American Journal of Epidemiology

Vol. 187, No. 1
DOI: 10.1093/aje/kwx245
Advance Access publication:
June 21, 2017

Practice of Epidemiology

Long-Term Effectiveness of the Live Zoster Vaccine in Preventing Shingles: A Cohort Study

Roger Baxter†, Joan Bartlett, Bruce Fireman*, Morgan Marks, John Hansen, Edwin Lewis, Laurie Aukes, Yong Chen, Nicola P. Klein, and Patricia Saddier

* Correspondence to Bruce Fireman, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612 (e-mail: bruce.fireman@kp.org).
†Deceased.

Initially submitted January 20, 2017; accepted for publication June 8, 2017.

A live attenuated zoster vaccine was licensed in the United States in 2006 for prevention of shingles in persons aged 60 years or older; the indication was extended in 2011 to cover those aged 50–59 years. We assessed vaccine effectiveness (VE) against shingles for 8 years after immunization at Kaiser Permanente Northern California. VE was estimated by Cox regression with a calendar timeline that was stratified by birth year. We adjusted for demographics and time-varying covariates, including comorbidities and immune compromise. From 2007 to 2014, 1.4 million people entered the study when they became age eligible for vaccination; 392,677 (29%) received the zoster vaccine. During 5.8 million person-years of follow-up, 48,889 cases of shingles were observed, including 5,766 among vaccinees. VE was 49.1% (95% confidence interval (CI): 47.5, 50.6) across all follow-up. VE was 67.5% (95% CI: 65.4, 69.5) during the first year after vaccination, waned to 47.2% (95% CI: 44.1, 50.1) during the second year after vaccination, and then waned more gradually through year 8, when VE was 31.8% (95% CI: 15.1, 45.2). Unexpectedly, VE in persons vaccinated when they were aged 80 years or older was similar to VE in younger vaccinees, and VE in persons vaccinated when immune compromised was similar to VE in persons vaccinated when immune competent.

herpes zoster; herpes zoster vaccine; vaccine effectiveness

Abbreviations: CI, confidence interval; HZ, herpes zoster; IC, immune compromise; KPNC, Kaiser Permanente Northern California; VE, vaccine effectiveness

Shingles, also known as herpes zoster (HZ), is a painful eruption that occurs along a dermatome and is due to reactivation of varicella virus, which typically has been latent since childhood chicken pox. Old age, with its attendant decrease in cell-mediated immunity, appears to be the most important risk factor for HZ (1, 2), but immunocompromising medications or conditions also increase risk (3). Incidence of HZ increases with age from 5 per 1,000 person-years in persons aged 50–59 years to 12 per 1,000 in those 80 years old and older (1). Approximately 1 in 3 people develops HZ in their lifetime (1), and for persons living to age 85 years, the lifetime risk is approximately 50% (3). Depending on age, 5%–30% of persons with HZ go on to have long-lasting pain called postherpetic neuralgia that persists after the shingles lesions resolve (4).

A live attenuated zoster vaccine (Zostavax; Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey) has been licensed in the United States since 2006 for persons aged 60 years and older (5). In 2011, the licensure was extended to include persons 50–59 years old (6). The Advisory Committee on Immunization Practices has recommended routine vaccination for people aged 60 years or older but has made no such recommendation for those aged 50–59 years, in part due to concerns about waning of efficacy over time (7). Currently, there is no recommendation for a booster.

The efficacy of the zoster vaccine was established through clinical studies, including a large randomized, placebo-controlled trial (8) and a follow-up study (9). Vaccine efficacy (VE) against HZ in the trial was 51.3% during follow-up lasting a median of 3.1 years. Although the trial found evidence that VE wanes, precise estimates were not reported for VE by year after vaccination or for how much protection remains after 3 years. Also, it is important to better describe VE in people who are at especially high

risk of HZ because they are aged 80 years or older or immunocompromised. Although immune compromise (IC) has been a contraindication to vaccination since licensure, in practice, some persons with IC do receive the vaccine.

Our aims in this study were to 1) estimate more precisely the effectiveness of the zoster vaccine by year for 8 years after vaccination, 2) estimate VE in people vaccinated when aged 80 years or older and in people vaccinated when immunocompromised, and 3) illustrate an innovative approach to estimating how VE changes by time since vaccination.

METHODS

Setting

Kaiser Permanente Northern California (KPNC) delivers integrated health care services to approximately 3.8 million members, including approximately 1.4 million persons aged 50 years or older. The socioeconomic makeup of health plan members is similar to that of the general population of northern California, though less representative of the lowest incomes (10, 11). The 10-year retention rate of members aged 50 years or older is approximately 50%. KPNC databases include comprehensive information on membership, demographics, vaccinations, diagnoses, outpatient visits, hospitalizations, prescriptions, and laboratory tests. The KPNC Institutional Review Board approved this study.

Study population and data

This is a prospective cohort study with continuous accrual of people as they become age eligible for zoster vaccination. The study began on January 1, 2007, and continues through 2023. Eligibility is based on US dates of approval of the vaccine for people aged 60 years and older (May 2006, with study entry starting January 2007) and for people 50–59 years old (March 2011). To ensure accurate ascertainment of vaccination status and baseline covariates, we restrict study entry to KPNC members with continuous membership since becoming age eligible for the zoster vaccine and at least 12 months of continuous membership before study entry. We exclude individuals who had an HZ diagnosis in the year before study entry. The cohort is updated annually to include newly age-eligible KPNC members.

All members of the cohort start follow-up unvaccinated but are age eligible for vaccination. They contribute unvaccinated person-time while they remain unvaccinated; if they receive the zoster vaccine, they then contribute vaccinated person-time. They contribute unvaccinated or vaccinated person-time until HZ diagnosis or follow-up is censored by disenrollment from KPNC, receipt of a second dose of zoster vaccine (rare), death, or the end of available data (December 31, 2014).

The outcome of interest is the onset of a new episode of HZ, identified by the first health care encounter with an HZ diagnosis (*International Classification of Diseases, Ninth Revision*, codes 053.xx). Of the 59,519 first HZ diagnoses, we counted as outcome events the 48,889 (82%) that were accompanied by an antiviral prescription (without evidence of herpes simplex infection) or a laboratory test positive for varicella-zoster infection. Chart review, adjudicated by 2 physicians, confirmed 97.5% of a random sample of 200 such cases as new HZ cases. The positive predictive value of the remaining 10,630 possible cases was lower and they were not counted as outcome events; instead, follow-up was censored at the onset of these less-certain HZ episodes. We included in a sensitivity analysis 5,909 (56%) of the 10,630 less-certain cases, a subset for whom the HZ diagnosis was primary and the positive predictive value was fairly high (85.5%).

Estimation of VE was adjusted for time-fixed factors, including sex and race, and for time-varying factors, including influenza vaccination during the prior year, outpatient visit frequency, comorbidities, and IC status, as well as birth year and calendar date, which, together, adjusted for year of age. Visit frequency was summarized by the number of weeks during the prior year in which the individual had at least 1 outpatient visit. Two scores were used to summarize each individual's comorbidities during the prior year: 1) an HZ risk score developed using data from our unvaccinated study population and Cox regression to examine time to HZ occurrence in relation to 126 diagnosis categories defined by the Healthcare Cost and Utilization Project (12), and 2) a commercially available cost predictor (13), which uses diagnoses grouped in 184 categories to predict costs during the upcoming year. IC status was measured by the following 8 variables that indicate conditions or treatments during the past year that weaken the immune system: blood cancer, metastatic cancer, bone marrow or hematopoietic stem cell transplantation, human immunodeficiency virus/acquired immunodeficiency syndrome, rare immune deficiency conditions, cancer radiotherapy, corticosteroid medications, and other immunosuppressive medications such as antineoplastic, antirheumatic, or antirejection drugs. The measures of influenza vaccination, outpatient visit frequency, and IC status were updated quarterly (for rolling 12-month periods); the HZ risk score and the cost predictor were updated yearly.

To examine the possibility that VE is low in persons who were immunocompromised when vaccinated, we also made a 3-level measure to categorize the IC status of vaccinees at the time of vaccination. The levels are no IC, low IC, and high IC. The 3-level measure was based on the 8 IC variables during the 12-month period ending 30 days after vaccination, and was only assessed for vaccinees. This let us examine whether VE was modified by IC status at the time of vaccination, with adjustment for IC status later at the time of risk.

Details on measurement of IC status at time of vaccination and time of risk are provided in the Web Appendix (available at https://academic.oup.com/aje). Web Table 1 shows rules used to update IC status over time; Web Table 2 specifies conversion factors used to calculate prednisone-equivalent doses for corticosteroid medications; Web Table 3 lists the IC medications used; Web Tables 4–7 list the diagnosis codes used.

Statistical analysis

We examined the risk of HZ in relation to year since vaccination. We compared vaccinees' risk during each year since vaccination with risk in otherwise similar people who were unvaccinated. A Cox regression model, stratified by year of birth, was specified with a calendar timeline; the model included all the time-fixed and time-varying covariates described in

the Methods. For each day when an HZ case occurred, a risk set was formed, including the case and all persons born the same year and who were still in follow-up. Binary variables were included in the model, indicating for each vaccinee the number of years since zoster vaccination, as follows: 30 days to <1 year, 1 to <2 years, . . ., and 7 to < 8 years. Unvaccinated persons constituted the reference group. We estimated the HZ hazard ratio for each year after vaccination. VE for each year was estimated by 1 minus the hazard ratio estimate, and then scaled as a percentage. To allow time for the vaccine to take effect, VE estimates did not include days 1–29 after vaccination as vaccinated (or unvaccinated).

A second Cox regression model was used to examine the risk of HZ in relation to year since vaccination and to age at vaccination. To estimate VE in each of 8 years after vaccination in each of 4 age groups (50–59, 60–69, 70–79, and ≥80 years), 32 vaccination indicator variables were included in this model. A third model was used to examine VE by IC status at the time of vaccination. In this model, 3 vaccination indicator variables were included to estimate VE over all follow-up time for vaccinees with high IC, low IC, or no IC when vaccinated compared with unvaccinated individuals.

Finally, we fitted a model that included only 1 vaccination indicator (yes or no) to estimate a summary measure of overall VE, ignoring how VE was modified by year since vaccination, age at vaccination, or IC at vaccination. Insofar as VE wanes over time, this measure reflects the distribution of year since vaccination in the available follow-up. Therefore, another summary measure, average VE, was calculated for each age group from an average of year-specific hazard ratios (on the log scale) that were estimated from the second Cox model described in the previous paragraph. Average VE weights the estimates for each year since vaccination equally (with the estimate for the first year slightly downweighted because it omits days 1–29). This summary measure of average VE is reported by age group for the first 3 and 5 years after vaccination.

We also used Cox regression to describe the associations of the covariates with vaccination status and with HZ. We fitted a model for time to vaccination and a model for time to HZ in unvaccinated persons. These models were like our VE models: We included the same covariates (except vaccination status) and used a calendar timeline stratified by year of birth.

Analyses were done with SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). We used the Lexis macro to partition person-time (http://bendixcarstensen.com/Lexis/Lexis.sas).

RESULTS

From 2007 through 2014, 1,355,720 persons entered the study population; 635,366 (47%) entered at ages 50–59 years, and 720,354 (53%) entered at age 60 years or older. During the study period, 392,677 people (29%) received the zoster vaccine. Average duration of follow-up was 4.3 years per person. The average duration of unvaccinated follow-up was 3.5 years, including time before vaccination as well as time of never-vaccinated persons. The average duration of vaccinated follow-up was 2.5 years. In vaccinees aged 60 years or older, 31.6% of follow-up was longer than 3 years after vaccination (Table 1), but nearly all follow-up in vaccinees aged 50–59 was within 3 years because Zostavax was not licensed for persons aged 50–59 years until 2011. During the 5.8 million person-years of follow-up in the study population, 48,889 cases of HZ were identified, including 5,766 among vaccinees.

Vaccine uptake in persons aged 60 years or older increased gradually from 2007 through 2012 (Figure 1), and then more rapidly after July 2013, when KPNC instituted a reminder recommending zoster vaccine to persons aged 60 years or older at visits and online. By 2014, vaccine coverage was greater than 50% in persons aged 60 years or older but only 4.5% in those aged 50–59 years.

Among the unvaccinated, the crude incidence of HZ per 1,000 person-years was relatively stable during the study period; it rose slightly each year during the first 4 years, increasing from 9.5 in 2007 to 10.2 in 2010, and then decreasing after the entry of persons aged 50–59 years to 8.1 in 2014.

Table 1. Person-Years of Follow-Up in Persons Vaccinated Against Herpes Zoster, by Time Since Vaccination and Age at Vaccination, Kaiser Permanente Northern California, 2007–2014

Time Since Vaccination	Age at Vaccination									
	50–59 Years		60–69 Years		70–79 Years		≥80 Years		All Ages	
	Person-Years (n = 48,287)	%	Person-Years (n = 556,616)	%	Person-Years (n = 301,594)	%	Person-Years (n = 91,980)	%	Person-Years (n = 998,477)	%
30 days to <1 year	23,184	48.0	174,828	31.4	84,487	28.0	32,465	35.3	314,964	31.5
1 to <2 years	17,356	35.9	124,488	22.4	64,181	21.3	21,219	23.1	227,244	22.8
2 to <3 years	6,866	14.2	87,012	15.6	47,749	15.8	13,732	14.9	155,359	15.6
3 to <4 years	881	1.8	63,688	11.4	36,905	12.2	9,539	10.4	111,013	11.1
4 to <5 years	0	0.0	49,135	8.8	29,776	9.9	7,137	7.8	86,048	8.6
5 to <6 years	0	0.0	33,326	6.0	21,543	7.1	4,696	5.1	59,565	6.0
6 to <7 years	0	0.0	18,987	3.4	13,142	4.4	2,530	2.8	34,659	3.5
7 to <8 years	0	0.0	5,152	0.9	3,811	1.3	662	0.7	9,625	1.0

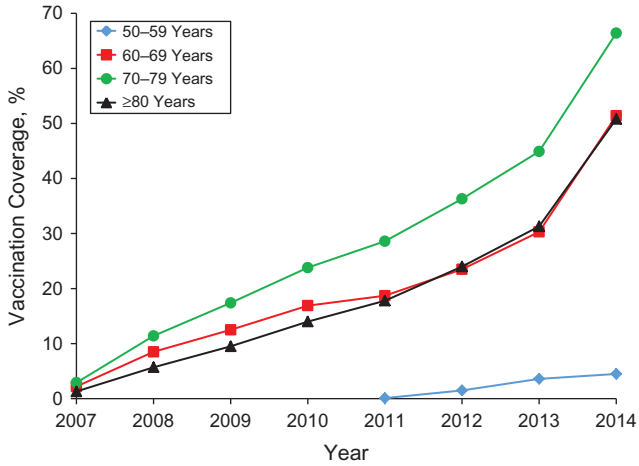

Figure 1. Zoster vaccine coverage on July 1 of each year by age group, Kaiser Permanente Northern California study population, 2007–2014.

Among the unvaccinated, HZ incidence per 1,000 person-years rose with age from 6.8 at age 50–59 years to 11.9 at ages 80 years and older (Table 2). Crude HZ incidence rates were much lower among the vaccinated than among the unvaccinated, by 56%, 46%, 40%, and 35% at ages 50–59, 60–69, 70–79, and 80 years or older, respectively.

Female sex, influenza vaccination, and HZ risk score were positively associated with both vaccination and HZ (Table 3). All IC indicators and Hispanic ethnicity were negatively associated with vaccination and positively associated with HZ. Black race was negatively associated with both vaccination and HZ. There was less potential for confounding from the cost predictor or visit frequency; the cost predictor was only weakly associated with HZ and visit frequency was only weakly associated with vaccination.

After covariate adjustment, overall VE was 49.1% (95% confidence interval (CI): 47.5, 50.6) across all follow-up in all age groups. The overall VE estimate was nearly the same, 48.2%, in a sensitivity analysis that included the 5,909 people with less-certain HZ who were excluded from the primary analyses because of absence of an antiviral prescription or positive laboratory test result.

VE decreased by time since vaccination (Table 4). In each age group, VE was substantially higher during the first year after vaccination than in later years. In all age groups combined, VE was 67.5% during the first year. During the second year after vaccination, VE decreased in each age group, to 47.2% in all ages combined. After the second year, VE continued to decrease but did so more gradually.

VE did not vary much by age at vaccination (Table 4). Average VE by age group over the first 3 years after vaccination was 59.5% (95% CI: 51.7, 66.1), 54.7% (95% CI: 52.3, 57.0), 49.8% (95% CI: 46.6, 52.8), and 48.0% (95% CI: 42.5, 53.0) in the age groups 50–59, 60–69, 70–79, and 80 years and older, respectively. Average VE over the first 5 years was 49.2% (95% CI: 46.8, 51.5), 45.5% (95% CI: 42.5, 48.4), and 43.9% (95% CI: 38.3, 49.0) in the age groups 60–69, 70–79, and 80 years and older, respectively. As yet, only sparse follow-up data are available after year 3 for ages 50–59 years and after year 6 for ages 80 years and older. Through year 6, VE in the group of people aged 80 years or older was similar to VE in the age groups 60–69 years and 70–79years (Table 4).

Among the 392,677 vaccinees, 21,665 (5.5%) were vaccinated while immunocompromised, including 4,367 (1.1%) who were highly IC when vaccinated. Individuals vaccinated while immunocompromised had similar VE to immunocompetent vaccinees, after covariate adjustment (Table 5). Adjustment for the time-varying covariates, especially the HZ risk score and the indicators for IC at time of risk, had a large effect on the VE estimate for vaccinees who were highly immunocompromised when vaccinated, but had little effect on the VE estimate for immunocompetent vaccinees. Vaccinees in the high-IC level spent 64% of their postvaccination follow-up with high-IC status, much more than immunocompetent vaccinees (1.2% of their postvaccination follow-up) or the unvaccinated (2.3% of follow-up).

DISCUSSION

This large, ongoing study of Zostavax VE examined 5.8 million person-years of vaccine-eligible follow-up in 1.4 million

Table 2. Incidence of Herpes Zoster by Age and Vaccination Status, Kaiser Permanente Northern California, 2007–2014

Variable	Incidence in Unvaccinated Persons per 1,000 Person-Years			Incidence in Vaccinees per 1,000 Person-Years			Incidence Rate Ratio	
	HZ Cases	Person-Years	Incidence	HZ Cases	Person-Years	Incidence	Rate Ratio	95% CI
Age range, years								
50–59	10,105	1,494,694	6.76	111	36,904	3.01	0.44	0.37, 0.54
60–69	15,311	1,777,156	8.62	2,117	453,799	4.67	0.54	0.52, 0.57
70–79	10,080	901,894	11.18	2,395	358,314	6.68	0.60	0.57, 0.63
≥80	7,354	620,358	11.85	1,143	149,460	7.65	0.65	0.61, 0.69
Total	42,850[a]	4,794,102	8.94	5,766	998,477	5.77	0.65	0.63, 0.66

Abbreviations: CI, confidence interval; HZ, herpes zoster.

[a] An additional 273 cases occurred during 30,955 person-years in the "washout" period from 1–29 days after vaccination. These cases and person-years are not included as either vaccinated or unvaccinated.

Table 3. Associations of Covariates With the Propensity for Zoster Vaccination and the Risk of Herpes Zoster in Unvaccinated Persons, Kaiser Permanente Northern California, 2007–2014

Covariate	Zoster Vaccination		Herpes Zoster	
	Hazard Ratio[a]	95% CI	Hazard Ratio[a]	95% CI
Female sex	1.14	1.13, 1.14	1.33	1.30, 1.35
Race or ethnic group (vs. white)				
Asian or Pacific Islander	0.93	0.92, 0.94	1.17	1.13, 1.20
Black	0.68	0.67, 0.69	0.75	0.72, 0.78
Hispanic (regardless of race)	0.77	0.76, 0.78	1.16	1.13, 1.19
Other or unknown	0.54	0.53, 0.56	0.76	0.71, 0.82
Influenza vaccination	2.20	2.18, 2.21	1.13	1.11, 1.16
IC corticosteroids (vs. none)				
Low IC	0.93	0.91, 0.94	1.49	1.43, 1.56
High IC	0.66	0.63, 0.69	1.75	1.63, 1.89
IC medication other than corticosteroids (vs. none)				
Low IC	0.52	0.50, 0.54	1.24	1.16, 1.32
High IC	0.24	0.23, 0.25	1.42	1.34, 1.51
Metastatic cancer	0.76	0.74, 0.79	1.04	0.98, 1.11
Rare immune deficiency condition	0.61	0.50, 0.74	1.08	0.83, 1.41
Blood cancer	0.58	0.55, 0.61	1.54	1.42, 1.66
Cancer radiotherapy	0.88	0.84, 0.92	1.22	1.10, 1.34
HIV (vs. no HIV)				
HIV with high CD4 count	0.76	0.71, 0.82	1.13	0.95, 1.34
HIV with low or missing CD4 count	0.16	0.09, 0.28	2.11	1.40, 3.18
Bone marrow or stem cell transplant	0.72	0.56, 0.92	1.66	1.30, 2.13
Visit frequency (vs. first quintile)				
Second quintile	0.95	0.94, 0.96	1.13	1.09, 1.16
Third quintile	0.90	0.89, 0.91	1.24	1.19, 1.28
Fourth quintile	0.90	0.89, 0.91	1.28	1.23, 1.32
80th to <90th percentile	0.91	0.90, 0.93	1.34	1.28, 1.39
90th to <95th percentile	0.93	0.92, 0.95	1.38	1.31, 1.45
95th to <97.5th percentile	0.97	0.94, 0.99	1.37	1.29, 1.46
97.5th to 100th percentile	1.02	0.99, 1.04	1.52	1.43, 1.61
Cost predictor (vs. first quintile)				
Second quintile	0.98	0.97, 0.99	1.03	0.99, 1.07
Third quintile	0.96	0.95, 0.97	0.99	0.96, 1.02
Fourth quintile	0.90	0.89, 0.91	0.97	0.94, 1.00
80th to <90th percentile	0.84	0.83, 0.85	0.96	0.93, 1.00
90th to <95th percentile	0.77	0.75, 0.78	0.98	0.94, 1.03
95th to <97.5th percentile	0.70	0.68, 0.72	0.95	0.90, 1.01
97.5th to 100th percentile	0.54	0.52, 0.55	1.00	0.94, 1.06
HZ risk score (vs. first quintile)				
Second quintile	1.33	1.31, 1.34	1.18	1.14, 1.22
Third quintile	1.46	1.44, 1.48	1.27	1.22, 1.31
Fourth quintile	1.56	1.55, 1.58	1.35	1.30, 1.40
80th to <90th percentile	1.62	1.60, 1.64	1.49	1.43, 1.56
90th to <95th percentile	1.65	1.62, 1.68	1.59	1.51, 1.67
95th to <97.5th percentile	1.65	1.62, 1.69	1.77	1.67, 1.88
97.5th to 100th percentile	1.62	1.57, 1.66	1.97	1.86, 2.10

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HZ, herpes zoster; IC, immune compromise.

[a] Hazard ratio estimates from the analysis of zoster vaccination and the analysis of herpes zoster were adjusted for the covariates included in this table and for age and calendar date, because risk sets were defined on a calendar timeline and stratified by year of birth.

Table 4. Effectiveness of Zoster Vaccine Against Herpes Zoster, by Time Since Vaccination and Age at Vaccination, Kaiser Permanente Northern California, 2007–2014

Years Since Vaccination	Age Range, Years									
	50–59		60–69		70–79		≥80		All Ages Combined	
	VE[a]	95% CI	VE[a]	95% CI	VE[a]	95% CI	VE[a]	95% CI	VE[a]	95% CI
<1	64.6	55.1, 72.2	70.6	67.9, 73.2	64.5	60.5, 68.1	63.7	57.3, 69.1	67.5	65.4, 69.5
1 to <2	55.7	43.4, 65.3	48.8	44.5, 52.7	45.2	39.5, 50.3	41.8	31.9, 50.3	47.2	44.1, 50.1
2 to <3	58.1	37.9, 71.8	40.5	35.1, 45.5	36.8	29.9, 43.0	35.4	22.3, 46.3	39.3	35.4, 42.9
3 to <4	35.8	−54.7, 73.3	40.0	33.8, 45.6	44.2	36.9, 50.7	34.7	18.8, 47.5	41.0	36.6, 45.2
4 to <5			39.9	32.8, 46.2	32.6	23.6, 40.5	39.8	21.8, 53.7	37.2	32.1, 42.0
5 to <6			34.3	25.3, 42.2	29.1	18.3, 38.4	35.8	12.0, 53.2	32.6	26.2, 38.5
6 to <7			34.7	22.7, 44.7	26.9	12.3, 39.0	−1.9	−43.5, 27.6	29.2	20.5, 37.0
7 to <8			32.1	8.1, 49.9	21.8	−8.1, 43.5			31.8	15.1, 45.2

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.
[a] VE estimates are adjusted for sex, race, influenza vaccination, immune compromise status, outpatient visit frequency, the cost predictor, the herpes zoster risk score, and for age and calendar date, because risk sets were defined on a calendar timeline and stratified by year of birth.

people, including nearly 400,000 vaccinees. Our VE estimates are generally consistent with those reported by the randomized trial (8) and other published studies (9, 14–18). Our overall VE estimate of 49.1% is consistent with the 51.3% VE estimate from the initial report on the pivotal trial (8) and the 48.7% estimate based on longer follow-up from the trial (9), as well as the 55% estimate from the initial report on the Kaiser Permanente Southern California population (16) and the 51% estimate from longer follow-up on the same population (17). Our overall VE estimate is also consistent with the 48% estimate from a study of Medicare beneficiaries (18). A lower VE estimate, 33% for the first 3 years, was recently reported from another study of Medicare beneficiaries (19).

Our large population, long follow-up, and innovative study design yielded relatively precise estimates of VE by year since vaccination for 8 years. VE was 67.5% (95% CI: 65.4, 69.5) in the first year after vaccination, decreased to 47.2% (95% CI: 44.1, 50.1) in the second year after vaccination, and then decreased more gradually. During the eighth year, VE was approximately 30%, an amount that is clinically as well as statistically significant ($P < 0.001$, testing the 2-sided null hypothesis that VE = 0) but much lower than VE during the first year. This pattern of waning VE is generally consistent with results from the randomized trial (8) and its follow-up studies (9, 14), and from cohort studies from Medicare (19) and Kaiser Permanente Southern California (16), although the VE estimates from these studies were lower than ours in the later years after vaccination. A booster dose at some point after immunization may be needed. We expect this ongoing study, which will continue through 2023, will yield more evidence regarding the need for revaccination.

Summarizing VE over multiple years is like summarizing the location of a moving target; when interpreting overall or average VE, it is important to keep in mind the trajectory of VE over time: the substantial decrease after the first year and then the more gradual decrease. A summary measure of VE

Table 5. Effectiveness of Zoster Vaccine Against Herpes Zoster, by Immune Compromise Status at the Time of Vaccination, Kaiser Permanente Northern California, 2007–2014

Immune Compromise Status at Time of Vaccination	Unadjusted for Covariates[a]		Adjusted for Fixed Covariates[b]		Adjusted for Fixed Covariates[b] and Time-Varying Covariates[c]	
	VE	95% CI	VE	95% CI	VE	95% CI
Not immune compromised	45.8	44.1, 47.5	47.2	45.6, 48.8	49.0	47.4, 50.6
Low immune compromise	30.2	21.1, 38.2	31.0	22.0, 38.9	50.8	44.3, 56.5
High immune compromise	−9.4	−31.8, 9.3	−8.2	−30.4, 10.2	49.2	38.7, 57.9

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.
[a] All VE estimates, including those unadjusted for covariates, were adjusted for age and calendar date, because risk sets were defined on a calendar timeline and stratified by year of birth.
[b] The fixed covariates were sex and race.
[c] The time-varying covariates were influenza vaccination, immune compromise status, outpatient visit frequency, the cost predictor, and the herpes zoster risk score.

can be sensitive to how much follow-up occurred early versus late, how year-specific VE estimates were averaged, and whether deaths were censoring events or competing risks (i.e., whether deaths keep us from observing later HZ or deaths preclude later HZ).

Unexpectedly, we found that VE in persons vaccinated when aged 80 years or older was similar to VE in persons vaccinated at 60–79 years old. An unpublished analysis of subjects randomly assigned when aged 80 years or older in the 2005 trial (8) yielded a VE estimate of 18% (95% CI: −29, 48), but this estimate is imprecise owing to the trial's few subjects in this age group. Our 5-year average VE estimate for this age group was 43.9% (95% CI: 38.3, 49.0). Two cohort studies (17, 19) also found that VE in persons vaccinated when aged 80 years or older was similar to or only slightly lower than VE in younger vaccinees. Although the Advisory Committee on Immunization Practices set no upper age limit for the zoster vaccine, some providers may be less likely to recommend it to persons aged 80 years or older. Our results underscore that persons aged 80 years or older, who are at increased risk of HZ, can receive protection from vaccination.

Our adjusted VE estimates (Table 4) were higher than the crude estimates implicit in the incidence rate ratios (Table 2). Adjustment increased the VE estimates more for the oldest age group and for all age groups combined than for the younger age groups. Adjustment increased the VE estimate for the oldest age group from 35% to 47%, and for all age groups combined from 35% to 49%, mostly due to the close adjustment for age accomplished by conditioning the Cox regression on risk sets comprising people born the same year and at risk on the same day.

More than 5% of zoster vaccinees were immunocompromised when they were vaccinated. VE in these vaccinees was similar to VE in persons who were immunocompetent when vaccinated. This is noteworthy because risk of HZ is high in immunocompromised persons, and the finding is consistent with evidence from other studies that the vaccine can be effective in individuals who are immunocompromised (18, 20, 21).

VE estimates for the immunocompromised vaccinees were much higher after adjustment for the time-varying covariates than before such adjustment (Table 5), because comorbidities as well as IC continued to be more prevalent in immunocompromised vaccinees throughout follow-up than in the rest of the study population. In the overall study population, 93.1% of person-time was immunocompetent. Among persons who were immunocompetent when vaccinated, adjustment for the time-varying covariates increased the VE estimate only a little, from 47.2% to 49.0% (Table 5).

Most cohort studies of VE use a time-since-vaccination timeline, as is often recommended in emulation of a randomized controlled trial (22). Our design has several distinctive features that differ from such a trial-emulating design:

- We use a calendar timeline rather than a time-since-vaccination timeline. Risk sets are stratified by year of birth. Thus, on the date of each HZ outcome, we restrict comparisons to persons of the same age as we examine their HZ risk relative to their vaccination status.
- Vaccination status is a multilevel time-dependent covariate. Everyone begins follow-up unvaccinated. If they receive the zoster vaccine, their status changes to "vaccinated within a year," and then their status is updated annually on the anniversary of vaccination to "vaccinated 1 to <2 years ago," . . ., "vaccinated 7 to <8 years ago." Thus, there are 9 levels of vaccination status, including unvaccinated as the reference level.
- Time-varying covariates are assessed during a baseline year before the start of follow-up and then updated periodically. Updating the covariates sustains their relevance to risk of HZ; this has advantages for precision and bias if our assumption is correct that the vaccine does not affect the covariates.

These features of the study design have practical advantages for data management and data analysis in this long study, which will be updated periodically. Risk sets anchored to the calendar become complete as soon as outcome events are ascertained. Furthermore, Cox models assume that the hazard ratio is constant over the timeline. Because VE wanes over time since vaccination but is not expected to vary by calendar period, the calendar was a natural timeline for this study.

These features of the study design can increase precision and reduce bias. Precision is increased because every case of HZ can be informative. In the usual trial-emulating approach, unvaccinated persons are not informative until they are matched to vaccinees or otherwise assigned a start time alongside vaccinees, as if they had been randomized to their vaccination status. When unvaccinated persons are vaccinated, their unvaccinated follow-up ends. They can start follow-up as vaccinees only if other unvaccinated persons are available for comparison. If vaccine coverage becomes very high in future years, then some vaccinees will become less informative, or uninformative, as only a dwindling number of unvaccinated persons remains for comparison.

In contrast, our design permits vaccinees to be informative, even if no one remains unvaccinated, as long as persons of the same age continue to vary in their years since vaccination. Given plans for periodic reports from this study through 2023, we do not know who will remain unvaccinated, so it would be problematic to assign start dates to unvaccinated persons on a time-since-vaccination timeline.

Furthermore, a research design with a time-since-vaccination timeline might introduce bias by anchoring the baseline period and the start of follow-up to vaccination dates, despite possible differences between vaccinees and the unvaccinated in how these dates fit into the ebb and flow of health care. Bias might occur if vaccination is often occasioned by an episode of care during which otherwise overlooked risk factors are noted in the medical record.

A calendar timeline may have additional advantages if shingles incidence in the unvaccinated changes with diagnostic and coding practices, the incidence of chicken pox, or other trends in health care. On a calendar timeline, recent vaccinees are directly compared with remote vaccinees (and with the unvaccinated) in risk sets comprising people born the same year and at risk on the same day. In contrast, a time-since-vaccination timeline puts recent and remote vaccinees in different risk sets; inference about the waning of VE is less direct and can be more vulnerable to confounding trends.

Our data and methods have limitations. First, our ascertainment of HZ events is somewhat insensitive because

we did not count HZ as diagnosed unless it was medically attended and treated with antiviral medication. However, results changed little in sensitivity analyses that included additional HZ diagnoses that had not been counted because of the absence of antiviral treatment. Second, there may be selection bias; perhaps patients are less prone to zoster vaccination and more vulnerable to HZ when they are near death or otherwise frail in unmeasured ways, as was found earlier for influenza vaccination (23). Third, there may be residual confounding due to other unmeasured health-related behaviors and the severity of comorbidities and IC. Estimation of VE in highly immunocompromised vaccinees is especially challenging because severe IC is a contraindication for vaccination. Fourth, covariates may be misclassified. IC status was especially challenging to classify. Fifth, some findings may have limited generalizability. The high VE found for patients who were immunocompromised when vaccinated may not be generalizable to other settings where immunocompromised vaccinees may differ in severity of IC when vaccinated.

Conclusion

In summary, the live attenuated zoster vaccine was 68% effective at preventing shingles in the first year after vaccination. VE decreased to 47% in the second year, and then waned more gradually over the next 6 years. VE in persons vaccinated when aged 80 years or older was similar to VE in younger vaccinees, and VE in persons vaccinated when immunocompromised was similar to VE in persons vaccinated when immunocompetent.

ACKNOWLEDGMENTS

Author affiliations: Kaiser Permanente Vaccine Study Center, Oakland, California (Roger Baxter, Joan Bartlett, Bruce Fireman, John Hansen, Edwin Lewis, Laurie Aukes, Nicola P. Klein); and Pharmacoepidemiology Department, Merck & Co., Inc., Kenilworth, New Jersey (Morgan Marks, Yong Chen, Patricia Saddier).

This work was supported by Merck & Co., Inc., the vaccine manufacturer. Our results are based on a study of the long-term effectiveness of Zostavax conducted as part of a commitment by Merck to regulatory agencies (ClinicalTrials.gov number NCT01600079).

We thank our study review committee: Dr. Alan Brookhart, Dr. Stefan Gravenstein, and Dr. Alec Walker.

Conflict of interest: P.S. and M.M. are employees of Merck & Co, Inc., the manufacturer of the vaccine and sponsor of the study. Y.C. was employed by Merck while much of the study was conducted. The study was conducted and analyzed at Kaiser Permanente, where all the other authors have been employed. N.P.K. has received research grant support for unrelated studies from GlaxoSmithKline, Sanofi Pasteur, Pfizer, Merck, MedImmune, and Protein Sciences.

REFERENCES

1. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc*. 2007; 82(11):1341–1349.
2. Lin YH, Huang LM, Chang IS, et al. Disease burden and epidemiology of herpes zoster in pre-vaccine Taiwan. *Vaccine*. 2010;28(5):1217–1220.
3. Cohen JI. Clinical practice: herpes zoster. *N Engl J Med*. 2013; 369(3):255–263.
4. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open*. 2014;4(6):e004833.
5. Harpaz R, Ortega-Sanchez IR, Seward JF, et al. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008; 57(RR-5):1–30; quiz CE2-4.
6. Centers for Disease Control and Prevention (CDC). Update on herpes zoster vaccine: licensure for persons aged 50 through 59 years. *MMWR Morb Mortal Wkly Rep*. 2011;60(44):1528.
7. Hales CM, Harpaz R, Ortega-Sanchez I, et al. Update on recommendations for use of herpes zoster vaccine. *MMWR Morb Mortal Wkly Rep*. 2014;63(33):729–731.
8. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271–2284.
9. Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clin Infect Dis*. 2012; 55(10):1320–1328.
10. Gordon NP. *Similarity of the Adult Kaiser Permanente Membership in Northern California to the Insured and General Population in Northern California: Statistics From the 2011 California Health Interview Survey*. 2015. https://divisionofresearch.kaiserpermanente.org/projects/memberhealthsurvey/SiteCollectionDocuments/chis_non_kp_2011.pdf. Published June 19, 2015. Accessed October 6, 2017.
11. Selby JV, Uratsu CS, Fireman B, et al. Kaiser permanente medical care program. In: Strom B, ed. *Pharmacoepidemiology*. 4th ed. West Sussex, England: John Wiley & Sons Ltd; 2005:241–260.
12. Healthcare Cost and Utilization Project (HCUP). *Clinical Classifications Software (CCS) for ICD-9-CM*. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed October 6, 2017.
13. Omachi TA, Gregorich SE, Eisner MD, et al. Risk adjustment for health care financing in chronic disease: what are we missing by failing to account for disease severity? *Med Care*. 2013;51(8):740–747.
14. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis*. 2015; 60(6):900–909.
15. Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50–59 years. *Clin Infect Dis*. 2012;54(7):922–928.
16. Tseng HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA*. 2011;305(2):160–166.
17. Tseng HF, Harpaz R, Luo Y, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. *J Infect Dis*. 2016;213(12):1872–1875.
18. Langan SM, Smeeth L, Margolis DJ, et al. Herpes zoster vaccine effectiveness against incident herpes zoster and

post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med*. 2013;10(4):e1001420.
19. Izurieta HS, Wernecke M, Kelman J, 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):785–793.
20. Tseng HF, Tartof S, Harpaz R, et al. Vaccination against zoster remains effective in older adults who later undergo chemotherapy. *Clin Infect Dis*. 2014;59(7):913–919.
21. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308(1):43–49.
22. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
23. Fireman B, Lee J, Lewis N, et al. Influenza vaccination and mortality: differentiating vaccine effects from bias. *Am J Epidemiol*. 2009;170(5):650–656.