IL NUOVO VACCINO ANTI- HERPES ZOSTER

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COI DISCLOSURE

- AG received consultancy fees from Mylan and Jansen
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Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

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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has increased each year, and by 2016, 33% of adults aged ≥60 years reported receipt of the vaccine (CDC, provisional unpublished data).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.

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?"

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

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 to 4 years post vaccination)	14,693 (1)	2 dose RZV vs placebo	VE remained about 85% in the first 4 years following 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)

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Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

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ABSTRACT

BACKGROUND

In previous phase 1–2 clinical trials involving older adults, a subunit vaccine containing varicella–zoster virus glycoprotein E and the AS01$_B$ adjuvant system (called HZ/su) had a clinically acceptable safety profile and elicited a robust immune response.

METHODS

We conducted a randomized, placebo-controlled, phase 3 study in 18 countries to evaluate the efficacy and safety of HZ/su in older adults (≥50 years of age), stratified according to age group (50 to 59, 60 to 69, and ≥70 years). Participants received two intramuscular doses of the vaccine or placebo 2 months apart. The primary objective was to assess the efficacy of the vaccine, as compared with placebo, in reducing the risk of herpes zoster in older adults.

RESULTS

A total of 15,411 participants who could be evaluated received either the vaccine (7698 participants) or placebo (7713 participants). During a mean follow-up of 3.2 years, herpes zoster was confirmed in 6 participants in the vaccine group and in 210 participants in the placebo group (incidence rate, 0.3 vs. 9.1 per 1000 person-years) in the modified vaccinated cohort. Overall vaccine efficacy against herpes zoster was 97.2% (95% confidence interval [CI], 93.7 to 99.0; P<0.001). Vaccine efficacy was between 96.6% and 97.9% for all age groups. Solicited reports of injection-site and systemic reactions within 7 days after vaccination were more frequent in the vaccine group. There were solicited or unsolicited reports of grade 3 symptoms in 17.0% of vaccine recipients and 3.2% of placebo recipients. The proportions of participants who had serious adverse events or potential immune-mediated diseases or who died were similar in the two groups.

CONCLUSIONS

The HZ/su vaccine significantly reduced the risk of herpes zoster in adults who were 50 years of age or older. Vaccine efficacy in adults who were 70 years of age or older was similar to that in the other two age groups. (Funded by GlaxoSmithKline Biologicals; ZOE-50 ClinicalTrials.gov number, NCT01165177.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heineman at Global Clinical Research and Development, GSK Vaccines, 2301 Renaissance Blvd., King of Prussia, PA 19406, or at thomas.c.heineman@gsk.com.

Drs. Chlibek, Diez-Domingo, Hwang, Levin, McElhaney, Poder, Puig-Barberà, Vesikari, Watanabe, Weckx, and Zahaf contributed equally to this article.

*A complete list of investigators in the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) is provided in the Supplementary Appendix, available at NEJM.org.

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Participants who were 50 years of age or older were eligible for inclusion unless they had a history of herpes zoster, were previously vaccinated against varicella or herpes zoster, or had an immunosuppressive condition

Table 1. Characteristics of the Participants at Baseline (Total Vaccinated Cohort).*

Characteristic	HZ/su Group (N=7698)	Placebo Group (N=7713)	All Participants (N=15,411)
Age			
Mean (±SD) at first dose	62.4±9.0	62.3±9.0	62.3±9.0
Age group — no. (%)			
50–59 yr	3645 (47.3)	3644 (47.2)	7,289 (47.3)
60–69 yr	2244 (29.2)	2246 (29.1)	4,490 (29.1)
70 yr or older	1809 (23.5)	1823 (23.6)	3,632 (23.6)
Sex — no. (%)			
Female	4711 (61.2)	4713 (61.1)	9,424 (61.2)
Male	2987 (38.8)	3000 (38.9)	5,987 (38.8)
Race — no. (%)†			
White	5532 (71.9)	5535 (71.8)	11,067 (71.8)
Black	140 (1.8)	130 (1.7)	270 (1.8)
Asian	1466 (19.0)	1470 (19.1)	2,936 (19.1)
Other	560 (7.3)	578 (7.5)	1,138 (7.4)
Region — no. (%)			
Asia or Australia	1642 (21.3)	1642 (21.3)	3,284 (21.3)
Europe	3941 (51.2)	3948 (51.2)	7,889 (51.2)
Latin America	772 (10.0)	779 (10.1)	1,551 (10.1)
North America	1343 (17.4)	1344 (17.4)	2,687 (17.4)

* There were no significant differences between the groups. The percentages may not total 100 because of rounding.
† Race was self-reported.

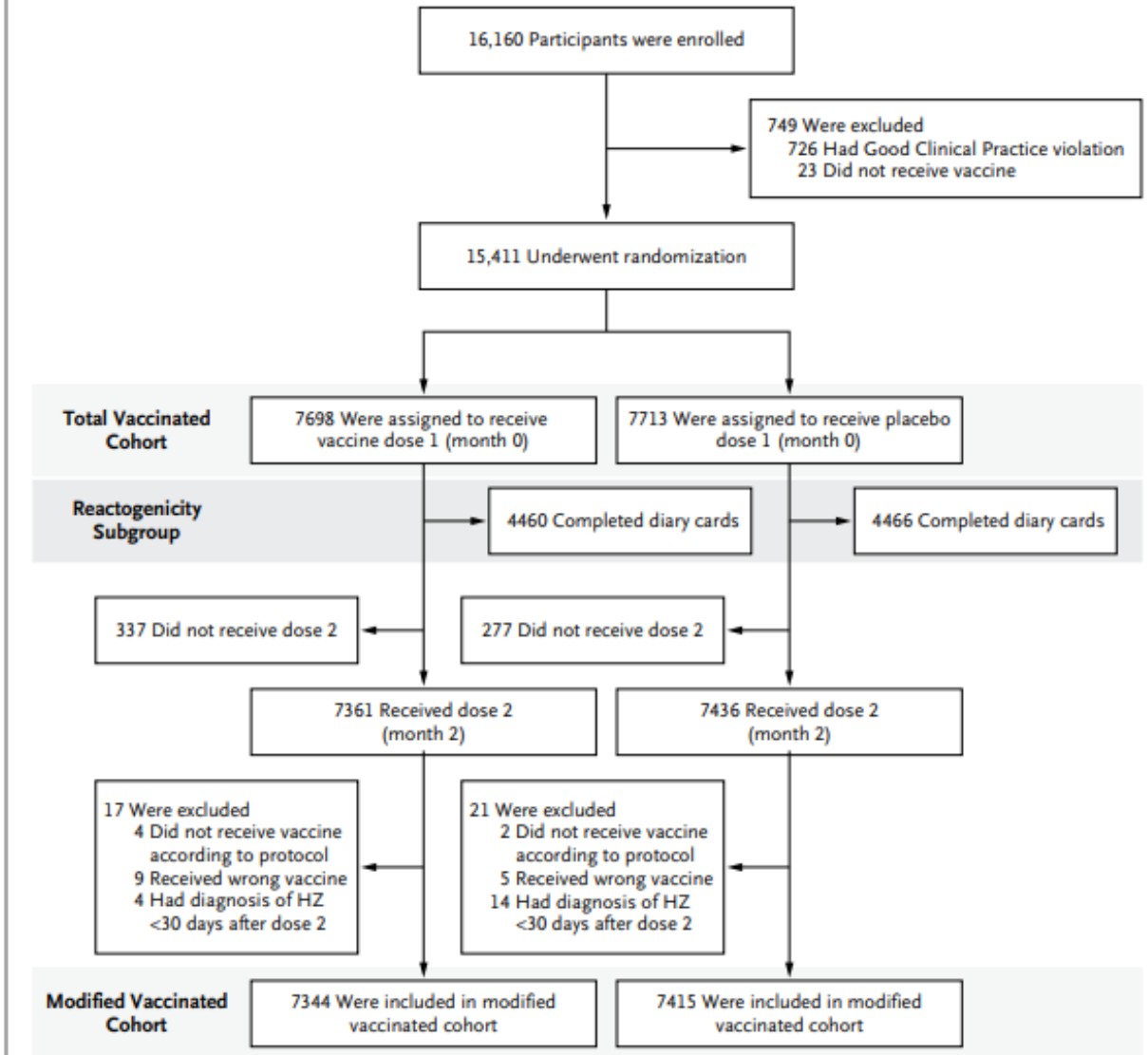

Figure 1. Enrollment and Outcomes.

During the course of the study of the herpes zoster subunit (HZ/su) vaccine, two study centers were closed because of Good Clinical Practice violations. All participants who were enrolled in these centers were excluded from the statistical analyses. Because the ongoing study remains blinded, participants who withdrew from the study after dose 2 will be included in the modified vaccinated cohort until study completion.

Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡	Rate of Herpes Zoster	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡	Rate of Herpes Zoster	
			person-yr	*no./1000 person-yr*			*person-yr*	*no./1000 person-yr*	*% (95% CI)*
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
Total vaccinated cohort									
All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

* The total vaccinated cohort included all vaccinated participants for whom data related to efficacy end points were available. The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose. Efficacy was calculated by means of the Poisson method.

† $P<0.001$ for all efficacy comparisons with placebo. Vaccine efficacy in each age group was adjusted for region. Overall vaccine efficacy was adjusted for age group and region.

‡ Data were censored at the time of the first confirmed diagnosis of herpes zoster.

Table 3. Adverse Events and Reactogenicity.*

Variable	HZ/su Group		Placebo Group	
	no. of participants/total no.	*% (95% CI)*	*no. of participants/total no.*	*% (95% CI)*
Reactogenicity subgroup	4460		4466	
Within 30 days after vaccination				
Unsolicited report of adverse event	1308	29.3 (28.0–30.7)	1226	27.5 (26.1–28.8)
Grade 3 unsolicited report of adverse event†	208	4.7 (4.1–5.3)	151	3.4 (2.9–4.0)
Within 7 days after vaccination				
Solicited or unsolicited report of adverse event	3765	84.4 (83.3–85.5)	1689	37.8 (36.4–39.3)
Grade 3 solicited or unsolicited report of adverse event†	760	17.0 (15.9–18.2)	145	3.2 (2.7–3.8)
Grade 3 solicited or unsolicited report of adverse event related to vaccination	694	15.6 (14.5–16.7)	83	1.9 (1.5–2.3)
Solicited report of injection-site reaction	3571/4382	81.5 (80.3–82.6)	522/4377	11.9 (11.0–12.9)
Pain	3464/4382	79.1 (77.8–80.2)	490/4377	11.2 (10.3–12.2)
Redness	1664/4382	38.0 (36.5–39.4)	59/4377	1.3 (1.0–1.7)
Swelling	1153/4382	26.3 (25.0–27.6)	46/4377	1.1 (0.8–1.4)
Grade 3 solicited report of injection-site reaction†	417/4382	9.5 (8.7–10.4)	16/4377	0.4 (0.2–0.6)
Solicited report of systemic reaction	2894/4375	66.1 (64.7–67.6)	1293/4378	29.5 (28.2–30.9)
Myalgia	2025/4375	46.3 (44.8–47.8)	530/4378	12.1 (11.2–13.1)
Fatigue	2008/4375	45.9 (44.4–47.4)	728/4378	16.6 (15.5–17.8)
Headache	1716/4375	39.2 (37.8–40.7)	700/4378	16.0 (14.9–17.1)
Shivering	1232/4375	28.2 (26.8–29.5)	259/4378	5.9 (5.2–6.7)
Fever	939/4375	21.5 (20.3–22.7)	132/4378	3.0 (2.5–3.6)
Gastrointestinal symptoms	788/4375	18.0 (16.9–19.2)	387/4378	8.8 (8.0–9.7)
Grade 3 solicited report of systemic reaction†	498/4375	11.4 (10.5–12.4)	106/4378	2.4 (2.0–2.9)
Total vaccinated cohort	7698		7713	
Throughout study period				
Serious adverse event‡	689	9.0 (8.3–9.6)	686	8.9 (8.3–9.6)
Potential immune-mediated disease	78	1.0 (0.8–1.3)	97	1.3 (1.0–1.5)
Death	167	2.2 (1.9–2.5)	174	2.3 (1.9–2.6)
Within 30 days after vaccination				
Serious adverse event‡	87	1.1 (0.9–1.4)	97	1.3 (1.0–1.5)
Serious adverse event related to vaccination§	1	0.0 (0.0–0.1)	3	0.0 (0.0–0.1)
Death	8	0.1 (0.0–0.2)	7	0.1 (0.0–0.2)

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Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

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ABSTRACT

BACKGROUND

A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella–zoster virus glycoprotein E and the $AS01_B$ adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70).

METHODS

This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50.

RESULTS

In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95% CI, 86.8 to 94.5; P<0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1; P<0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups.

CONCLUSIONS

In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older. (Funded by GlaxoSmithKline Biologicals; ZOE-50 and ZOE-70 ClinicalTrials.gov numbers, NCT01165177 and NCT01165229.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Heineman at Genocea Biosciences, Cambridge Discovery Park, 100 Acorn Park Dr., 5th Floor, Cambridge, MA 02140, or at thomas.heineman@genocea.com.

*A complete list of investigators in the Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Cunningham and Lal contributed equally to this article. Authors from Dr. Godeaux to Dr. Zahaf (listed alphabetically) also contributed equally, as did authors from Dr. Ahonen to Dr. Yeo (listed alphabetically).

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Adults 70 years of age or older were eligible for inclusion in the trial unless they had a history of herpes zoster, had previously been vaccinated against varicella or herpes zoster, or had an immunosuppressive condition

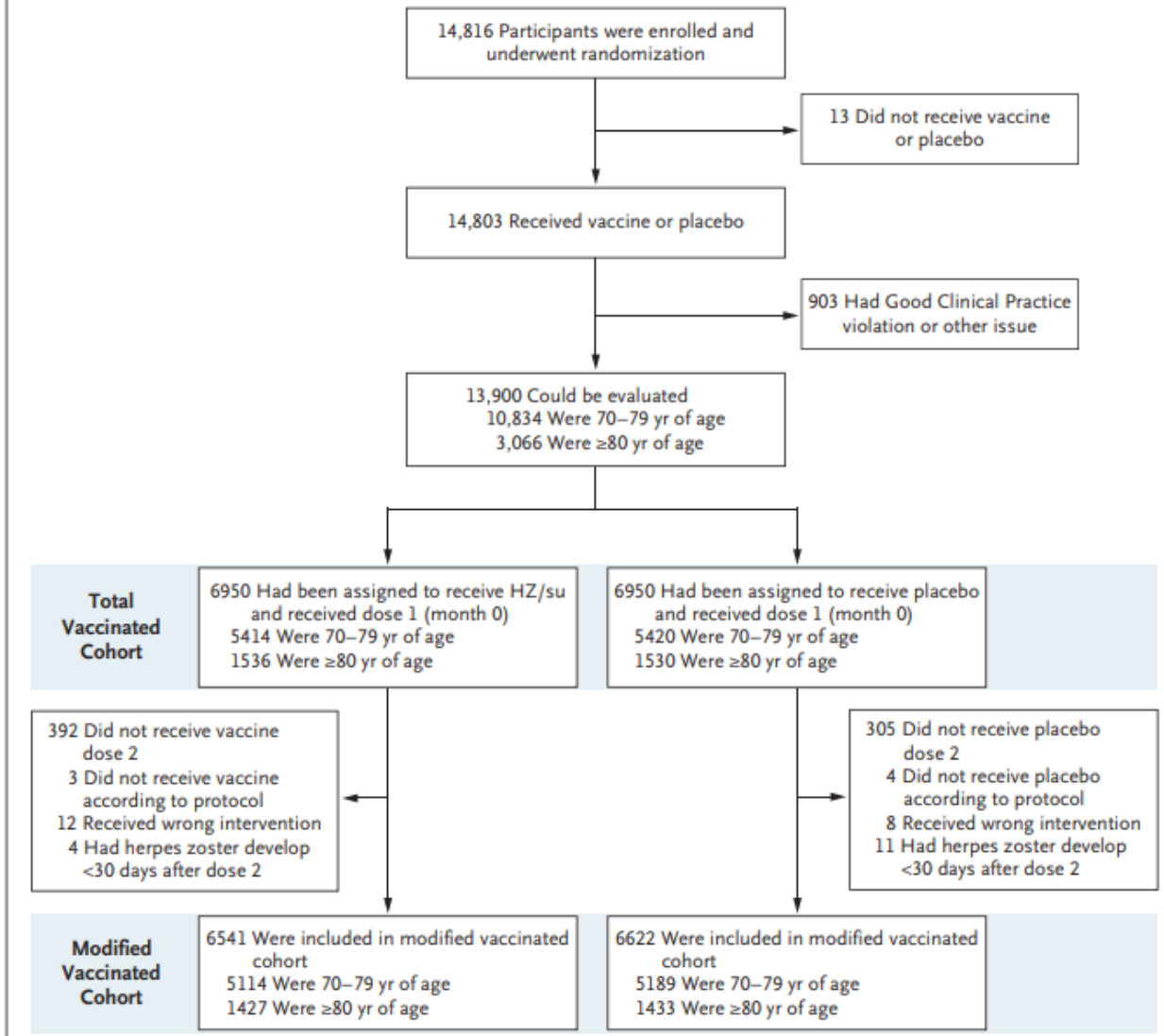

Figure 1. Enrollment and Randomization.

After enrollment, one study center was closed because of Good Clinical Practice violations, and one study center was closed for financial reasons (see the Supplementary Appendix). All participants who had been enrolled at these centers were excluded from all analyses. An additional four participants were excluded because of issues with informed consent. Some participants in the total vaccinated cohort had more than one reason for being excluded from the modified vaccinated cohort. HZ/su denotes herpes zoster subunit vaccine.

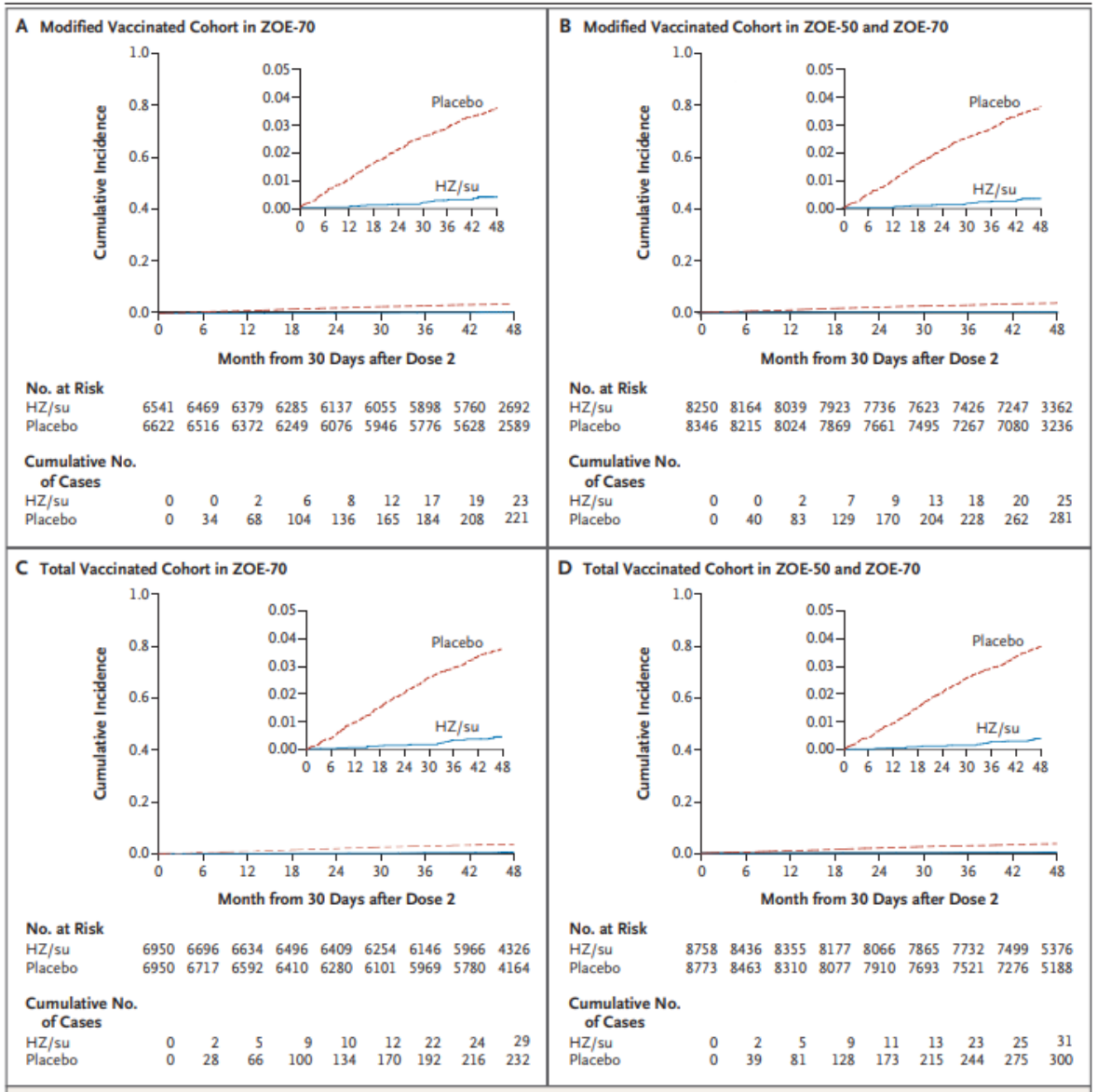

Figure 2. Risk of Development of Herpes Zoster after Vaccination.

Shown are the Kaplan–Meier estimates of the cumulative incidence (expressed as the percentage of the participants at risk) of the development of herpes zoster during the period from 30 days after receiving the second dose of HZ/su or placebo to the end of follow-up among participants 70 years of age or older. Because of the declining numbers of participants at risk, the Kaplan–Meier curves have been truncated at 48 months after the second dose of HZ/su. Some cases occurred after 48 months. In each panel, the inset shows the same data on an expanded y axis.

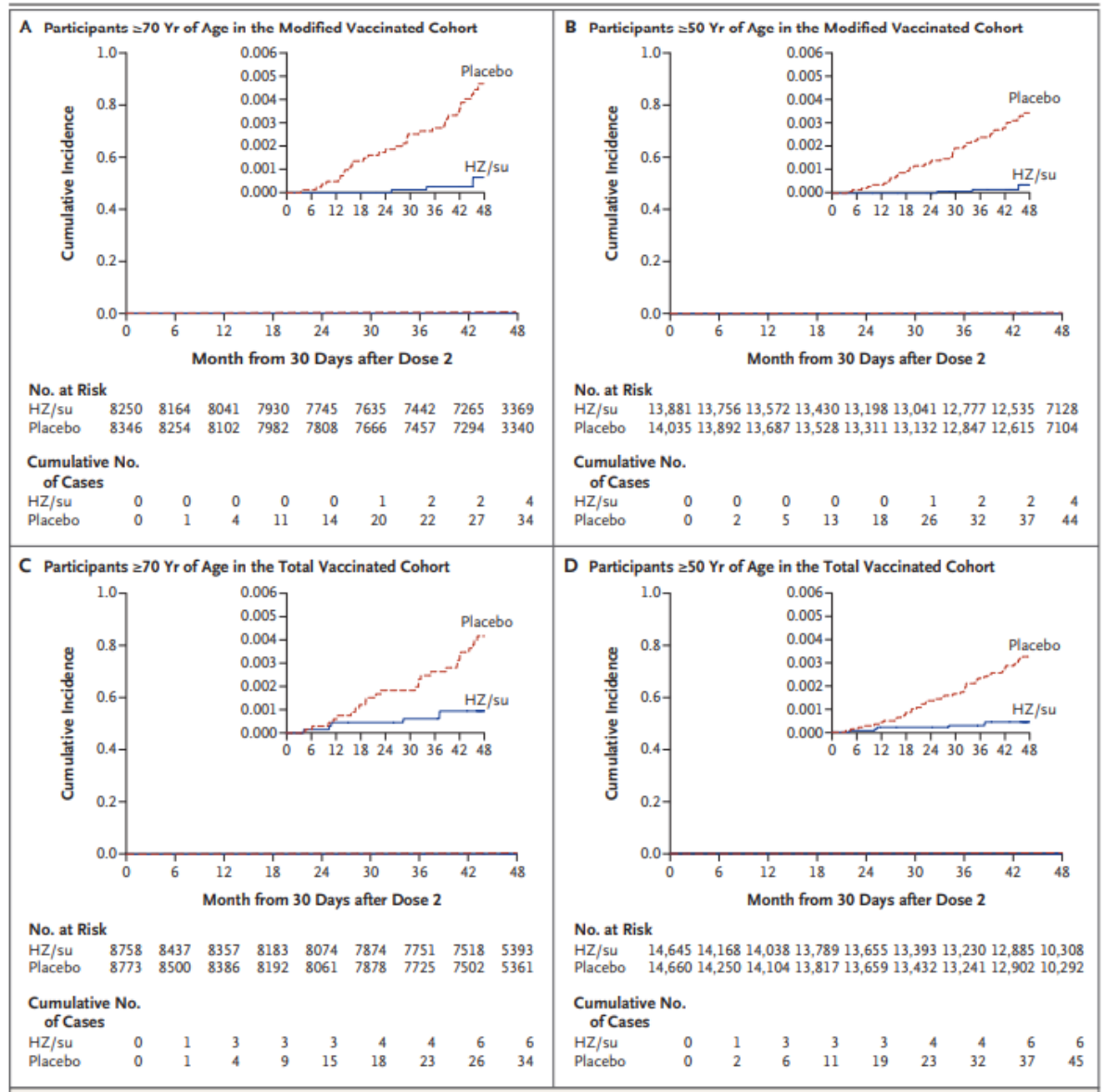

Figure 3. Risk of Development of Postherpetic Neuralgia after Vaccination in the Pooled Population.

Shown are the Kaplan–Meier estimates of the cumulative incidence (expressed as the percentage of the participants at risk) of the development of postherpetic neuralgia during the period from 30 days after receipt of the second dose of HZ/su or placebo to the end of follow-up in the pooled ZOE-70 and ZOE-50 populations. Because of the declining numbers of participants at risk, the Kaplan–Meier curves have been truncated at 48 months after the second dose of HZ/su. Some cases occurred after 48 months. In each panel, the inset shows the same data on an expanded y axis.

Table 2. Vaccine Reactogenicity and Safety Overall.

Time Period and Event	HZ/su Group		Placebo Group	
	no. of participants/ total no.	*% (95% CI)*	*no. of participants/ total no.*	*% (95% CI)*
Within 7 days after vaccination in the reactogenicity subgroup*				
Any reaction	399/505	79.0 (75.2–82.5)	149/505	29.5 (25.6–33.7)
Grade 3 reaction†	60/505	11.9 (9.2–15.0)	10/505	2.0 (1.0–3.6)
Injection-site reaction	374/505	74.1 (70.0–77.8)	50/505	9.9 (7.4–12.8)
Pain	347/505	68.7 (64.5–72.7)	43/505	8.5 (6.2–11.3)
Redness	198/505	39.2 (34.9–43.6)	5/505	1.0 (0.3–2.3)
Swelling	114/505	22.6 (19.0–26.5)	2/505	0.4 (0.0–1.4)
Grade 3 injection-site reaction†	43/505	8.5 (6.2–11.3)	1/505	0.2 (0.0–1.1)
Systemic reaction	267/504	53.0 (48.5–57.4)	127/505	25.1 (21.4–29.2)
Fatigue	166/504	32.9 (28.8–37.2)	77/505	15.2 (12.2–18.7)
Myalgia	157/504	31.2 (27.1–35.4)	41/505	8.1 (5.9–10.9)
Headache	124/504	24.6 (20.9–28.6)	55/505	10.9 (8.3–13.9)
Shivering	75/504	14.9 (11.9–18.3)	22/505	4.4 (2.7–6.5)
Fever	62/504	12.3 (9.6–15.5)	13/505	2.6 (1.4–4.4)
Gastrointestinal symptoms	55/504	10.9 (8.3–14.0)	40/505	7.9 (5.7–10.6)
Grade 3 systemic reaction†	30/504	6.0 (4.1–8.4)	10/505	2.0 (1.0–3.6)
Throughout the study period in the total vaccinated cohort‡				
Serious adverse event	1153/6950	16.6 (15.7–17.5)	1214/6950	17.5 (16.6–18.4)
Serious adverse event considered as related to vaccination §	12/6950	0.2 (0.1–0.3)	8/6950	0.1 (0.0–0.2)
Potential immune-mediated disease	92/6950	1.3 (1.1–1.6)	97/6950	1.4 (1.1–1.7)
Death	426/6950	6.1 (5.6–6.7)	459/6950	6.6 (6.0–7.2)

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.

Clinical Infectious Diseases

MAJOR ARTICLE

Herpes Zoster Risk in Immunocompromised Adults in the United States: A Systematic Review

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Background. The primary reported risk factors for herpes zoster (HZ) include increasing age and immunodeficiency, yet estimates of HZ risk by immunocompromising condition have not been well characterized. We undertook a systematic literature review to estimate the HZ risk in immunocompromised patients.

Methods. We systematically reviewed studies that examined the risk of HZ and associated complications in adult patients with hematopoietic cell transplants (HCT), cancer, human immunodeficiency virus (HIV), and solid organ transplant (SOT). We identified studies in PubMed, Embase, Medline, Cochrane, Scopus, and clinicaltrials.gov that presented original data from the United States and were published after 1992. We assessed the risk of bias with Cochrane or Grading of Recommendations Assessment, Development, and Evaluation methods.

Results. We identified and screened 3765 records and synthesized 34 studies with low or moderate risks of bias. Most studies that were included (32/34) reported at least 1 estimate of the HZ cumulative incidence (range, 0–41%). There were 12 studies that reported HZ incidences that varied widely within and between immunocompromised populations. Incidence estimates ranged from 9 to 92 HZ cases/1000 patient-years and were highest in HCT, followed by hematologic malignancies, SOT, and solid tumor malignancies, and were lowest in people living with HIV. Among 17 HCT studies, the absence of or use of antiviral prophylaxis at <1 year post-transplant was associated with a higher HZ incidence.

Conclusions. HZ was common among all immunocompromised populations studied, exceeding the expected HZ incidence among immunocompetent adults aged ≥60 years. Better evidence of the incidence of HZ complications and their severity in immunocompromised populations is needed to inform economic and HZ vaccine policies.

Keywords. herpes zoster; immunocompromised; postherpetic neuralgia; VZV; RZV.

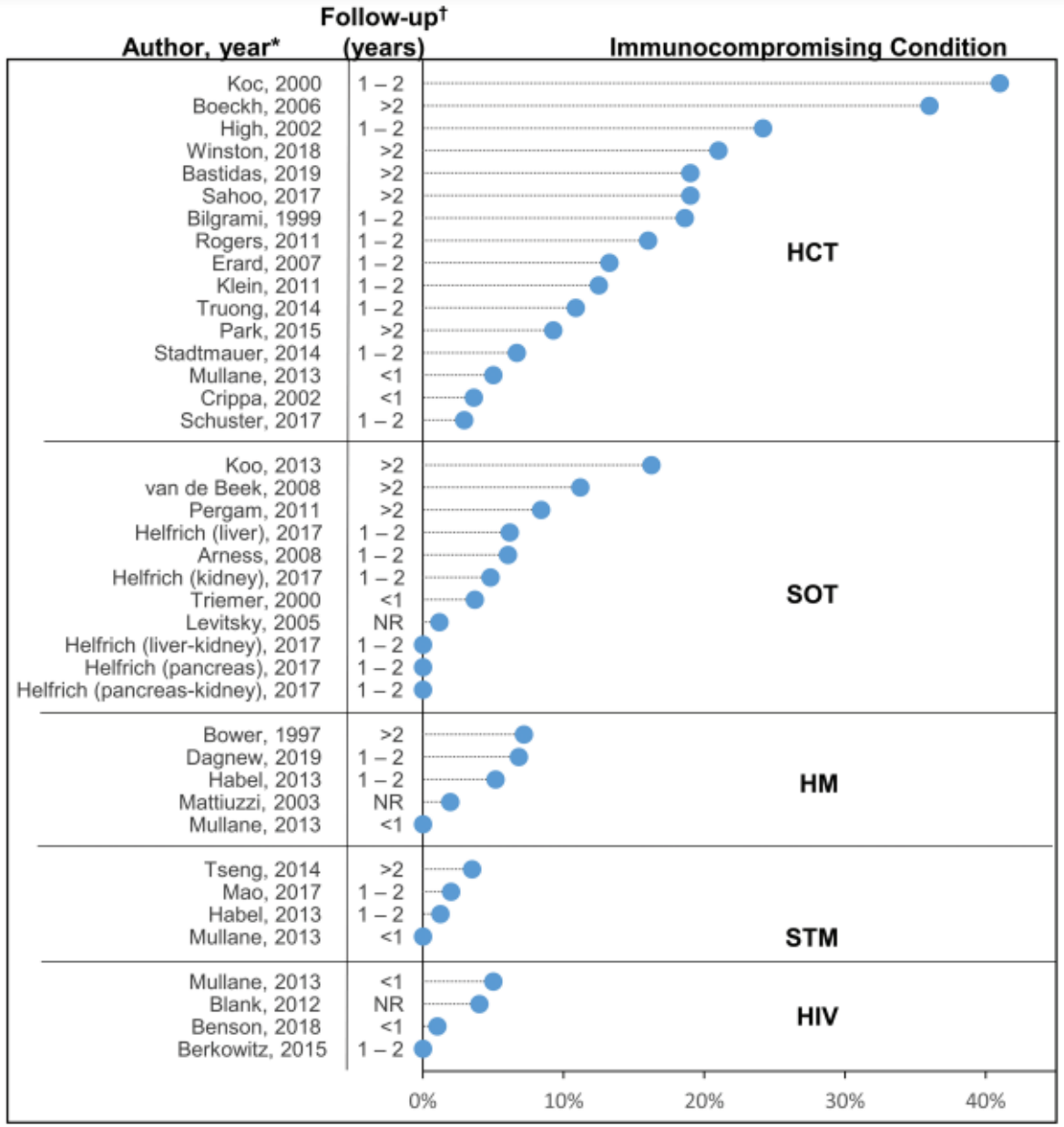

Figure 2. Studies reporting herpes zoster cumulative incidence for select immunocompromising conditions. *Studies with low or medium risk of bias. †Follow-up time reported as median, average, or maximum was categorized into <1 year, 1 to 2 years, or >2 years. Abbreviations: HCT, hematopoietic stem cell transplant; HIV, human immunodeficiency virus; HM, hematologic malignancy; NR, not reported; SOT, solid organ transplant; STM, solid tumor malignancy.

Shingles Home
About Shingles
Vaccination
Clinical Considerations for Use of Recombinant Zoster Vaccine (RZV, Shingrix) in Immunocompromised Adults Aged ≥19 Years
For Healthcare Professionals
Laboratory Testing
Burden and Trends
Resources & References
Multimedia

Related Links
Medline Plus
AgePage on Shingles

Clinical Considerations for Use of Recombinant Zoster Vaccine (RZV, Shingrix) in Immunocompromised Adults Aged ≥19 Years

Print

Purpose

Recombinant zoster vaccine (RZV, Shingrix) was licensed in the United States for the prevention of herpes zoster, or shingles, for adults aged ≥50 years by the Food and Drug Administration (FDA) and recommended for immunocompetent adults aged ≥50 years by the Advisory Committee on Immunization Practices (ACIP) in 2017* (1).

On July 23, 2021, the FDA expanded the indication for RZV to include adults aged ≥18 years who are or will be at increased risk for shingles because of immunodeficiency or immunosuppression caused by known disease or therapy (2). On October 20, 2021, ACIP recommended two doses of RZV for the prevention of shingles and related complications in adults aged ≥19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy.

These clinical considerations are intended to supplement the MMWR policy note published in January 2022 (3) and will be updated as new information becomes available.

Morbidity and Mortality Weekly Report

Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

Tara C. Anderson, DVM, PhD[1]; Nina B. Masters, PhD[1,2]; Angela Guo, MPH, MBA[1]; Leah Shepersky, MPH[1]; Andrew J. Leidner, PhD[3]; Grace M. Lee, MD[4]; Camille N. Kotton, MD[5]; Kathleen L. Dooling, MD[1]

MMWR / January 21, 2022 / Vol. 71 / No. 3

Estimates of vaccine efficacy (VE) came from three studies:

- with VE of 68.2% (95% CI = 55.6%–77.5%) for autologous hematopoietic cell transplant recipients (1)
- 87.2% (44.3%–98.6%) and 90.5% (73.5%–97.5%) in post hoc efficacy analyses for patients with hematologic malignancies (2) and potential immune-mediated diseases (3), respectively.

1. Bastidas A, de la Serna J, El Idrissi M, et al.; ZOE-HSCT Study Group Collaborators. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. JAMA 2019;322:123–33. PMID:31287523 https://doi. org/10.1001/jama.2019.9053 12.
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3. Dagnew AF, Rausch D, Hervé C, et al.; ZOE-50/70 Study Group. Efficacy and serious adverse events profile of the adjuvanted recombinant zoster vaccine in adults with pre-existing potential immune-mediated diseases: a pooled post hoc analysis on two parallel randomized trials. Rheumatology (Oxford) 2021;60:1226–33. PMID:32910152 https:// doi.org/10.1093/rheumatology/keaa424

Morbidity and Mortality Weekly Report

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Tara C. Anderson, DVM, PhD[1]; Nina B. Masters, PhD[1,2]; Angela Guo, MPH, MBA[1]; Leah Shepersky, MPH[1]; Andrew J. Leidner, PhD[3]; Grace M. Lee, MD[4]; Camille N. Kotton, MD[5]; Kathleen L. Dooling, MD[1]

MMWR / January 21, 2022 / Vol. 71 / No. 3

Overall, rates of SAEs were comparable between RZV and placebo recipients (risk ratios ranged from 0.79 to 1.99). SAEs deemed to be related to vaccination by study investigators ranged from 0% to 1.6% in the RZV group and 0% to 0.76% in the placebo group. The level of certainty for prevention of herpes zoster and occurrence of SAEs was type 2 (moderate)

1. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood 2014;124:2921–9.
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Clinical Guidance

Dosing schedule

Two doses of RZV are necessary regardless of previous history of shingles or previous receipt of zoster vaccine live (ZVL, Zostavax).[†]

- The second dose of RZV should typically be given 2–6 months after the first.
- However, for persons who are or will be immunodeficient or immunosuppressed and who would benefit from completing the series in a shorter period, the second dose can be administered 1–2 months after the first (2). For example, a shorter interval between doses may facilitate avoiding vaccination during periods of more intense immunosuppression.
- If the second dose of RZV is given sooner than 4 weeks after the first, a second valid dose should be repeated at least 4 weeks after the dose that was given too early.
- The vaccine series does not need to be restarted if more than 6 months have elapsed since the first dose.

Timing of vaccination

When possible, patients should be vaccinated before becoming immunosuppressed. If vaccination before immunosuppression is not possible, providers should consider timing vaccination when the immune response is likely to be most robust.

Factors to consider in assessing the general level of immune competence in a patient include:

- Disease severity and duration
- Clinical stability
- Complications and comorbidities
- Any potentially immunosuppressing treatment

Vaccine providers should consider consulting with the provider most responsible for managing the patient's immunocompromising condition or therapy, as needed.

For vaccination of persons with altered immunocompetence, various references, including ACIP's general best practices (4), Chapter 5 of the CDC Yellow Book (5), and the Infectious Diseases Society of America's 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host (6), can be consulted for additional information about the degree of immune suppression associated with different medical conditions and treatments.

The risk of deferring vaccination, and thus not mitigating the increased risk for shingles and related complications in immunocompromised patients, should be weighed against a possible diminished response to RZV if given during periods of more intense immunosuppression.

Grazie per l’attenzione