Effectiveness of the live zoster vaccine during the 10 years following vaccination: real world cohort study using electronic health records

Nicola P Klein, [1] Joan Bartlett, [1] Bruce Fireman, [1] Morgan A Marks, [2] John Hansen, [1] Edwin Lewis, [1] Laurie Aukes, [1] Patricia Saddier[2]

[1] Kaiser Permanente Vaccine Study Center, Oakland, CA, USA

[2] Epidemiology Department, Merck & Co, Rahway, NJ, USA

Correspondence to: N P Klein
nicola.klein@kp.org
https://orcid.org/0000-0003-1777-4814

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ABSTRACT

OBJECTIVES

To assess the effectiveness of live zoster vaccine during more than 10 years after vaccination; and to describe methods for ascertaining vaccine effectiveness in the context of waning.

DESIGN

Real world cohort study using electronic health records.

SETTING

Kaiser Permanente Northern California, an integrated healthcare delivery system in the US, 1 January 2007 to 31 December 2018.

POPULATION

More than 1.5 million people aged 50 years and older followed for almost 9.4 million person years.

MAIN OUTCOME MEASURE

Vaccine effectiveness in preventing herpes zoster, postherpetic neuralgia, herpes zoster ophthalmicus, and admission to hospital for herpes zoster was assessed. Change in vaccine effectiveness by time since vaccination was examined using Cox regression with a calendar timeline. Time varying indicators were specified for each interval of time since vaccination (30 days to less than one year, one to less than two years, etc) and adjusted for covariates.

RESULTS

Of 1 505 647 million people, 507 444 (34%) were vaccinated with live zoster vaccine. Among 75 135 incident herpes zoster cases, 4982 (7%) developed postherpetic neuralgia, 4439 (6%) had herpes zoster ophthalmicus, and 556 (0.7%) were admitted to hospital for herpes zoster. For each outcome, vaccine effectiveness was highest in the first year after vaccination and decreased substantially over time. Against herpes zoster, vaccine effectiveness waned from 67% (95% confidence interval 65% to 69%) in the first year to 15% (5% to 24%) after 10 years. Against postherpetic neuralgia, vaccine effectiveness waned from 83% (78% to 87%) to 41% (17% to 59%) after 10 years. Against herpes zoster ophthalmicus, vaccine effectiveness waned from 71% (63% to 76%) to 29% (18% to 39%) during five to less than eight years. Against admission to hospital for herpes zoster, vaccine effectiveness waned from 90% (67% to 97%) to 53% (25% to 70%) during five to less than eight years. Across all follow-up time, overall vaccine effectiveness was 46% (45% to 47%) against herpes zoster, 62% (59% to 65%) against postherpetic neuralgia, 45% (40% to 49%) against herpes zoster ophthalmicus, and 66% (55% to 74%) against admission to hospital for herpes zoster.

CONCLUSIONS

Live zoster vaccine was effective initially. Vaccine effectiveness waned substantially yet some protection remained 10 years after vaccination. After 10 years, protection was low against herpes zoster but higher against postherpetic neuralgia.

TRIAL REGISTRATION

ClinicalTrials.gov number NCT01600079; EU PAS register number EUPAS17502

Introduction

Herpes zoster (HZ), also known as shingles, is a painful rash caused by reactivation of the varicella virus. Without vaccination, lifetime risk of HZ is 30%.[1] Complications and manifestations of HZ include postherpetic neuralgia, when pain persists for months in the area of the rash; herpes zoster ophthalmicus (HZO), when the rash occurs in or around the eye; and admission to hospital for HZ. In the United States in people aged 60 years and older, HZ incidence is approximately 10 per year per 1000 people.[1] Among people diagnosed with HZ, an estimated 5-30% develop postherpetic neuralgia,[2-5] 9-25% have HZO,[3 4 6-8] and 1-4% are admitted to hospital for HZ.[1 3 9]

Live zoster vaccine was the first vaccine against shingles. Over 50 million people have received the vaccine worldwide. The United States licenced it in 2006 for people 60 years and older. The license was expanded in 2011 to include people aged 50-59 years. The US Advisory Committee on Immunization Practices recommended routine use of live zoster vaccine for people aged 60 years and older in October 2006 but never extended this recommendation to people aged 50-59 years, in part due to concerns about the duration of protection.[10] In October 2017, a new vaccine against shingles—recombinant zoster vaccine—was licensed and recommended for routine use for people aged 50 years and older. The US Advisory Committee on Immunization Practices preferentially recommended the recombinant zoster vaccine over the live zoster vaccine because of its higher and longer lasting effectiveness.[11] Live zoster vaccine is no longer used in the US but use has continued elsewhere, including the UK and Australia.

We studied the effectiveness of live zoster vaccine at Kaiser Permanente Northern California (KPNC) from 2007 to 2018. We previously reported on vaccine effectiveness of the live zoster vaccine against HZ up to the end of 2014[12] and postherpetic neuralgia up to the end of 2016.[13] Here, we report final vaccine effectiveness estimates from the completed study for HZ and postherpetic neuralgia up to the end of 2018. Also, we report for the first time our findings on vaccine effectiveness against HZO and admission to hospital for HZ. We describe our innovative methods, which could be useful in studies assessing change over time in the effectiveness of other vaccines.

Methods

Study setting

KPNC is an integrated healthcare delivery system with 4.3 million members, of whom 1.6 million are 50 years or older. KPNC's diverse population is similar demographically to the overall Northern California population. KPNC's electronic medical records contain data for diagnoses, healthcare visits, hospital admissions, immunizations, prescriptions, and laboratory tests. KPNC provided live zoster vaccines free of charge. Starting in July 2013, an electronic medical records prompt targeted members aged 60 years or older for vaccination with the live zoster vaccine. The institutional review board at KPNC approved this study.

Study design and study population

Our study population is described elsewhere.[12 13] In brief, we conducted a prospective cohort study with follow-up from 1 January 2007 to 31 December 2018 of KPNC members who were eligible by age for live zoster vaccine. Vaccine eligibility was based on US licensure dates for people aged 60 years or older (25 May 2006, with study entry starting 1 January 2007) and for people aged 50-59 years (24 March 2011). We restricted study entry to people with continuous membership since becoming eligible by age for live zoster vaccine. We excluded individuals who received live zoster vaccine before study entry, or who had an HZ diagnosis in the year before study entry. We followed study participants until the first occurrence of: HZ diagnosis, disenrollment from the health plan, a second dose of live zoster vaccine, receipt of recombinant zoster vaccine, death, or end of study (31 December 2018).

Vaccination status was a time varying covariate. All people started follow-up unvaccinated. If vaccinated, their status was updated annually on the anniversary of vaccination (first year, second year, etc).

Outcomes

We identified incident cases based on diagnoses, prescriptions, and laboratory tests, validating samples of cases by chart review. We defined an incident HZ case as the first encounter during follow-up with an HZ diagnosis (International Classification of Diseases (ICD)-9 code 053.xx or ICD-10 code B02.xx) with an antiviral prescription or positive varicella zoster laboratory test. Approximately 84% of all first HZ diagnoses met these criteria and chart review (n=200) showed 98% as incident HZ cases. We therefore considered all HZ cases identified with this definition as incident without chart review. Among HZ cases, we then identified the subsets with postherpetic neuralgia, HZO, or admission to hospital for HZ.

We defined postherpetic neuralgia cases based on postherpetic neuralgia diagnoses from an encounter or prescription between 90 days and 1 year after the initial HZ diagnosis.[13] After chart review of 200 such potential cases, we included those with postherpetic neuralgia diagnoses in both an encounter and a prescription without additional review, while the remainder underwent chart review to ascertain case status.

We defined HZO cases based on HZO diagnoses (ICD-9 053.2x and ICD-10 B02.3x) at an ophthalmology visit within 30 days of the initial HZ diagnosis (94% of all HZO diagnoses were recorded in ophthalmology visits). Chart review of 40 of these potential cases confirmed that 100% were HZO, therefore, we included all without further review.

Admission to hospital with a principal diagnosis of HZ had to be within 30 days after the initial HZ diagnosis. Among all admissions to hospitals for HZ within one year of the initial diagnosis, 94% occurred within the first 30 days.

Statistical analysis

We calculated the incidence of HZ, postherpetic neuralgia, HZO, and admission to hospital for HZ by vaccination status overall and by age group (50-59, 60-69, 70-79, and ≥80 years). We also calculated the percentage of HZ cases who had postherpetic neuralgia, HZO, or admission to hospital for HZ.

For each outcome, we examined the vaccine effectiveness of live zoster vaccine using Cox regression. Cox models were specified with a calendar timeline stratified by birth year to adjust for confounding associated with age as well as calendar time. For each day on which a case occurred, a risk set was formed, including the case along with all people in follow-up that day who were born the same year as the case. All models were also adjusted for covariates including sex, race/ethnicity, and time varying factors, including influenza vaccination, visit frequency, comorbidities, and immunocompromise status.[12]

We used a Cox model to estimate vaccine effectiveness in relation to the number of years since receipt of live zoster vaccine. For the HZ outcome, we fitted a model with 12 time varying binary (yes/no) vaccination indicators to denote—at each time point during follow-up—either the time since vaccination (eg, 1-29 days, 30 days to less than one year, one to less than two years, two to less than three years, etc) or that the individual was unvaccinated (reference group). We estimated vaccine effectiveness against HZ for each year following vaccination. For postherpetic neuralgia, HZO, and admission to hospital for HZ, the models were similar to that for HZ except, due to fewer cases, we included fewer indicators of time since vaccination (eg, 1-29 days, 30 days to less than one year, one to less than three years, three to less than five years, etc). For each outcome, we estimated a hazard ratio for each time since vaccination interval (beginning on day 30 to allow time for an immune response) in comparison to the unvaccinated group. We then estimated vaccine effectiveness as 1 minus the hazard ratio estimate, scaled as a percentage.

For each outcome, we also calculated two summary measures of vaccine effectiveness across more than 10 years of follow-up time. One measure that we refer to as "overall vaccine effectiveness" summarises vaccine effectiveness in the usual way, as if the hazard ratio was not changing over time. This measure is the same summary measure commonly referred to simply as vaccine effectiveness in most clinical trials and observational studies. This summary measure can be problematic if vaccine effectiveness wanes because it gives more weight to the earlier years postvaccination when vaccine effectiveness is higher (since people who were vaccinated later in the study period can only contribute earlier years postvaccination). Our other measure, "average vaccine effectiveness", averages all the time specific hazard ratios across the 10 years after vaccination. This measure indicates the average percentage reduction in incidence among individuals who live 10 years after vaccination. To estimate overall vaccine effectiveness, we included a single vaccination indicator (yes/no) in the Cox model. To estimate average vaccine effectiveness, we included multiple indicators of time since vaccination in the Cox model and weighted the indicators in accordance with their relative durations. We calculated average vaccine effectiveness for the 10 years after vaccination, as well as for the first three, five, and eight years. We used the term overall vaccine effectiveness only when needed to contrast with average vaccine effectiveness. Otherwise, we simply use the term "vaccine effectiveness", as in other studies.

For each outcome, we also used Cox regression to estimate vaccine effectiveness in subgroups defined by age group at vaccination (50-59, 60-69, 70-79, and ≥80 years), sex, race or ethnic group (white, black, Asian or Pacific Islander, Hispanic, American Indian or Alaskan Native, or other or unknown), and immunocompromise status at vaccination (none, low, or high immunocompromise).

Analyses were done with SAS 9.3. We used the Lexis macro to partition person time (http://bendixcarstensen.com/Lexis/Lexis.sas).

Patient and public involvement

No patients were involved in formulating the research question or study design. Patient involvement was uncommon in this field when we started this study.

Results

From 1 January 2007 to 31 December 2018, 1 505 647 individuals 50 years or older contributed 9 379 685 person years of follow-up to the study, including 507 444 (34%) who received a live zoster vaccine. Vaccination uptake in people aged 60 years or older increased rapidly after implementation of the electronic medical record prompt in July 2013. By study end, vaccine coverage was more than 60% in people aged 60-69 years and ≥80 years, and more than 80% in people aged 70-79 years, but remained low (<5%) in people aged 50-59 years (fig 1). Approximately 5.7% of vaccinated people were immunocompromised when vaccinated, including 1.2% who were highly immunocompromised. We identified 75 135 incident cases of HZ, of which 4982 (7%) developed postherpetic neuralgia, 4439 (6%) had HZO, and 556 (0.7%) led to admission to hospital for HZ.

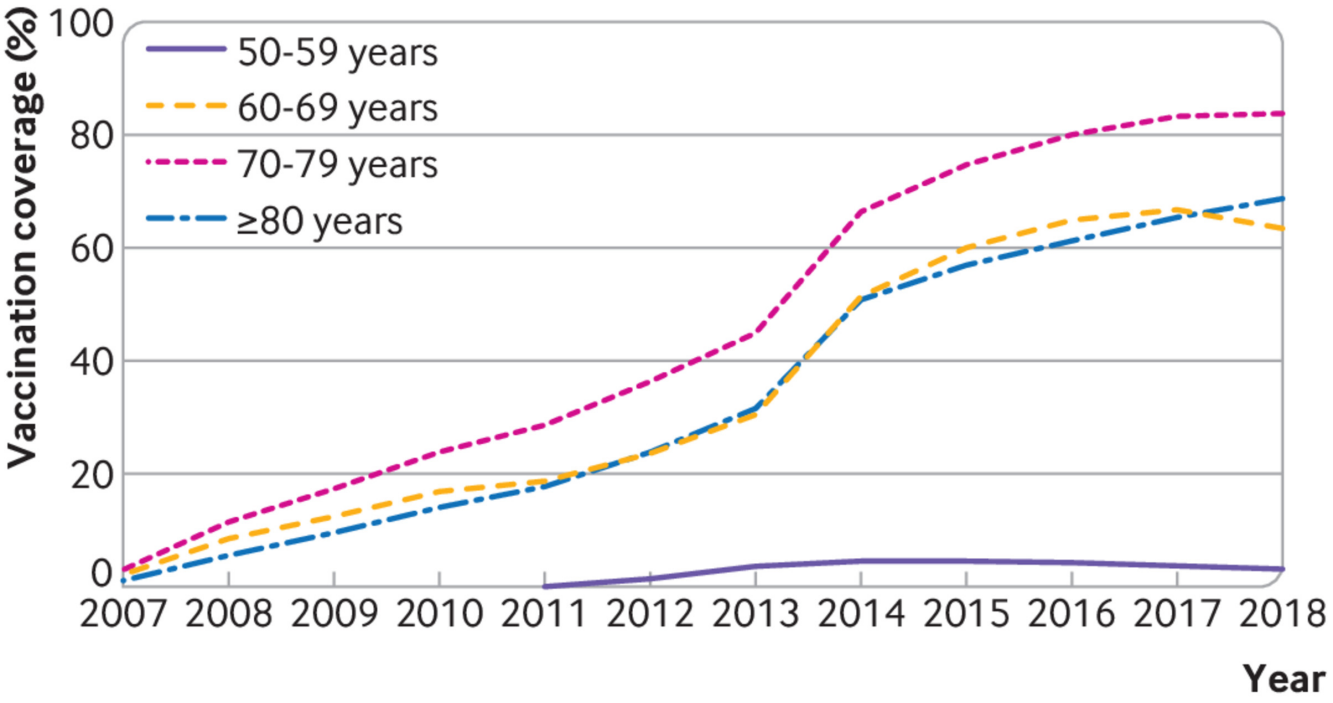

Fig 1 | Live zoster vaccine coverage in the study population by age group, 2007-18. Coverage is the proportion of the study population who had received the vaccine by midpoint of each year

Among people who were unvaccinated, the crude incidence per 100 000 person years was 863.2 for HZ, 57.2 for postherpetic neuralgia, 48.9 for HZO, and 6.9 for admission to hospital for HZ (table 1). Incidence rates increased with age, especially for postherpetic neuralgia and admission to hospital for HZ. Crude incidence was lower among vaccinated people than among unvaccinated people for every outcome and age group, except for admission to hospital for HZ in people aged 50-59 years, where incidence was low in both vaccinated and unvaccinated people.

Table 1 | Incidence of herpes zoster (HZ), postherpetic neuralgia, HZ ophthalmicus, and admission to hospital for HZ per 100 000 person years, by age and live zoster vaccine status (2007-18)

Age group*	Vaccination status with live zoster vaccine	Person years	Herpes zoster		Postherpetic neuralgia†		HZ ophthalmicus‡		Hospital admission for HZ§	
			N	Rate (95% CI)	N (% of HZ)	Rate (95% CI)	N (% of HZ)	Rate (95% CI)	N (% of HZ)	Rate (95% CI)
50-59 years	Unvaccinated	2 862 837	19 579	683.9 (674.4 to 693.5)	579 (3.0)	20.2 (18.6 to 21.9)	922 (4.7)	32.2 (30.2 to 34.4)	58 (0.3)	2.0 (1.5 to 2.6)
	Vaccinated (≥30 days)	92 298¶	338¶	366.2 (328.2 to 407.4)	11 (3.3)	11.9 (5.9 to 21.3)	20 (5.9)	21.7 (13.2 to 33.5)	2 (0.6)	2.2 (0.3 to 7.8)
60-69 years	Unvaccinated	2 177 244	18 798	863.4 (851.1 to 875.8)	983 (5.2)	45.1 (42.4 to 48.1)	1 069 (5.7)	49.1 (46.2 to 52.1)	102 (0.5)	4.7 (3.8 to 5.7)
	Vaccinated (≥30 days)	1 154 638¶	5740¶	497.1 (484.3 to 510.2)	228 (4.0)	19.7 (17.3 to 22.5)	353 (6.1)	30.6 (27.5 to 33.9)	20 (0.3)	1.7 (1.1 to 2.7)
70-79 years	Unvaccinated	1 023 904	11 454	1118.7 (1 098.3 to 1 139.3)	1 183 (10.3)	115.5 (109.0 to 122.3)	710 (6.2)	69.3 (64.3 to 74.6)	115 (1.0)	11.2 (9.3 to 13.5)
	Vaccinated (≥30 days)	865 416¶	6310¶	729.1 (711.2 to 747.3)	459 (7.3)	53.0 (48.3 to 58.1)	449 (7.1)	51.9 (47.2 to 56.9)	29 (0.5)	3.4 (2.2 to 4.8)
≥80 years	Unvaccinated	765 792	9 126	1191.7 (1 167.4 to 1 216.4)	1 159 (12.7)	151.3 (142.8 to 160.3)	639 (7.0)	83.4 (77.1 to 90.2)	199 (2.2)	26.0 (22.5 to 29.9)
	Vaccinated (≥30 days)	397 377¶	3439¶	865.4 (836.7 to 894.8)	352 (10.2)	88.6 (79.6 to 98.3)	256 (7.4)	64.4 (56.8 to 72.8)	30 (0.9)	7.5 (5.1 to 10.8)
All ages ≥50	Unvaccinated	6 829 777	58 957	863.2 (856.3 to 870.2)	3 904 (6.6)	57.2 (55.4 to 59.0)	3340 (5.7)	48.9 (47.3 to 50.6)	474 (0.8)	6.9 (6.3 to 7.6)
	Vaccinated (≥30 days)	2 509 729¶	15 827¶	630.6 (620.8 to 640.5)	1 050 (6.6)	41.8 (39.3 to 44.4)	1078 (6.8)	43.0 (40.4 to 45.6)	81 (0.5)	3.2 (2.6 to 4.0)

CI=confidence interval.

* Age at HZ onset.

† Postherpetic neuralgia diagnosis between 90 days and one year after incident HZ.

‡ HZ ophthalmicus diagnosis within 30 days of incident HZ.

§ Hospital admission for HZ within 30 days of incident diagnosis.

¶ This table does not show events and person years that occurred during the first 29 days after vaccination. Therefore, the 75 135 incident HZ cases referred to in the text is 351 higher than the total of the numbers shown here. Similarly, this table does not include 28 postherpetic neuralgia, 21 HZO, and 1 admitted to hospital for HZ that occurred during the first 29 days.

For each outcome, vaccine effectiveness was highest in the first year after vaccination and then waned substantially over time (table 2). Against HZ, vaccine effectiveness was 67.2% in the first year, decreased to 49.6% in the second year, and then decreased more gradually to 14.9% during years 10 to less than 12. Against postherpetic neuralgia, vaccine effectiveness was 83.0% in the first year and decreased to 41.4% during years 10 to less than 12. Against HZO, vaccine effectiveness was 70.6% in the first year and decreased to 29.4% during years five to less than eight. Against admission to hospital for HZ, vaccine effectiveness was 89.5% in the first year and decreased to 52.5% during years five to less than eight.

Table 2 | Vaccine effectiveness, percentage (95% confidence interval), of live zoster vaccine against herpes zoster, postherpetic neuralgia, herpes zoster ophthalmicus, and admission to hospital for herpes zoster by time since vaccination, overall vaccine effectiveness, and average vaccine effectiveness (2007-18)

Outcome	Herpes zoster	Postherpetic neuralgia	Herpes zoster ophthalmicus	Admission to hospital for herpes zoster
Time since vaccination:				
30 days to <1 year	67.2 (65.4 to 68.8)	83.0 (78.0 to 86.8)	70.6 (63.4 to 76.4)	89.5 (67.0 to 96.6)
1 to <2 years	49.6 (47.4 to 51.7)	64.6 (59.8 to 68.9)	48.1 (41.1 to 54.2)	69.6 (51.6 to 80.9)
2 to <3 years	42.0 (39.5 to 44.4)			
3 to <4 years	39.9 (37.1 to 42.5)	58.0 (52.2 to 63.1)	32.4 (23.0 to 40.7)	69.8 (50.9 to 81.5)
4 to <5 years	37.0 (33.9 to 39.9)			
5 to <6 years	33.5 (29.7 to 37.1)	51.4 (44.2 to 57.6)	29.4 (17.9 to 39.2)	52.5 (24.5 to 70.1)
6 to <7 years	27.3 (22.6 to 31.7)			
7 to <8 years	26.9 (21.4 to 32.0)			
8 to <9 years*	25.1 (18.8 to 30.9)	46.4 (33.9 to 56.5)	12.4 (−10.6 to 30.6)	42.8 (−12.3 to 70.9)
9 to <10 years*	19.1 (11.2 to 26.3)			
10 to <12 years*	14.9 (5.1 to 23.7)	41.4 (16.8 to 58.7)	—¶	—¶
Overall vaccine effectiveness (2007-18)†	45.7 (44.5 to 46.9)	62.3 (59.1 to 65.2)	44.5 (39.5 to 49.1)	65.9 (55.3 to 74.0)
Average vaccine effectiveness‡:				
First three years	53.8 (52.5 to 55.1)	71.9 (68.2 to 75.1)	56.6 (51.3 to 61.3)	78.2 (64.5 to 86.6)
First five years	48.1 (46.8 to 49.3)	66.9 (63.6 to 69.9)	48.0 (42.8 to 52.8)	75.1 (64.2 to 82.7)
First eight years	41.6 (40.2 to 43.0)	61.7 (58.2 to 64.9)	41.6 (35.9 to 46.8)	68.2 (56.8 to 76.6)
First 10 years*	38.1 (36.5 to 39.7)	59.0 (55.2 to 62.5)	36.6 (30.1 to 42.6)	64.2 (51.7 to 73.5)

Vaccine effectiveness was calculated as (1−hazard ratio)×100. The unvaccinated are the reference group.

* No follow-up after the eighth year for people vaccinated at ages 50-59 years because they started receiving vaccine in 2011.

† Calculated using a Cox model with a single vaccination indicator (yes/no).

‡ Calculated as the weighted average of the time since vaccination estimates of vaccine effectiveness, where each year (or group of years) was weighted in proportion to its duration.

¶ Insufficient precision.

Our two summary measures of VE are also shown in table 2. Overall vaccine effectiveness across all follow-up time was 45.7% against HZ, 62.3% against postherpetic neuralgia, 44.5% against HZO, and 65.9% against admission to hospital for HZ (table 2). Average vaccine effectiveness was lower, especially for HZ and HZO, the outcomes for which there was more waning. Over the first 10 years following vaccination, average vaccine effectiveness was 38.1% for HZ, 59.0% for postherpetic neuralgia, 36.6% for HZO, and 64.2% for admission to hospital for HZ (table 2).

Vaccine effectiveness was generally similar across subgroups defined by age, sex, race or ethnicity, or immunocompromise status at vaccination (table 3).

Table 3 | Vaccine effectiveness, percentage (95% confidence interval), of live zoster vaccine against herpes zoster, postherpetic neuralgia, herpes zoster ophthalmicus, and admission to hospital for herpes zoster (2007-18)

Outcome	Herpes zoster	Postherpetic neuralgia	Herpes zoster ophthalmicus	Admission to hospital for herpes zoster
Overall vaccine effectiveness (2007-18)	45.7 (44.5 to 46.9)	62.3 (59.1 to 65.2)	44.5 (39.5 to 49.1)	65.9 (55.3 to 74.0)
Age at vaccination:				
50-59 years	47.6 (43.6 to 51.3)	62.8 (43.3 to 75.5)	50.3 (31.2 to 64.1)	27.3 (−136.1 to 77.6)
60-69 years	47.4 (45.8 to 48.9)	64.5 (59.9 to 68.6)	45.5 (38.9 to 51.4)	61.1 (40.0 to 74.8)
70-79 years	44.0 (42.0 to 46.0)	60.1 (55.2 to 64.4)	43.3 (35.1 to 50.5)	65.2 (47.8 to 76.7)
≥80 years	41.4 (38.0 to 44.7)	62.2 (54.7 to 68.4)	41.1 (27.4 to 52.2)	76.0 (57.0 to 86.6)
Sex:				
Female	44.2 (42.7 to 45.6)	60.9 (57.0 to 64.5)	39.7 (33.3 to 45.5)	70.3 (57.6 to 79.2)
Male	48.3 (46.6 to 49.9)	64.6 (59.9 to 68.7)	51.4 (45.0 to 57.0)	60.0 (42.5 to 72.1)
Race/ethnicity:				
White	44.0 (42.6 to 45.3)	60.7 (56.8 to 64.2)	43.4 (37.6 to 48.6)	67.9 (55.7 to 76.7)
Black	53.0 (48.5 to 57.2)	71.6 (59.0 to 80.3)	48.7 (25.7 to 64.6)	74.8 (17.6 to 92.3)
Asian or Pacific Islander	47.2 (44.7 to 49.5)	60.1 (51.8 to 66.9)	44.8 (34.8 to 53.3)	46.7 (42.6 to 87.1)
Hispanic (regardless of race)	51.1 (48.3 to 53.7)	69.5 (62.5 to 75.1)	53.4 (39.6 to 64.1)	72.8 (42.6 to 87.1)
American Indian or Alaskan Native	45.8 (33.6 to 55.8)	63.7 (25.3 to 82.4)	1.0 (−119.2 to 55.3)	25.0 (−274.2 to 85.0)
Other or unknown	41.8 (16.7 to 59.3)	39.9 (−161.8 to 86.2)	Insufficient data	Insufficient data
Immunocompromise status at vaccination*:				
No immunocompromise	45.6 (44.3 to 46.8)	61.9 (58.6 to 65.0)	44.6 (39.5 to 49.3)	65.0 (53.6 to 73.6)
Low immunocompromise	47.4 (43.4 to 51.1)	67.7 (57.3 to 75.6)	46.5 (28.9 to 59.8)	68.0 (27.3 to 85.9)
High immunocompromise	47.4 (40.9 to 53.2)	61.9 (45.1 to 73.6)	35.8 (0.4 to 58.6)	76.4 (25.5 to 92.5)

Vaccine effectiveness overall and by age, sex, race/ethnicity, and immunocompromise status at time of vaccination. Vaccine effectiveness was calculated as (1−hazard ratio)×100. The unvaccinated are the reference group.

* No. (%) by immunocompromise status among the 507 444 vaccinees: no immunocompromise=478 847 (94.4%); low immunocompromise=22 686 (4.5%); high immunocompromise=5911 (1.2%).

Additional findings on uptake of live zoster vaccine, HZ incidence, and vaccine effectiveness are in supplemental tables.

Discussion

Principal findings

This study estimated the effectiveness of live zoster vaccine in people aged 50 years and older during 10 years following vaccination. The effectiveness of live zoster vaccine was highest during the first year after vaccination and then waned substantially. First year vaccine effectiveness was 67% against HZ, 83% against postherpetic neuralgia, 71% against HZO, and 90% against admission to hospital for HZ. Against HZ, vaccine effectiveness waned to 50% in the second year, then decreased to 27% in the eighth year, and then to 15% after 10 years. The trajectory of vaccine effectiveness for HZO was similar. Against postherpetic neuralgia and admission to hospital, vaccine effectiveness started higher and also waned, but continued to confer substantial protection for as long as the available data permitted estimation of vaccine effectiveness. Vaccine effectiveness was 41% after 10 years for postherpetic neuralgia. Vaccine effectiveness was 53% during five to less than eight years for admission to hospital for HZ.

Comparison with other studies

These findings are generally consistent with those from randomised trials and observational studies.[11 14 -16] A randomised trial reported that live zoster vaccine efficacy against HZ in people 60 years and older was 62% in year one, decreased to 49% in year two, and then to 31% in year eight.[17 18] Similarly, a large observational study reported that live zoster vaccine effectiveness against HZ in people 60 years and older was 69% in year one, decreased to 50% in year two, and then to 33% in year seven.[19] While our results were similar up to year eight, we had more follow-up beyond eight years and found that live zoster vaccine continued to confer a small amount of protection (15%) against HZ after 10 years. For vaccine effectiveness against postherpetic neuralgia, the randomised trial had precise vaccine effectiveness estimates for only the first two years after vaccination, 83% for year one and 70% for year two, similar to ours.[18] Our findings are also consistent with an observational study that reported substantial (60%) vaccine effectiveness against postherpetic neuralgia at seven years or more.[8]

The waning effectiveness of the live zoster vaccine was an important reason why the US Advisory Committee on Immunization Practices preferentially recommended recombinant zoster vaccine over live zoster vaccine.[11] Given that waning was substantial, a more appropriate way to characterise vaccine effectiveness over 10 years was to describe the trajectory of vaccine effectiveness over time, rather than feature a summary measure. However, we did report summary measures of overall vaccine effectiveness to facilitate comparisons across subgroups, and comparisons with other studies. Such comparisons can be problematic because estimates of overall vaccine effectiveness are in effect weighted towards what vaccine effectiveness was earlier after vaccination rather than later, due to more follow-up being available in the early years postvaccination. To address this problem, we reported a measure we called average vaccine effectiveness, which indicates what overall vaccine effectiveness would be if all vaccinated people were followed until

an outcome event or 10 years postvaccination. When vaccine effectiveness wanes, estimates of overall vaccine effectiveness can be misleading because they are higher than the average vaccine effectiveness to the extent that follow-up skews towards earlier years postvaccination.

We found that incidence rose with age whereas vaccine effectiveness decreased a little with age. Taken together, these findings suggest that the benefit of vaccination increases with age when evaluated on an absolute scale, such as the risk difference per person year. For example, although the estimated vaccine effectiveness against HZ was 6.2 percentage points lower for people aged 80 years or older than for people aged 50-59 years (table 3, 41.4% *v* 47.6%), incidence in the unvaccinated group was 74% higher for people aged 80 years or older (table 1, 1191.7 *v* 366.2 per 100 000 person years). Taken together, the risk difference per person year was substantially higher for people aged 80 years or older. In some countries, including UK and Australia, live zoster vaccine has not been recommended for people aged 80 years or older[20 21]; our evidence suggests that vaccination would benefit people in this age group.

Strengths of this study

A strength of this study is that we used methods that are well suited to examining the trajectory of waning vaccine effectiveness. We fitted Cox regression models using a calendar timeline rather than a time since vaccination timeline. On a calendar timeline, people who have been vaccinated more recently are directly compared with people who were vaccinated less recently (and with people who were unvaccinated) in risk sets, including people who were born the same year and at risk of HZ on the same day. This innovative method emulates a type of challenge randomized control trial, which randomises when treatment is received rather than the usual randomized control trial, which randomizes whether treatment is received. Typical cohort studies can be viewed as emulating the usual randomized control trial when they make risk sets for Cox regression on a time since treatment (eg, time since vaccination) timeline. Then, the waning of vaccine effectiveness can be estimated by the difference between a vaccine effectiveness estimate for a period soon after randomisation and a vaccine effectiveness estimate for a period later after randomisation; each of these vaccine effectiveness estimates is based on a comparison of vaccinees with the unvaccinated. A disadvantage of this usual approach is that bias can arise from change over time in HZ incidence unrelated to waning but due instead to change in diagnostic and coding practices, health seeking behaviours, or other factors. To avoid such biases associated with calendar time, we made the risk sets for Cox regression on a calendar timeline; this can be viewed as emulating a challenge randomized control trial in which individuals who were vaccinated more recently are compared with individuals who were vaccinated less recently when they were at risk (ie, they were challenged) on the same day. Waning of vaccine effectiveness was then estimated from a series of such comparisons conducted within risk sets made on every calendar date when cases occurred. This approach has been useful in analyses of the waning of covid-19 vaccine effectiveness,[22 23] and of the waning of pertussis vaccine effectiveness,[24-26] where outcome incidence varies greatly over calendar time. In this study, this approach reduced the potential for confounding arising from the transition from ICD-9 to ICD-10; people diagnosed by ICD-9 codes were never compared with people diagnosed by ICD-10 codes.

These features of the study design can also increase precision because more cases of HZ can be informative. In the usual approach, with a time since vaccination timeline, unvaccinated people cannot be informative until they are either matched to vaccinated people or, in an unmatched analysis, assigned a start time. Also, if vaccination coverage becomes very high, then analyses of vaccine effectiveness in relation to time since vaccination become underpowered when only a dwindling number of unvaccinated people remain for comparison. By contrast, our approach permits direct comparison of recently vaccinated people with less recently vaccinated people; our approach can estimate waning without direct comparisons to the unvaccinated.

Other strengths of our study include its large and diverse population and high live zoster vaccine uptake. We closely adjusted for single years of age (stratifying by birth year) and for single days of calendar time. Also, we used time varying measures for several potential confounders, including immunocompromise status, which frequently changed during this lengthy study. We used highly specific outcome definitions, validated by chart review. Our outcomes included several manifestations and complications of HZ (ie, HZO, postherpetic neuralgia, and admission to hospital for HZ), for which care seeking and diagnosis are less discretionary, and therefore vaccine effectiveness estimation was less susceptible to confounding.

Limitations of this study

Our data and methods have limitations. Firstly, we may have missed some HZ events because our criteria for incident HZ required an antiviral prescription in addition to an HZ diagnosis. We prioritized specificity over sensitivity. Incidence of outcome events meeting our criteria was lower than reported elsewhere, especially for HZO[3 6-8] and admission to hospital for HZ.[1 3 9] Secondly, residual confounding is possible from aspects of health seeking behaviour and comorbidities that were unmeasured or mis-measured; tracking immunocompromise over time was especially challenging. Thirdly, our findings may not be generalizable to other settings because of differences in diagnostic practices or access to care. Fourthly, our vaccine effectiveness estimates did not have precision when outcome events were sparse, as they were for admission to hospital in people aged 50-59 years, and for HZO and admission to hospital for HZ beyond eight years after vaccination.

Conclusions

This study used innovative methods to estimate change in the real world effectiveness of live zoster vaccine against HZ, postherpetic neuralgia, HZO, and admission to hospital for HZ over 10 years following vaccination in a large, diverse population of people aged 50 years or older. We found that live zoster vaccine conferred much protection initially but protection waned substantially over time. After 10 years, protection was low against HZ but higher against postherpetic neuralgia.

What is already known on this topic

- Live zoster vaccine was initially effective at reducing the risk of herpes zoster (shingles) and postherpetic neuralgia in people aged ≥50 years
- The effectiveness of live zoster vaccine waned over time

What this study adds

- Live zoster vaccine was effective at reducing the risk of herpes zoster ophthalmicus and admission to hospital for herpes zoster
- At 10 to <12 years after vaccination, live zoster vaccine still conferred a small amount of protection against herpes zoster, and a higher amount of protection against postherpetic neuralgia
- A description of methods that are useful for real world studies examining the duration of vaccine protection

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critically for important intellectual content and gave final approval of the version to be published. NPK, JB, BF, JH, EL, and LA had access to the data in the study and all authors take responsibility for the integrity and accuracy of the analysis. NPK attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted, and is the guarantor. MAM is now an employee of Moderna Inc, Cambridge, MA, United States.

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Competing Interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: PS is an employee of Merck Sharp and Dohme LLC, the manufacturer of the vaccine and sponsor of the study. MAM was an employee of Merck Sharp and Dohme LLC during the study and now is an employee of Moderna Inc. The study was conducted and analysed at Kaiser Permanente, where all the other authors have been employed. NPK has received research grant support for unrelated studies from GlaxoSmithKline, Sanofi Pasteur, Pfizer, and the US Centers for Disease Control and Prevention.

The lead author NPK affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related and public communities: Study results will be disseminated via a press release with mainstream media, and the study results have been added to the patient information leaflet/label of live zoster vaccine in many countries, including all EU countries, the US and Australia. The product label is a public document used by healthcare professionals and is available to patients.

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Data sharing: No data are available.

1 Centers for Disease Control and Prevention (CDC). Shingles (Herpes Zoster) https://www.cdc.gov/shingles/surveillance.html.

2 Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;82:-9. doi: 10.4065/82.11.1341. pmid: 17976353

3 Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014;4:e004833. doi: 10.1136/bmjopen-2014-004833. pmid: 24916088

4 Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Fam Pract* 2002;19:-5. doi: 10.1093/fampra/19.5.471. pmid: 12356697

5 Czernichow S, Dupuy A, Flahault A, Chosidow O. [Herpes zoster: incidence study among "sentinel" general practitioners]. *Ann Dermatol Venereol* 2001;128:-501.pmid: 11395646

6 Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. *Mayo Clin Proc* 2013;88:-70. doi: 10.1016/j.mayocp.2013.03.014. pmid: 23664666

7 Harpaz R, Ortega-Sanchez IR, Seward JFAdvisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008;57(RR-5):-30, quiz CE2-4.pmid: 18528318

8 Izurieta HS, Wernecke M, Kelman J, etal. 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:-93. doi: 10.1093/cid/ciw854. pmid: 28362955

9 Tseng HF, Bruxvoort K, Ackerson B, etal. The epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥50 years old: incidence, complications, hospitalization, mortality, and recurrence. *J Infect Dis* 2020;222:-806. doi: 10.1093/infdis/jiz652. pmid: 31830250

10 Hales CM, Harpaz R, Ortega-Sanchez I, Bialek SRCenters for Disease Control and Prevention (CDC). Update on recommendations for use of herpes zoster vaccine. *MMWR Morb Mortal Wkly Rep* 2014;63:-31.pmid: 25144544

11 Dooling KL, Guo A, Patel M, etal. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep* 2018;67:-8. doi: 10.15585/mmwr.mm6703a5. pmid: 29370152

12 Baxter R, Bartlett J, Fireman B, etal. Long-term effectiveness of the live zoster vaccine in preventing shingles: a cohort study. *Am J Epidemiol* 2018;187:-9. doi: 10.1093/aje/kwx245. https://pubmed.ncbi.nlm.nih.gov/29309521/. pmid: 29309521

13 Klein NP, Bartlett J, Fireman B, etal. Long-term effectiveness of zoster vaccine live for postherpetic neuralgia prevention. *Vaccine* 2019;37:-7. doi: 10.1016/j.vaccine.2019.07.004. https://www.ncbi.nlm.nih.gov/pubmed/31301920. pmid: 31301920

14 Lal H, Cunningham AL, Godeaux O, etalZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015;372:-96. doi: 10.1056/NEJMoa1501184. pmid: 25916341

15 Cunningham AL, Lal H, Kovac M, etalZOE-70 Study Group. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med* 2016;375:-32. doi: 10.1056/NEJMoa1603800. pmid: 27626517

16 Oxman MN, Levin MJ, Johnson GR, etalShingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:-84. doi: 10.1056/NEJMoa051016. pmid: 15930418

17 Schmader KE, Oxman MN, Levin MJ, etalShingles Prevention Study Group. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clin Infect Dis* 2012;55:-8. doi: 10.1093/cid/cis638. pmid: 22828595

18 Morrison VA, Johnson GR, Schmader KE, etalShingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 2015;60:-9. doi: 10.1093/cid/ciu918. pmid: 25416754

19 Tseng HF, Harpaz R, Luo Y, etal. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. *J Infect Dis* 2016;213:-5. doi: 10.1093/infdis/jiw047. pmid: 26908728

20 NHS. Shingles vaccine overview 2021. https://www.nhs.uk/conditions/vaccinations/shingles-vaccination/.

21 Australian Government. National Immunisation Program Schedule. Immunisation for Adults https://www.health.gov.au/topics/immunisation/when-to-get-vaccinated/immunisation-for-adults.

22 Ferdinands JM, Rao S, Dixon BE, etal. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study. *BMJ* 2022;379:e072141. doi: 10.1136/bmj-2022-072141. pmid: 36191948

23 Ferdinands JM, Rao S, Dixon BE, etal. Waning 2-dose and 3-dose effectiveness of mrna vaccines against covid-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION Network, 10 states, August 2021-January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:-63. doi: 10.15585/mmwr.mm7107e2. pmid: 35176007

24 Zerbo O, Bartlett J, Goddard K, Fireman B, Lewis E, Klein NP. Acellular pertussis vaccine effectiveness over time. *Pediatrics* 2019;144:e20183466. doi: 10.1542/peds.2018-3466. pmid: 31182549

25 Klein NP, Bartlett J, Fireman B, etal. Waning protection following 5 doses of a 3-component diphtheria, tetanus, and acellular pertussis vaccine. *Vaccine* 2017;35:-400. doi: 10.1016/j.vaccine.2017.05.008. pmid: 28506516

26 Klein NP, Bartlett J, Fireman B, Baxter R. Waning tdap effectiveness in adolescents. *Pediatrics* 2016;137:e20153326. doi: 10.1542/peds.2015-3326. pmid: 26908667

Web appendix: Online appendix