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Long-term effectiveness of zoster vaccine live for postherpetic neuralgia prevention

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ABSTRACT

Background: Postherpetic neuralgia (PHN) occurs in 5–30% of individuals with herpes zoster (HZ) and is characterized by long-lasting pain. Zoster vaccine live (ZVL) is licensed for people 50 years and older to prevent HZ and PHN. This study evaluated vaccine effectiveness (VE) of ZVL against PHN.

Methods: We conducted an open cohort study within Kaiser Permanente Northern California with continuous accrual of people as they became age-eligible for ZVL. We defined PHN using a PHN diagnosis between 90 and 365 days after an incident episode of HZ. We estimated VE against PHN using Cox regression with a calendar timeline stratified by year of birth and adjusted for sex, race, influenza vaccination, outpatient visit frequency, comorbidities, and immune compromise status.

Results: From 2007 to 2016, 1·5 million people entered the study population and 33% received ZVL. During 7·6 million person-years of follow-up, there were 62,205 HZ cases, 4150 (6·7%) of which went on to develop PHN. Overall VE for PHN was 64·8% (95% CI 61·3, 68). VE was 82·8% (95% CI 77·6, 86·7) during the first year after vaccination, 58·3% (95% CI 50.1, 65.2) during the third year, and then waned more gradually to 48·7% (95% CI 30·2, 62·3) during the eighth year. VE in persons vaccinated when aged 80 years or older was similar to VE in younger vaccinees. VE in persons vaccinated when immune compromised was similar to VE in immune competent.

Conclusions: Overall, ZVL was 65% effective against PHN. It was effective in all age groups and provided moderate protection through 8 years.

1. Background

Shingles, also known as herpes zoster (HZ), is a painful skin eruption due to reactivation of latent varicella zoster virus (VZV). Lifetime risk of HZ is 30% [1], with incidence increasing with age from ~6 per 1000 person-years at ages 50–59 years to ~12 per 1000 person-years for those aged 80 years and older [1,2]. Depending on age and definition of postherpetic neuralgia (PHN), between 5 and 30% of persons with shingles develop PHN, a complication characterized by long-lasting pain in the area of the rash, with symptoms persisting for months or even years after resolution of the HZ skin eruption [3–6]. PHN has a major impact on patient quality of life [7]. Risk factors for PHN include older age, female sex, severe HZ rash, severe pain during the acute HZ episode, and being immunocompromised due to medical conditions or treatments [8–10].

ZOSTAVAX™ (Zoster vaccine live [ZVL]), a live attenuated zoster vaccine developed by Merck & Co., Inc., Kenilworth, NJ, USA, has been licensed in over 50 countries, and since 2006 in the United States for persons aged 60 years or older. In 2011, licensure was extended to those aged 50–59 years. ZVL efficacy was established through clinical studies, including a large randomized, placebo-controlled trial [2] and a follow-up study [11]. In the trial, ZVL efficacy against PHN in persons 60 years or older was 66.5% over 3 years of follow-up and 60.1% over 7 years.

We are conducting a prospective cohort study in Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system, to assess the long-term effectiveness of ZVL in

Abbreviations: CI, Confidence interval; HR, Hazard ratio; HZ, Herpes zoster; IC, Immune compromise; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; KPNC, Kaiser Permanente Northern California; PHN, Postherpetic neuralgia; PPV, Positive predictive value; VE, Vaccine effectiveness; VZV, Varicella zoster virus; ZVL, Zoster vaccine live.

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protecting individuals aged 50 years or older from HZ and PHN. We previously reported that vaccine effectiveness (VE) against HZ was 49.1% over a follow-up period of 8 years, with a decline in VE over time from 67.5% in the first year after vaccination to 31.8% at year 8 [1]. Here, we report the VE of ZVL against PHN during a 10-year follow-up period, overall, by age at vaccination, by year since vaccination, and by immune compromise (IC) status at the time of vaccination.

2. Methods

2.1. Study design & study population

This is an open cohort study within KPNC with continuous accrual of people as they become age-eligible for zoster vaccination (at age 60 years and older starting in 2007 and then at age 50 years and older from 2011 onward), with follow-up starting on 01 January 2007 and continuing through 2023 as previously described [1]. This report focuses on PHN diagnosed in individuals whose HZ met study eligibility criteria within the previous year. The KPNC Institutional Review Board approved this study.

2.2. Follow-up and vaccine exposure

To identify incident HZ cases, we followed all study participants until the first occurrence of the following: HZ diagnosis, receipt of a subsequent zoster vaccine, discontinuation of KPNC membership, death, or the end of the analysis period (31 December 2016). To identify PHN cases, we followed all incident HZ cases for one-year (through 31 December 2017) after HZ diagnosis.

All individuals were unvaccinated at study entry. Persons contributed unvaccinated person-time from the date they entered the study until they received the zoster vaccine, or until the end of follow-up for never-vaccinated persons. Persons contributed vaccinated person-time starting 30 days after vaccination. The person-time for days 1–29 after vaccination, time that the vaccine needs to induce immunity, was not counted as either vaccinated or unvaccinated.

2.3. Study outcome

We included all PHN cases that occurred following incident HZ. Thus, PHN episodes were a subset of HZ episodes, and VE was assessed in relation to vaccination status on the HZ diagnosis date. Updated HZ results over the longer 10-year follow-up period are provided in Appendix 1.

We identified incident HZ cases from the first health care encounter with an HZ diagnosis (International Classification of Diseases, Ninth Revision (ICD-9) codes 053.xx or ICD-10 codes B02.xx) if there was an accompanying antiviral prescription or positive laboratory test [1]. We identified potential PHN cases among those who had a PHN diagnosis (all ICD-9 codes 053.12, 053.13; all ICD-10 codes B02.22, B02.23; and ICD-9 code 053.19 and ICD-10 code B02.29 where the internal KPNC diagnosis text indicated PHN) associated with a clinical encounter (clinic visit, emergency room visit, or hospital stay) and/or a PHN diagnosis linked to a prescription between 90 days and 1 year after the HZ diagnosis. All ICD-9 and ICD-10 codes at KPNC have diagnostic text associated with them that made our diagnosis specific for PHN. We reviewed the medical charts of 200 potential PHN cases to validate this algorithm. PHN diagnosis codes associated with both an encounter and a prescription had a positive predictive value (PPV) of 96% (95% CI: 90, 99), while a code associated with either an encounter or a prescription had PPVs ranging from 73 to 89%. Based on this, we considered as a PHN case those with PHN diagnoses codes recorded in both a clinical encounter and a prescription without additional medical chart review, while the remaining potential PHN cases underwent chart review to confirm case status.

2.4. Covariates

We adjusted VE estimates for time-fixed covariates, including sex and race, and for time-varying covariates, including influenza vaccination during the prior year, outpatient visit frequency, comorbidities (as measured through a cost predictor and a herpes zoster risk score), and IC status as described previously [1]. We closely adjusted for age by using a calendar timeline stratified by year of birth in our analysis. A complete description of the covariates has been previously published [1]. The URL is provided here for easy access (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6018833/).

2.5. Statistical analysis

We calculated the percentage of HZ cases who went on to develop PHN by age group (50–59, 60–69, 70–79, or ≥80 years) and vaccination status, and calculated the incidence of PHN by vaccination status, age group, gender, and race/ethnicity.

We examined VE against PHN using Cox regression with a calendar timeline stratified by birth year, adjusted for the time-fixed and time-varying covariates listed above. We estimated overall VE against PHN across all 10 years of follow-up by fitting a model with only 1 vaccination indicator (yes or no). We estimated the PHN hazard ratio (HR) – comparing vaccinees' risk with risk in the unvaccinated – and then estimated VE by 1 minus the HR, scaled as a percentage.

We also estimated VE by year since vaccination, by age group at vaccination, and by IC status at vaccination. To examine VE in relation to year since vaccination, we fitted a model with 10 binary variables that together indicated the vaccination status of everyone at risk and, if vaccinated, the number of years since vaccination (30 days to <1 year, 1 to <2 years, . . ., and 9 to <10 years). To examine VE by age at vaccination, we similarly included 4 binary variables to indicate each vaccinee's age group at the time of vaccination (50–59, 60–69, 70–79, or ≥80 years). We implemented a similar approach to examine VE by immune compromise status: we included 3 binary variables specifying vaccinees' immune compromise status (no IC, low IC, or high IC) at the time of vaccination. Finally, we estimated VE in relation to both year-since-vaccination and age at vaccination, using 40 indicator variables to identify 40 categories of vaccinees (10 years-since-vaccination by 4 age-groups-at-vaccination). In each model, unvaccinated persons constituted the reference group.

We calculated a summary measure of average VE for the first 3, 5 and 8 years after vaccination for all ages combined, and for each vaccination age group, based on the year-specific hazard ratios (on the log scale) estimated from the Cox models described above. The average VE gave equal weight to the estimates for each year-since-vaccination.

We conducted all analyses using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and used the Lexis macro to partition person-time (http://bendixcarstensen.com/Lexis/Lexis.sas).

3. Results

From 2007 to 2016, 1,454,841 persons entered the study and contributed 7.6 million person-years of follow-up (an average of 5.2 years per person). During the study period, 480,413 persons (33%) received the ZVL vaccine. By 2016, vaccine coverage was 71% in persons aged 60 years and older but only 4% for those aged

50–59 years. The average duration of follow-up after vaccination was 3.7 years. Among persons vaccinated when they were aged 60 years or older, 36% of follow-up was more than 3 years after vaccination and 16% of follow-up was more than 5 years after vaccination. Among vaccinees aged 50–59 years, 21% of follow-up was after year 3, while <1% of follow-up was after year 5 because the vaccine was not licensed for ages 50–59 until 2011.

During the 7.6 million years of follow-up, we identified 62,205 HZ cases through 2016. Among those identified with HZ, 4175 (6.7%) subsequently developed PHN. Nearly half of the PHN cases had both a clinical encounter and a prescription with a PHN diagnosis (46.5%), and were confirmed without chart review, while the rest underwent chart review (Table 1). The percentage of HZ cases with PHN increased markedly with age from 2.9% in unvaccinated persons aged 50–59 years to 12.5% in unvaccinated persons aged 80 years or older (80+) (Table 2). In persons aged 60 years or older, the percentage of HZ cases that went on to develop PHN was lower among the vaccinated than the unvaccinated.

The crude PHN incidence rate was 59.5 per 100,000 person-years (95% CI 57.5, 61.5) among the unvaccinated and 38.3 (95% CI 35.4, 41.3) among the vaccinated. PHN incidence increased steeply with age, with incidence among the unvaccinated ranging from 20.0 in 50–59 year olds to 148.3 in 80+ year olds. PHN incidence was higher in women than in men. PHN incidence among the unvaccinated differed across race and ethnic groups, with lower rates in persons of Black or Asian/Pacific Islander race, and higher rates in persons of Hispanic ethnicity or American Indian/Alaskan Native race (Table 3).

After covariate adjustment, the overall VE of ZVL in preventing PHN was 64.8% (95% CI 61.3, 68.0) across all follow-up in all age groups. VE did not vary much by age at vaccination (Table 4).

For all ages combined, VE against PHN was 82.8% (95% CI 77.6, 86.7) during the first year following vaccination, decreased to 70.8% (95% CI 64.4, 76.1) in the second year, and to 58.3% (95% CI 50.1, 65.2) in the third year, after which it decreased more gradually to 48.7% (95% CI 30.2, 62.3) in the eighth year (Table 4). We were unable to precisely estimate VE after year 8 due to the small number of PHN cases. Average VE over the first 3 years after vaccination was 72.0% (95% CI 68.2, 75.5), which decreased to an average of 62.6% (95% CI 58.5, 66.3) over 8 years (Table 4).

After covariate adjustment, persons vaccinated while immune compromised had similar VE against PHN to persons vaccinated while immunocompetent (Table 5). Adjustment for the time-varying covariates mattered more to the estimate of VE in persons who were immune compromised when vaccinated, but not for the VE estimate in immunocompetent vaccinees (Table 5).

4. Discussion

In this large cohort study, we found that ZVL was 65% effective against PHN overall across all follow-up in all age groups. Importantly, ZVL was effective in preventing PHN at the same level in all age groups, including those who were vaccinated when aged 80 years and older. VE was highest at 82.8% during the first year after vaccination, waned to 58.3% in the third year after vaccination, and then decreased more gradually to 48.7% by the eighth year.

Even though ZVL is not indicated in IC persons, over 5% of ZVL vaccinees had some level of immunocompromise at the time of vaccination. Our study found that VE against PHN in persons vaccinated when immunocompromised was similar to VE in persons vaccinated when immunocompetent. Immunocompromised status varied during follow-up, yet was more prevalent throughout follow-up in those who were immunocompromised when vaccinated. Adjustment for variation over time in immunocompromise status was important to VE estimation in the subgroup of vaccinees who were immunocompromised when vaccinated (but had little impact on VE estimates for immunocompetent vaccinees). Similarly, adjustment for time-varying co-morbidity measures was important for the estimation of VE in immunocompromised vaccinees. After similar adjustment for time-varying covariates, our previous study of VE against HZ, also found that VE was not attenuated by immunocompromise at the time of vaccination [1].

We found that VE against PHN was higher than our previously reported VE against HZ [1], overall across all follow-up (65% vs 49%), as well as in all the subgroups of vaccinees defined by age

Table 1
Number of potential postherpetic neuralgia cases according to detection definition, Kaiser Permanente Northern California, 2007–2016.

Categories of potential PHN cases[a]	Potential PHN cases N = 4457 (%)	PHN cases included in analysis N = 4175 (%)
– Visit with PHN diagnosis and prescription with PHN diagnosis	1941 (43.5%)	1941 (46.5%)
– Visit with primary PHN diagnosis(no prescription with PHN diagnosis)	481 (10.8%)	469 (11.2%)
– Visit with secondary PHN diagnosis(no prescription with PHN diagnosis)	1427 (32.0%)	1255 (30.1%)
– Prescription with PHN diagnosis(no visit with PHN diagnosis)	608 (13.6%)	510 (12.2%)

Abbreviations: PHN, Postherpetic neuralgia.
[a] Categories are mutually exclusive.

Table 2
Percentage of herpes zoster cases that developed postherpetic neuralgia by age group and vaccination status, Kaiser Permanente Northern California, 2007 to 2016.

Variable	Total[a]		Unvaccinated			Vaccinated		
	PHN Cases[b]	HZ Cases	PHN Cases	HZ Cases	PHN/HZ % (95% CI)	PHN Cases	HZ Cases	PHN/HZ % (95% CI)
Total	4150	61,877	3485	51,433	6.8 (6.6, 7.0)	665	10,444	6.4 (5.9, 6.9)
Age Group, years[c]								
50–59	447	15,261	440	15,019	2.9 (2.7, 3.2)	7	242	2.9 (1.2, 6.0)
60–69	1049	21,024	891	17,198	5.2 (4.8, 5.5)	158	3826	4.1 (3.5, 4.8)
70–79	1399	15,026	1114	10,869	10.2 (9.7, 10.9)	285	4157	6.9 (6.1, 7.7)
≥80	1255	10,566	1040	8347	12.5 (11.7, 13.2)	215	2219	9.7 (8.4, 11.1)

Abbreviations: CI, confidence interval; HZ, herpes zoster; PHN, postherpetic neuralgia.
[a] HZ cases occurring the first 30 days after vaccination, and associated PHN cases (N = 25), were excluded from this table.
[b] PHN occurring between 90 days and one year after incident HZ.
[c] Age group was age at HZ onset.

Table 3
Incidence of postherpetic neuralgia, by age group, sex, race/ethnicity, and vaccination status, Kaiser Permanente Northern California, 2007 to 2016.

Variable	Total[a]		Unvaccinated			Vaccinated		
	PHN cases	Person-years	PHN cases	Person-years	Incidence Rate[b] (95% CI)	PHN Cases	Person-years	Incidence Rate[b] (95% CI)
Total	4150	7,597,008	3485	5,858,887	59.5 (57.5, 61.5)	665	1,738,121	38.3 (35.4, 41.3)
Age Group, years[c]								
50–59	447	2,265,505	440	2,196,747	20.0 (18.2, 22.0)	7	68,758	10.2 (4.1, 21.0)
60–69	1049	2,793,281	891	1,989,460	44.8 (41.9, 47.8)	158	803,821	19.7 (16.7, 23.0)
70–79	1399	1,570,580	1114	971,457	114.7 (108.0, 121.6)	285	599,1231	47.6 (42.2, 53.4)
≥80	1255	967,642	1040	701,222	148.3 (139.4, 157.6)	215	266,420	80.7 (70.3, 92.2)
Sex								
Female	2601	4,112,749	2158	3,116,883	69.2 (66.3, 72.2)	443	995,866	44.5 (40.4, 48.8)
Male	1549	3,484,259	1327	2,742,004	48.4 (45.8, 51.1)	222	742,255	29.96 (26.1, 34.1)
Race/Ethnicity								
White	2706	4,777,747	2217	3,560,435	62.3 (59.7, 64.9)	489	1,217,312	40.2 (36.7, 43.9)
Asian/Pacific Islander	526	1,163,820	437	905,571	48.3 (43.8, 53.0)	89	258,249	34.5 (27.7, 42.4)
Hispanic	631	915,934	570	757,924	75.2 (69.2, 81.6)	61	158,010	38.6 (29.5, 49.6,)
Black/African American	235	549,495	214	463,704	46.2 (40.2, 52.8)	21	85,791	24.5 (15.2, 37.4)
American Indian/Alaskan Native	40	60,961	37	48,799	75.8 (53.4, 104.5)	3	2162	24.7 (5.1, 72.1)
Multiracial	2	2958	2	2196	91.1 (11.0, 329.0)	0	762	0 (0, 393.1)
Missing	10	126,093	8	120,258	6.7 (2.9, 13.1)	2	5835	34.3 (4.2, 123.8)

Abbreviations: CI, confidence interval; HZ, herpes zoster; PHN, postherpetic neuralgia.
[a] The total excludes 25 PHN cases that followed HZ cases diagnosed during the first 30 days after vaccination. Person-years during those 30 days are also excluded.
[b] Per 100,000 person-years.
[c] Age group was age at HZ diagnosis.

Table 4
Effectiveness of zoster vaccine live against postherpetic neuralgia, overall, by time since vaccination and age at vaccination, Kaiser Permanente Northern California, 2007 to 2016.

	Age group at vaccination, Years				
	50–59 VE[a] (95% CI)	60–69 VE[a] (95% CI)	70–79 VE[a] (95% CI)	≥80 VE[a] (95% CI)	All Ages Combined VE[a] (95% CI)
Overall VE 2007–2016	63.8 (36.9, 79.2)	66.2 (60.9, 70.8)	64.1 (58.8, 68.8)	63.3 (54.7, 70.2)	64.8 (61.3, 68.0)
Years since vaccination					
30 days to <1	41.6 (−41.4, 75.9)	85.5 (77.4, 90.7)	85.9 (77.4, 91.1)	76.8 (61.2, 86.1)	82.8 (77.6, 86.7)
1 to <2	78.9 (15.0, 94.7)	72.9 (62.7, 80.3)	69.2 (58.0, 77.4)	69.4 (52.0, 80.4)	70.8 (64.4, 76.1)
2 to <3	78.6 (13.9, 94.7)	67.1 (55.1, 75.9)	48.0 (32.6, 59.8)	58.3 (36.3, 72.7)	58.3 (50.1, 65.2)
3 to <4	53.8 (−45.1, 85.3)	64.3 (49.9, 74.6)	70.7 (56.8, 80.1)	38.9 (4.0, 61.1)	62.7 (53.6, 70.1)
4 to <5	63.6 (−162.0, 94.9)	51.8 (32.6, 65.6)	55.8 (36.9, 69.1)	57.3 (17.1, 78.0)	54.1 (42.3, 63.5)
5 to <6	¶	61.2 (41.3, 74.3)	64.1 (44.9, 76.6)	52.4 (−1.21, 77.6)	61.5 (49.2, 70.9)
6 to <7	¶	48.6 (23.7, 65.4)	56.5 (33.0, 71.8)	18.0 (−60.8, 58.2)	49.2 (33.4, 61.2)
7 to <8	¶	49.1 (19.4, 67.8)	41.7 (11.2, 61.7)	85.3 (−5.6, 97.9)	48.7 (30.2, 62.3)
8 to <9	¶	32.4 (−13.6, 59.7)	4.3 (−48.6, 38.3)	40.8 (−144.1, 85.6)	20.6 (−10.2, 42.8)
9 to <10	¶	59.1 (−29.8, 87.1)	60.1 (−26.9, 87.5)	¶	62.8 (15.8, 83.6)
Average VE[b]					
0–3 years	70.8 (39.1, 86.0)	76.2 (70.4, 80.9)	71.1 (64.4, 76.6)	68.8 (59.0, 76.6)	72.0 (68.2, 75.5)
0–5 years	66.5 (36.2, 82.4)	70.2 (64.6, 74.9)	68.4 (62.5, 73.4)	61.9 (51.6, 70.0)	67.2 (63.5, 70.6)
0–8 years	¶	64.7 (58.7, 69.8)	63.9 (57.9, 69.0)	61.7 (46.9, 72.4)	62.6 (58.5, 66.3)

Abbreviations: VE, vaccine effectiveness; CI, confidence interval.
[a] VE was calculated as (1-hazard ratio)*100. All VE estimates were closely adjusted for age and calendar date, based on risk sets that were defined on a calendar timeline and stratified by year of birth. Time-fixed covariates were sex and race. Time-varying covariates were influenza vaccination, immune compromise status, outpatient visit frequency, the cost predictor, and the herpes zoster risk score.
[b] Average VE was calculated as the weighted average of the annual VE estimates where each year was weighted equally. VE for all ages combined was calculated from estimates in the Cox model that included 10 indicator variables for years-since-vaccination while VE for each age group was calculated from the Cox model that included 40 indicator variables for years-since-vaccination and age-since-vaccination.
¶ Insufficient data.

Table 5
Vaccine effectiveness of zoster vaccine live against postherpetic neuralgia, by immune compromise status at the time of vaccination, Kaiser Permanent Northern California, 2007–2016.

Immune Compromise Status at Time of Vaccination	Adjusted for Fixed Covariates[a]		Adjusted for Fixed[a] and Time-Varying Covariates[b]	
	VE[c]	95% CI	VE	95%CI
Not immune compromised	64.0	60.4, 67.3	64.7	61.1, 68.0
Low immune compromise	48.2	27.2, 63.2	68.3	55.3, 77.5
High immune compromise	−10.1	−69.5, 28.5	60.7	39.3, 74.6

Abbreviations: VE, vaccine effectiveness; CI, confidence interval
[a] The fixed covariates were sex and race.
[b] The time-varying covariates were influenza vaccination, immune compromise status, outpatient visit frequency, the cost predictor, and the herpes zoster risk score.
[c] All VE estimates were closely adjusted for age and calendar date, based on risk sets that were defined on a calendar timeline and stratified by year of birth. VE was calculated as (1-hazard ratio) * 100.

at vaccination and immunocompromise status. As noted above, a lower percentage of vaccinated HZ cases progressed to PHN, compared with unvaccinated cases, suggesting vaccine effectiveness is higher against PHN than against HZ. For both PHN and HZ, VE was highest in the first year, decreased substantially by the third year, and then decreased more gradually. The ZVL vaccine continued to offer protection in the eighth year for both HZ (~30%) and PHN (49%).

Overall, our results are generally consistent with prior clinical trials [11,12] and observational studies [13,14]. As in the current study, clinical trials and observational studies have reported that ZVL was effective against PHN in all age groups [11–14]. In addition, similar to the 7-year follow-up Shingles Prevention Study extension which reported an estimated VE against PHN of 64.9% [11], our average VE estimate for the 8 years after vaccination was 62.6%. Further, our estimated average VE of 72% against PHN during the 3 years after vaccination was consistent with other observational studies which estimated VE as 57–59% in the first 2–3 years after vaccination [13,14]. Finally, in our study, the proportion of unvaccinated HZ cases who went on to develop PHN was 6.8%, which is consistent with the 5 to 30% range previously reported in the literature from studies using varying, often less stringent PHN definition, while our study required a minimum duration of 90 days [3,4,5,6,10,15].

Our study had several important strengths, including a large sample size (1.5 million people with 7.6 million person-years of follow-up), high vaccine uptake in persons aged 60 years and older, and careful adjustment for age, calendar time and other potential confounders including immune compromise status, comorbidities, and health seeking behavior. Consistent with other studies, our study observed a sharp rise in the incidence of PHN with age which was higher than the rise in the incidence of HZ, further supporting the representativeness of our study population and the validity of our PHN identification algorithm.

This study had limitations. First, VE estimates for years 9 and 10 after vaccination were imprecise, especially for the youngest age group. Second, while our PHN definition was associated with a high specificity, it likely underestimated PHN incidence also because we limited PHN ascertainment to individuals who had received medical care for incident HZ. Third, there was a potential for misclassification of immunocompromise due to missing or miscoded data. However, such misclassification was expected to be non-differential across the vaccinated and unvaccinated groups. Fourth, potential unmeasured confounders not routinely captured in KPNC databases could be an additional source of bias. Fifth, our results—especially about the effectiveness of vaccination-while-immunocompromised, may not be fully generalizable outside of KPNC. However, as our vaccinated population is diverse, large, and representative of all US ethnic groups, our results are likely to be more generalizable to the general population than were those of clinical trials.

Finally, the ACIP recommended in October 2017 preferential use of a new recombinant zoster vaccine (RZV) for persons aged 50 years and above (Shingrix) and recommended that those previously vaccinated with ZVL be revaccinated with RZV [16]. This will make it challenging to complete study follow-up through 2023, as originally planned. However, our PHN results continue to be of scientific interest and to have clinical relevance for those countries that continue to use ZVL.

5. Conclusions

On average, ZVL was 65% effective against PHN. Persons vaccinated when aged 80 years or older had similar levels of protection against PHN as persons vaccinated at younger ages. Individuals who were immunocompromised at the time of vaccination had similar levels of protection against PHN to immunocompetent vaccinees. ZVL continued to provide protection against PHN eight years after vaccination.

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Declaration of Competing Interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.004.

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