critical
Prevent postherpetic neuralgia	Critical
Duration of protection	Important
Harms	
Serious adverse events	Critical
Reactogenicity	Important

Evidence Retrieval

- Systematic review of studies in any language from PubMed, Embase, CINAHL, Cochrane, Scopus, and clinicaltrials.gov
- Efforts made to obtain unpublished or other relevant data
- Initial search terms included: “zostavax”, or “zoster” and “vaccine ADJ2 live”, or “zoster” and “attenuated ADJ2 live”, or “zoster” and “vaccine ADJ2 attenuated”, or “zoster vaccine live”, or “zoster vaccine attenuated”
- Articles were included if they presented data on the herpes zoster live attenuated vaccine (ZVL) and
  - Involved immunocompetent adults aged 50 years or older
  - Included data for relevant intervention (ZVL, one dose, minimum of 19,400 PFU)
  - Included data relevant to the outcome measures being assessed
  - Reported primary data

Evidence Retrieval



Evidence types

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

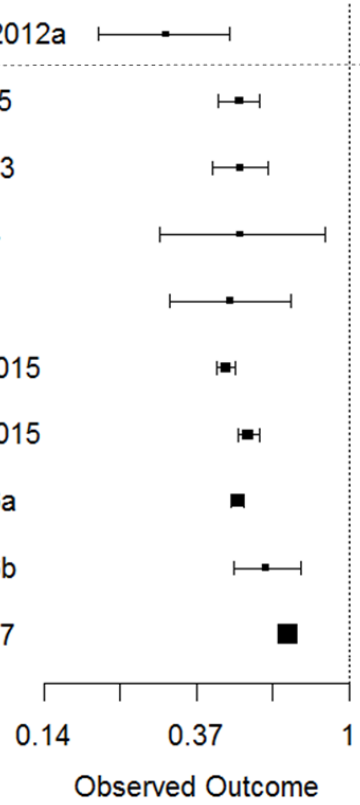
GRGRADE of Evidence for ZVL: BenefitsDE of Evidence for ZVL: Benefits

Outcome #1: VE against herpes zoster
Characteristics of included studies, n=9

Study	Type	Population	Intervention	Comparison	Funding	Site
Oxman, 2005 (SPS)	RCT	Healthy adults ≥60y	One dose ZVL	Placebo	Dept. of Veteran Affairs, Merck	Multicenter, USA
Schmader, 2012a (ZEST)	RCT	Healthy adults 50-59y	One dose ZVL	Placebo	Dept. of Veteran Affairs, Merck	North America, Europe
Langan, 2013	Cohort	Medicare enrollees, ≥65y	One dose ZVL	No vaccine	NIHR	Medicare, USA
Tseng, 2014	Cohort	KPSC members with end-state renal disease, ≥60y	One dose ZVL	No vaccine	Kaiser Permanente Southern California	Kaiser Permanente Southern California
Baxter, 2015	Cohort	KPNC members, ≥60y	One dose ZVL	No vaccine	Merck	Kaiser Permanente Northern California
Marin, 2015	Case control	Adults ≥60y	One dose ZVL	No vaccine	CDC	Minnesota, USA
Tseng, 2016a	Cohort	KPSC members, ≥60y	One dose ZVL	No vaccine	CDC	Kaiser Permanente Southern California
Tseng, 2016b	Cohort	KPSC members who received chemotherapy, ≥60y	One dose ZVL before chemotherapy	No vaccine	Kaiser Permanente Southern California	Kaiser Permanente Southern California
Izurieta, 2017	Cohort	Medicare enrollees, ≥65y	One dose ZVL	No vaccine	FDA	Medicare, USA

Outcome #1: VE against herpes zoster (HZ)
Estimates of Effect

Figure 1. Comparative VE of Zostavax for the prevention of herpes zoster



Author, Year	RR/OR/HR and 95% CI	VE (95% CI)	Mean Age[a]	Mean Follow up[b]
Schmader, 2012a		70% (54%-81%)	55	1.3
Oxman, 2005		51% (44%-58%)	69	3.13
Langan, 2013		51% (41%-59%)	≥65	≤2
Tseng, 2014		51% (15%-71%)	75	2.36
Marin, 2015		54% (32%-69%)	71	≤4
Baxter(a), 2015		55% (53%-58%)	60-69	≤3
Baxter(b), 2015		48% (45%-52%)	70-79	≤3
Tseng, 2016a		52% (50%-54%)	≥60	<5
Tseng, 2016b		42% (27%-53%)	68	2.25
Izurieta, 2017		33% (32%-35%)	77	2.5

Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;
[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.
[b]If mean follow up no available, length of study follow-up period post zoster vaccination in years was reported.

Outcome #1: VE against herpes zoster
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist-ency	Indirect-ness	Imprecis-ion	Other consider-ations	Evidence type	Outcome evidence type
Herpes Zoster	RCT (2)	1	No serious	No serious	No serious	No serious	No serious	1	**1**
	Obs (7)	3	**Serious**	No serious	No serious	No serious	No serious	4	

- Observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants

Outcome #2: Duration of protection against herpes zoster Characteristics of included studies, n=5

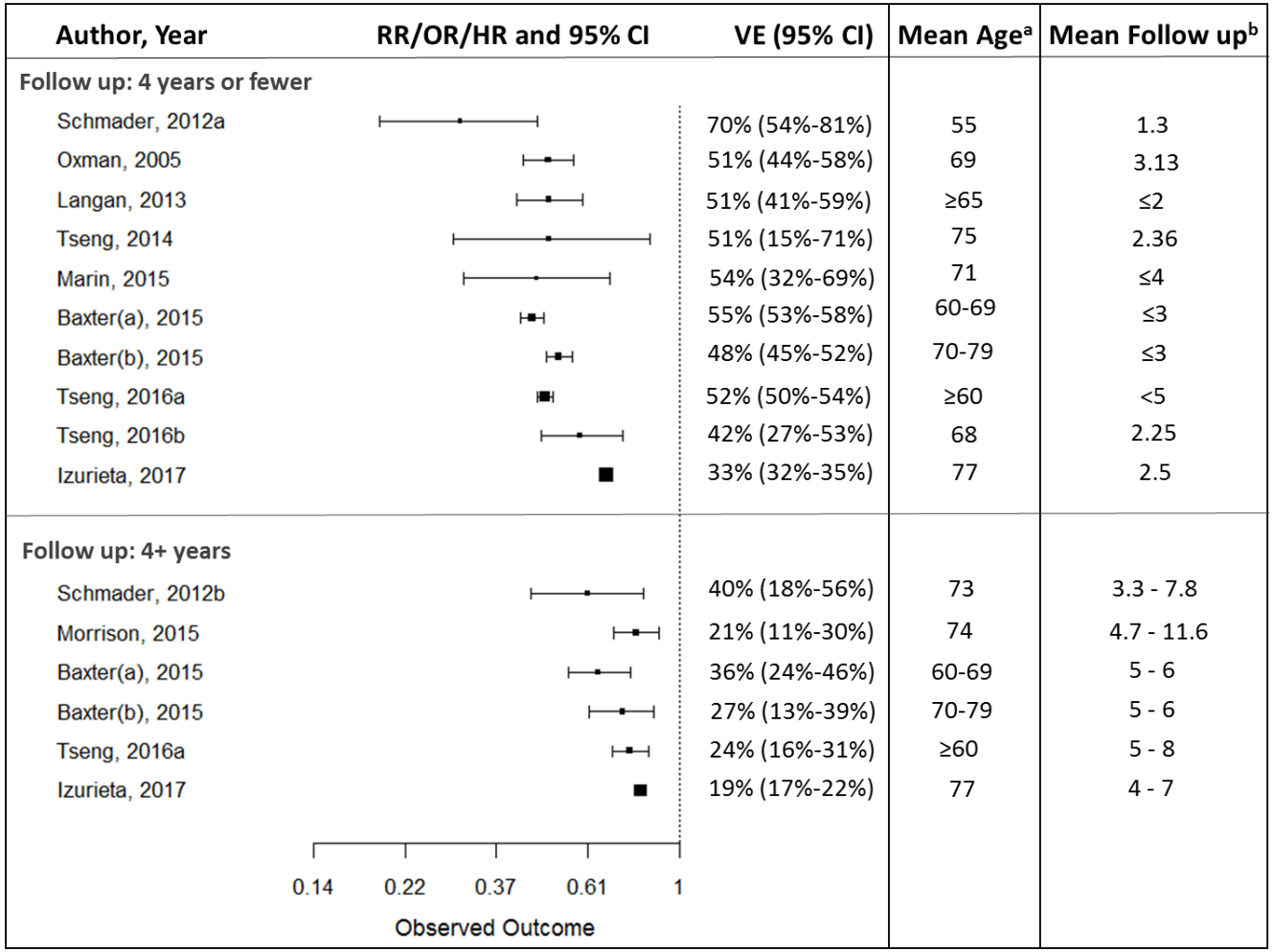
Study	Type	Population	Intervention	Comparison	Years post-vaccination	Funding	Site
Schmader, 2012b (STPS)	RCT w/ limitations	Healthy adults ≥60y	One dose ZVL	Placebo*	3.3-7.8	Dept. of Veteran Affairs, Merck	Multicenter, USA
Morrison, 2015 (LTPS)	RCT w/ limitations	Healthy adults ≥60y	One dose ZVL	Modeled from SPS and STPS placebo groups**	4.7-11.6	Dept. of Veteran Affairs, Merck	Multicenter, USA
Baxter, 2015	Cohort	KPNC members, ≥60y	One dose ZVL	No vaccine	5-6	Merck	Kaiser Permanente Northern California
Tseng, 2016a	Cohort	KPSC members, ≥60y	One dose ZVL	No vaccine	5-8	CDC	Kaiser Permanente Southern California
Izurieta, 2017	Cohort	Medicare enrollees, ≥65y	One dose ZVL	No vaccine	4–7	FDA	Medicare, USA

*During the STPS, participants were unblinded and placebo recipients were eligible to receive ZVL.

** Since the participants had been unblinded in the STPS, there were no placebo controls. Instead modeled comparision group using data from placebo groups from SPS and STPS.

Outcome #2: Duration of protection against herpes zoster
Estimates of effect

Figure 2. Comparative VE of Zostavax for the prevention of herpes zoster, by length of follow up time post-vaccination



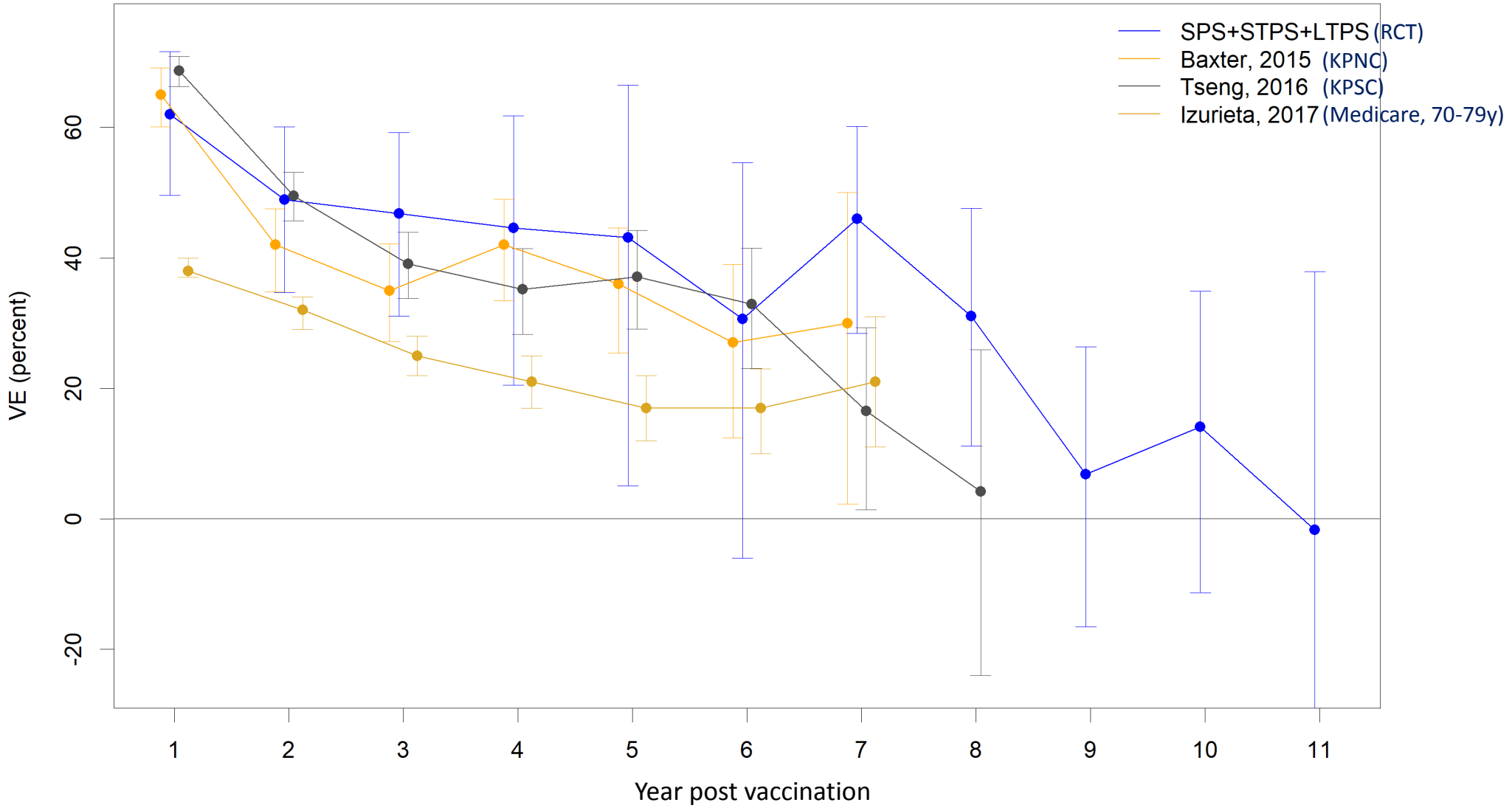
Author, Year	RR/OR/HR and 95% CI	VE (95% CI)	Mean Age[a]	Mean Follow up[b]
Follow up: 4 years or fewer				
Schmader, 2012a		70% (54%-81%)	55	1.3
Oxman, 2005		51% (44%-58%)	69	3.13
Langan, 2013		51% (41%-59%)	≥65	≤2
Tseng, 2014		51% (15%-71%)	75	2.36
Marin, 2015		54% (32%-69%)	71	≤4
Baxter(a), 2015		55% (53%-58%)	60-69	≤3
Baxter(b), 2015		48% (45%-52%)	70-79	≤3
Tseng, 2016a		52% (50%-54%)	≥60	<5
Tseng, 2016b		42% (27%-53%)	68	2.25
Izurieta, 2017		33% (32%-35%)	77	2.5
Follow up: 4+ years				
Schmader, 2012b		40% (18%-56%)	73	3.3 - 7.8
Morrison, 2015		21% (11%-30%)	74	4.7 - 11.6
Baxter(a), 2015		36% (24%-46%)	60-69	5 - 6
Baxter(b), 2015		27% (13%-39%)	70-79	5 - 6
Tseng, 2016a		24% (16%-31%)	≥60	5 - 8
Izurieta, 2017		19% (17%-22%)	77	4 - 7

Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;;

[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.

[b]Length of study follow-up period post zoster vaccination in years.

Outcome #2: 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.

Outcome #2: Duration of protection against herpes zoster Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist -ency	Indirect -ness	Imprecis -ion	Other consider -ations	Evidence type	Outcome evidence type
Duration of protection (4+ years post-vac)	RCT with limitations (2)	2	No serious	No serious	No serious	No serious	None	2	**2**
	Obs (3)	3	**Serious**	No serious	No serious	No serious	None	4	

- RCTs were given initial evidence level 2 due to comparison group limitations. 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 we no unvaccinated controls so comparison group was modeled.
- Observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants

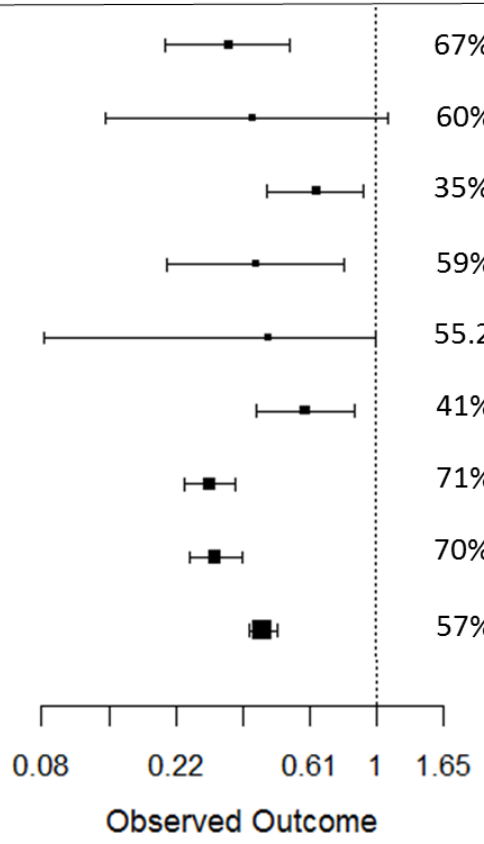
Outcome #3: VE against post-herpetic neuralgia (PHN) Characteristics of included studies, n=8

Study	Type	Population	Intervention	Comparison	Funding	Site
Oxman, 2005 (SPS)	RCT	Healthy adults ≥60y	One dose ZVL	Placebo	Dept. of Veteran Affairs, Merck	Multicenter, USA
Schmader, 2012b (STPS)	RCT w/ limitations	Healthy adults ≥60y	One dose ZVL	Placebo	Dept. of Veteran Affairs, Merck	Multicenter, USA
Morrison, 2015 (LTPS)	RCT w/ limitations	Healthy adults ≥60y	One dose ZVL	Modeled using SPS and STPS placebo groups	Dept. of Veteran Affairs, Merck	Multicenter, USA
Langan, 2013	Cohort	Medicare enrollees, ≥65y	One dose ZVL	No vaccine	NIHR	Medicare, USA
Tseng, 2015	Cohort	KPSC members, ≥60y	One dose ZVL	No vaccine	CDC	Kaiser Permanente Southern California
Baxter, 2016a	Cohort	KPNC members, ≥60y	One dose ZVL	No vaccine	Merck	Kaiser Permanente Northern California
Marin, 2015	Case control	Adults ≥60y	One dose ZVL	No vaccine	CDC	Minnesota, USA
Izurieta, 2017	Cohort	Medicare enrollees, ≥65y	One dose ZVL	No vaccine	FDA	Medicare, USA

Outcome #3: VE against PHN
Estimates of effect

Figure 3. Comparative VE of Zostavax for the prevention of post-herpetic neuralgia

Author, Year	RR/OR/HR and 95% CI	VE (95% CI)	Mean Age[a]	Mean Follow up[b]
Oxman, 2005		67% (48%-79%)	69	3.13
Schmader, 2012b		60% (-10%-87%)	73	3.3-7.8
Morrison, 2015		35% (9%-56%)	74	4.7-11.6
Langan, 2013		59% (21%-79%)	≥65	≤2
Marin, 2015		55.2% (0%-92%)	71	≤4
Tseng, 2015		41% (15%-59%)	≥60	NR
Baxter, 2016 (a)		71% (65%-76%)	60-69	≤3
Baxter, 2016 (b)		70% (63%-75%)	70-79	≤3
Izurieta, 2017		57% (52%-61%)	77	2.5



Abbreviations: RR, risk ratio; OR, odds ratio; CI, confidence interval; VE, vaccine efficacy/effectiveness;
[a]Mean age reported in years. If mean age was not available, age range for study participants was reported.
[b]If mean follow up no available, length of study follow-up period post zoster vaccination in years was reported.

Outcome #3: VE against PHN
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsis-tency	Indirect-ness	Imprecis-ion	Other consider-ations	Evidence type	Outcome evidence type
Post-Herpetic Neuralgia	RCT (1)	1	No serious	N/A	No serious	No serious	No serious	1	**1**
	RCTs w/ limitations (2)	2	No serious	No serious	No serious	**Serious**	No serious	3	
	Obs (5)	3	**Serious**	No serious	No serious	No serious	No serious	4	

- RCTs with limitations were given an initial evidence level 2 and downgraded for risk of bias due to concerns related to the comparison groups
- RCTS with limitations had large 95% confidence intervals and were downgraded for imprecision.
- Observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants and because PHN may have been underreported - PHN diagnosis based on healthcare encounters not self-report

GGrade of Evidence for ZVL: HarmsRADE of Evidence for ZVL: Harms

Outcome #4 and #5: Serious adverse events and reactogenicity
Characteristics of included studies with comparison groups, n=11

Study	N (ZVL)	Type	Population	Intervention	Comparison	Funding	Site
Oxman, 2005 (SPS)	19,270	RCT	Healthy adults ≥60y	One dose ZVL	Placebo	V.A.; Merck	Multicenter, USA
Zoran, 2016*	14,436	RCT	Healthy adults ≥60y (SPS and ZEST)	One dose ZVL	Placebo	Merck	USA
Schmader, 2012a (ZEST)	11,184	RCT	Healthy adults 50-59y	One dose ZVL	Placebo	V.A.; Merck	North America, Europe
Murray, 2010**	5,983	RCT	Healthy adults ≥60y	One dose ZVL	Placebo	Merck	Canada, Germany, Spain, UK, US
MacIntyre, 2010	236	RCT	Healthy adults ≥60y	One dose ZVL	Placebo	Merck	Australia, Canada, Germany, Italy, Spain, UK
Mills, 2010	98	RCT	Healthy adults ≥50y	One dose ZVL	Placebo, Crossover	Merck	USA
Beals, 2016	52	RCT	Healthy adults ≥50y	One dose ZVL	Placebo	Merck	USA
Hata, 2016	27	RCT	Adults aged 60-70y with diabetes mellitus	One dose ZVL	Placebo	Japan MoH	Japan
Macaladad, 2007	18	RCT	Healthy adults ≥30y	One dose ZVL	Placebo	Merck	Brazil, Costa Rica, Colombia, Mexico, Peru, Venezuela, Phillipines
Baxter, 2012**	29,010	Cohort	KPNC members, ≥60y	One dose ZVL	Self-controlled case series	Merck	Kaiser Permanente Northern California
Tseng, 2012	193,083	Cohort	Adults ≥50y	One dose ZVL	Case-centered; self-controlled case series	AHIP, CDC	USA, Vaccine Safety Datalink (VSD)

*Reactogenicity only, **SAE only

Outcome #4: Serious adverse events
Summary of Findings, studies with comparison groups, n=10

- In 8 placebo-controlled RCTs with 36,868 participants receiving ZVL, there were no imbalances in serious adverse events between vaccine and placebo groups
- 2 large observation studies with 222,093 participants receiving ZVL found no increased risk post vaccination for cardiovascular, neurologic or infectious conditions studied* [Baxter, 2012; Tseng, 2012]
- Overall found no serious adverse events associated with ZVL

**Conditions studied included: stroke or cerebrovascular events, acute myocardial infarction, meningitis, encephalitis and encephalopathy, Ramsey-Hunt syndrome and Bell's palsy, cellulitis and infection, coronary atherosclerosis and other heart disease*

Outcome #4: Serious Adverse Events
Additional safety studies with no comparison group, n=18

Type	Studies		Total # received ZVL	Safety Findings
RCT n=7	Berger, 1998 Kerzner, 2007 Tyring, 2007 Gilderman, 2008	Leroux-Roels, 2012 Vesikari, 2013 Diez-Domingo, 2015	N=1782*	• **No serious adverse events associated with ZVL** • **Consistent with findings from placebo-controlled studies**
Non-RCT N=6	Arnou, 2011 Hata, 2013 Morrison, 2013	Stanford, 2014 Yao, 2015 Choi, 2016	N=14,165†	
Obs N=5	Levin, 2003 Lelic, 2016 Levin, 2016	Baxter, 2016b Willis, 2016	N=377,316‡	

*Berger, 1998 does not report number that received ZVL. Total number of participants in study was 200.

†13,674 participants came from Morrison, 2013

‡376,531 participants came from Baxter, 2016b. Willis, 2016 included adverse events reported to the worldwide Merck Adverse Events Reporting Database and does not report number of individuals who received ZVL.

Outcome #4: Serious adverse events
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other consider-ations	Evidence type	Outcome evidence type
Serious adverse events related to vaccination	RCT (8)	1	No serious	No serious	No serious	No serious	No serious	1	**1**
	RCT with limitations (13)	2	**Serious**	No serious	No serious	No serious	No serious	3	
	Obs (7)	3	**Serious**	No serious	No serious	No serious	No serious	4	

- RCTs with limitations were given initial evidence level 2 and downgraded for risk of bias due to a lack of control group and because outcome assessors may have been aware of the intervention received by participants.
- Observational studies were downgraded for risk of bias because outcome assessors were aware of the intervention received by participants

Additional safety data: Case reports of SAEs and Oka-caused adverse events

- Merck's 10 year post-marketing review reported 13 reports of PCR-confirmed VZV rash caused by Oka/Merck vaccine strain [Willis, 2016]
- In clinical trials 2 subjects with varicella-like rashes and zoster like rashes had PCR confirmed Oka/Merck strain varicella. [FDA]
- 7 additional case reports of serious adverse events related to ZVL were not included in the GRADE analysis*
  - None of these events have been substantiated as a safety signal for ZVL through additional research or reporting through VAERs

**SAEs reported include: severe vision loss, bilateral vision loss, worsening of HZ opthalmicus, worsening of corneal edema, recurrent keratouveiitis, corneal perforation, swelling of almost the entire arm, VZV caused by Oka/Merck vaccine strain*

Outcome #5: Reactogenicity (injection-site and systemic) Summary of findings, n=25

- Injection-site reactions were the most common adverse reaction related to vaccination
- One large RCT in adults ≥ 60 y reported injection-site reactions among 48% of vaccine recipients compared to 17% among placebo [diff=31%; Oxman, 2005]
- One large RCT in adults aged 50-59 reported injection-site reactions among 64% of vaccine recipients compared to 14% among placebo [diff=50%; Schmader, 2012a]
- Range of injection-site reactions reported among remaining studies was 8%-62%.
  - Variation due to differences in sample sizes. Majority of studies reported an estimate within 35%-55%.
- 4 studies reported moderate/severe (grade 3) injection-site reactions that ranged between 0%-4% of vaccine recipients
  - Includes post-hoc analysis of Oxman, 2005 (SPS) that found <1% of participants reported grade 3 reactions post vaccination
- 7 studies reported vaccine-related systemic adverse events, with reactions reported among 0-8% of vaccine recipients

Outcome #5: Reactogenicity
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other consider-ations	Evidence type	Outcome evidence type
Reactogenicity (injection-site or systemic adverse events)	RCT (15)	1	No serious	No serious	No serious	No serious	No serious	1	**1**
	Non-RCT (5)	2	**Serious**	No serious	No serious	No serious	No serious	3	
	Obs (5)	3	**Serious**	No serious	No serious	No serious	No serious	4	

- Non-RCT and observational studies were downgraded for risk of bias because outcome assessors were aware or likely aware of the intervention received by participants

SuSummarymmary

Evidence Types

- ⨁⨁⨁⨁/A/High/Evidence Type 1: We are very confident that the true effect lies close to that of the estimate of the effect.
- ⨁⨁⨁◯/B/Moderate/Evidence Type 2**:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- ⨁⨁◯◯/C/Low/Evidence Type 3: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- ⨁◯◯◯/D/Very low/Evidence Type 4: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Not measuring how good the intervention is, but how much confidence we have in the estimates of effect

GRADE Summary

Comparison: One dose ZVL (≥19,000 PFU) versus placebo or no vaccine in adults ≥50

Outcome	Design (# of studies)	Findings	Evidence type	Overall evidence type
CRITICAL				
Prevent herpes zoster	RCT (2) Obs (7)	ZVL is effective in preventing herpes zoster	**1**	**1**
Prevent post-herpetic neuralgia	RCT (3) Obs (5)	ZVL is effective in preventing PHN	**1**	
Severe adverse events	RCT (14) Non-RCT (6) Obs (7)	No safety concerns for ZVL observed in real-world and clinical settings	**1**	
IMPORTANT				
Reactogenicity	RCT (15) Non-RCT (5) Obs (5)	Injection-site reactions more commonly reported among vaccine recipients compared to placebo, but tend to be mild	**1**	
Duration of protection (herpes zoster)	RCT (2) Obs (3)	ZVL effectiveness decreases 4+ years post vaccination and continues to decrease year-by-year	**2**	

References

1. Arnou, R., et al., *Immunogenicity and safety of ZOSTAVAX() approaching expiry potency in individuals aged >50 years. Human Vaccines, 2011.* ***7(10): p. 1060-5.***
2. Baxter, R., et al., *Effectiveness of Live Zoster Vaccine in Preventing Postherpetic Neuralgia (PHN). Open Forum Infectious Diseases, 2016.* ***3(suppl_1): p. 128-128.***
3. Baxter, R., et al., *Effectiveness of Live Zoster Vaccine in Preventing Herpes Zoster. Open Forum Infectious Diseases, 2015.* ***2(suppl_1): p. 1928-1928.***
4. Baxter, R., et al., *Sudden-Onset Sensorineural Hearing Loss after Immunization: A Case- Centered Analysis. Otolaryngology - Head and Neck Surgery (United States), 2016.* ***155(1): p. 81-86.***
5. Baxter, R., et al., *Safety of ZostavaxTM--a cohort study in a managed care organization. Vaccine, 2012.* ***30(47): p. 6636-41.***
6. Beals, C.R., et al., *Immune response and reactogenicity of intradermal administration versus subcutaneous administration of varicella-zoster virus vaccine: an exploratory, randomised, partly blinded trial. The Lancet Infectious Diseases, 2016.* ***16(8): p. 915-22.***
7. Berger, R., et al., *A dose-response study of a live attenuated varicella-zoster virus (Oka strain) vaccine administered to adults 55 years of age and older. Journal of Infectious Diseases, 1998.* ***178 Suppl 1: p. S99-103.***
8. Charkoudian, L.D., et al., *Acute retinal necrosis after herpes zoster vaccination. Arch Ophthalmol, 2011.* ***129(11): p. 1495-7.***
9. Choi, W.S., et al., *Immunogenicity and Safety of a Live Attenuated Zoster Vaccine (ZOSTAVAXTM) in Korean Adults. Journal of Korean Medical Science, 2016.* ***31(1): p. 13-7.***
10. Cook, I.F., *Herpes Zoster Vaccine (Zostavax): Cellulitic Injection Site Reaction Or Bacterial Cellulitis? Human vaccines & Immunotherapeutics, 2016: p. 0.*
11. Diez-Domingo, J., et al., *Comparison of intramuscular and subcutaneous administration of a herpes zoster live-attenuated vaccine in adults aged >50 years: a randomised non-inferiority clinical trial. Vaccine, 2015.* ***33(6): p. 789-95.***
12. Gilderman, L.I., et al., *A double-blind, randomized, controlled, multicenter safety and immunogenicity study of a refrigerator-stable formulation of Zostavax. Clinical & Vaccine Immunology: CVI, 2008.* ***15(2): p. 314-9.***
13. Hata, A., et al., *Efficacy and safety of live varicella zoster vaccine in diabetes: a randomized, double-blind, placebo-controlled trial. Diabetic Medicine, 2016.* ***33(8): p. 1094-101.***
14. Hata, A., et al., *Safety, humoral and cell-mediated immune responses to herpes zoster vaccine in subjects with diabetes mellitus. Journal of Infection, 2013.* ***67(3): p. 215-9.***
15. Hwang, C.W., Jr., et al., *Reactivation of herpes zoster keratitis in an adult after varicella zoster vaccination. Cornea, 2013.* ***32(4): p. 508-9.***
16. Izurieta, H.S., et al., *Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older. Clin Infect Dis, 2017.* ***64(6): p. 785-793.***
17. Jastrzebski, A., et al., *Reactivation of Herpes Zoster Keratitis With Corneal Perforation After Zoster Vaccination. Cornea, 2017.* ***36(6): p. 740-742.***
18. Kerzner, B., et al., *Safety and immunogenicity profile of the concomitant administration of ZOSTAVAX and inactivated influenza vaccine in adults aged 50 and older. Journal of the American Geriatrics Society, 2007.* ***55(10): p. 1499-507.***
19. Khalifa, Y.M., R.M. Jacoby, and T.P. Margolis, *Exacerbation of zoster interstitial keratitis after zoster vaccination in an adult. Arch Ophthalmol, 2010.* ***128(8): p. 1079-80.***
20. Langan, S.M., et al., *Herpes Zoster Vaccine Effectiveness against Incident Herpes Zoster and Post-herpetic Neuralgia in an Older US Population: A Cohort Study. PLOS Medicine, 2013.* ***10(4): p. e1001420.***
21. Lelic, A., et al., *Immunogenicity of Varicella Zoster Vaccine and Immunologic Predictors of Response in a Cohort of Elderly Nursing Home Residents. Journal of Infectious Diseases, 2016.* ***5: p. 5.***
22. Leroux-Roels, I., et al., *A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. Journal of Infectious Diseases, 2012.* ***206(8): p. 1280-90.***

References, cont.

23. Levin, M.J., et al., *Cellular and Humoral Responses to a Second Dose of Herpes Zoster Vaccine Administered 10 Years After the First Dose Among Older Adults. J Infect Dis, 2016.* ***213(1): p. 14-22.*** *persistence of zoster vaccine efficacy. Clinical Infectious Diseases, 2015.* ***60(6): p. 900-9.***
24. Levin, M.J., et al., *Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. Journal of Infectious Diseases, 2003.* ***188(9): p. 1336-44.***
25. Macaladad, N., et al., *Safety and immunogenicity of a zoster vaccine in varicella-zoster virus seronegative and low-seropositive healthy adults. Vaccine, 2007.* ***25(11): p. 2139-44.***
26. MacIntyre, C.R., et al., *Concomitant administration of zoster and pneumococcal vaccines in adults >60 years old. Human Vaccines, 2010.* ***6(11): p. 894-902.***
27. Marin, M., et al., *Herpes zoster vaccine effectiveness and manifestations of herpes zoster and associated pain by vaccination status. Human vaccines & Immunotherapeutics, 2015.* ***11(5): p. 1157-64.***
28. Mills, R., et al., *Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine, 2010.* ***28(25): p. 4204-9.***
29. Morrison, V.A., et al., *Long-term*
30. Morrison, V.A., et al., *Safety of zoster vaccine in elderly adults following documented herpes zoster. Journal of Infectious Diseases, 2013.* ***208(4): p. 559-63.***
31. Murray, A., et al. *Safety & tolerability of zoster vaccine in adults >60 years old. Journal of the American Geriatrics Society, 2010.* ***58, S21-s22 DOI: 10.1111/j.1532-5415.2010.02850.x.***
32. Oxman, M.N., et al., *A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. New England Journal of Medicine, 2005.* ***352(22): p. 2271-84.***
33. Rohan, P., *FDA clinical briefing document for Merck & Co, Inc, zoster vaccine live (Oka/Merck): December 15, 2005.*
34. Schmader, K.E., et al., *Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clinical Infectious Diseases, 2012.* ***54(7): p. 922-8.***
35. Schmader, K.E., et al., *Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clinical Infectious Diseases, 2012.* ***55(10): p. 1320-8.***
36. Sham, C.W. and R.D. Levinson, *Uveitis exacerbation after varicella-zoster vaccination in an adult. Archives of Ophthalmology, 2012.* ***130(6): p. 793-794.***
37. Stanford, U., A. National Institute of, and D. Infectious, *T Cell Responses to Varicella Zoster Virus (VZV). 2014.*
38. Tseng, H.F., et al., *Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged >60 Years. Journal of Infectious Diseases, 2016.* ***213(12): p. 1872-5.***
39. Tseng, H.F., et al., *Zoster Vaccine and the Risk of Postherpetic Neuralgia in Patients Who Developed Herpes Zoster Despite Having Received the Zoster Vaccine. Journal of Infectious Diseases, 2015.* ***212(8): p. 1222-31.***
40. Tseng, H.F., et al., *Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med, 2012.* ***271(5): p. 510-20.***
41. Tseng, H.F., et al., *Effectiveness of Herpes Zoster Vaccine in Patients 60 Years and Older With End-stage Renal Disease. Clin Infect Dis, 2016.* ***62(4): p. 462-7.***
42. Tseng, H.F., et al., *Herpes zoster caused by vaccine-strain varicella zoster virus in an immunocompetent recipient of zoster vaccine. Clinical Infectious Diseases, 2014.* ***58(8): p. 1125-8.***
43. Tseng, H.F., et al., *Vaccination against zoster remains effective in older adults who later undergo chemotherapy. Clin Infect Dis, 2014.* ***59(7): p. 913-9.***
44. Tyring, S.K., et al., *Safety and tolerability of a high-potency zoster vaccine in adults >/= 50 or years of age. Vaccine, 2007.* ***25(10): p. 1877-83.***
45. Vesikari, T., et al., *Immunogenicity and safety of a live attenuated shingles (herpes zoster) vaccine (Zostavax) in individuals aged > 70 years: a randomized study of a single dose vs. two different two-dose schedules. Human vaccines & Immunotherapeutics, 2013.* ***9(4): p. 858-64.***
46. Willis, E., et al., *Zoster Vaccine Live: A Review of Nearly 10 Years of Postmarketing Experience. Open Forum Infectious Diseases, 2016.* ***3(suppl_1): p. 714-714.***
47. Yao, C.A., L.K. Chen, and K.C. Huang, *The immunogenicity and safety of zoster vaccine in Taiwanese adults. Vaccine, 2015.* ***33(13): p. 1515-7.***
48. Zoran, P., *Low rates of severe injection-site and systemic adverse events within 7 days postvaccination with ZOSTAVAXTM, a post hoc analysis of two pivotal Phase 3 trials. European Geriatric Medicine, 2016.* ***7: p. S177.***