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Effectiveness of Recombinant Zoster Vaccine Against Herpes Zoster in a Real-World Setting

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Abstract

Background: A 2-dose series of recombinant zoster vaccine (RZV) was 97% effective against herpes zoster (HZ) in a pivotal clinical trial.

Objective: To evaluate real-world effectiveness of RZV against HZ.

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Author contributions are available at Annals.org.

Design: Prospective cohort study.

Setting: Four health care systems in the Vaccine Safety Datalink.

Participants: Persons aged 50 years or older.

Measurements: The outcome was incident HZ defined by a diagnosis with an antiviral prescription. Cox regression was used to estimate the hazard of HZ in vaccinated persons compared with unvaccinated persons, with adjustment for covariates. Vaccine effectiveness (VE) was calculated as 1 minus the adjusted hazard ratio and was estimated by time since the last RZV dose and by corticosteroid use.

Results: The study included nearly 2.0 million persons who contributed 7.6 million person-years of follow-up. After adjustment, VE of 1 dose was 64% and VE of 2 doses was 76%. After 1 dose only, VE was 70% during the first year, 45% during the second year, 48% during the third year, and 52% after the third year. After 2 doses, VE was 79% during the first year, 75% during the second year, and 73% during the third and fourth years. Vaccine effectiveness was 65% in persons who received corticosteroids before vaccination and 77% in those who did not.

Limitation: Herpes zoster could not be identified as accurately in these observational data as in the previous clinical trials.

Conclusion: Two doses of RZV were highly effective, although less effective than in the previous clinical trials. Two-dose effectiveness waned very little during the 4 years of follow-up. However, 1-dose effectiveness waned substantially after 1 year, underscoring the importance of the second dose.

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Herpes zoster (HZ), also known as shingles, is caused by reactivation of varicella-zoster virus, which has been latent in most adults since childhood chickenpox (1). Herpes zoster is a painful rash that occurs along 1 or more dermatomes, with complications that include persistent burning pain at the site of the initial rash, known as postherpetic neuralgia (2, 3). The incidence and severity of HZ increase markedly with age and immunocompromising conditions (4, 5).

In October 2017, the recombinant zoster vaccine (RZV) was licensed by the U.S. Food and Drug Administration and recommended by the Advisory Committee on Immunization Practices for immunocompetent persons aged 50 years or older as a 2-dose series administered 2 to 6 months apart to prevent HZ (6). The licensure was based on safety and efficacy data from clinical trials, including 2 phase 3 multicenter randomized controlled trials in adults aged 50 years or older (7) and adults aged 70 years or older (8), which reported that the effectiveness of 2 RZV doses was at least 90% over a 4-year period. Recombinant zoster vaccine was recommended as the preferred vaccine over zoster vaccine live (ZVL), the first vaccine against HZ. In 2021, the Advisory Committee on Immunization Practices recommended RZV for immunocompromised persons aged 19 years or older, based on additional safety and effectiveness data (9).

Studies in real-world settings have also shown the effectiveness of 2 doses of RZV. Two studies based on claims data found that RZV was 70% and 86% effective against HZ (10,

11). Another study using data from an integrated health care system reported that RZV was 84% effective (12).

Recently, a long-term RZV effectiveness study among participants in the original clinical trials reported in an interim analysis that vaccine effectiveness (VE) did not wane substantially during at least 7 years of follow-up (13). However, the long-term effectiveness of RZV has not been extensively studied in real-world settings. The objectives of this study were to further evaluate the 1- and 2-dose effectiveness of RZV, overall and by time since vaccination. We also assessed whether 2-dose VE varied by age at vaccination, by immunocompromise status at vaccination, and by whether the second dose was received later than recommended.

Methods

Study Setting

This prospective cohort study was conducted from 1 January 2018 through 31 December 2022 within the Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention and 9 integrated health care delivery systems with comprehensive electronic medical records that include data on immunizations, diagnoses, and prescriptions (14). This study included 4 VSD sites (3 Kaiser Permanente sites [Northern California, Colorado, and Northwest] and Marshfield Clinic). Recombinant zoster vaccine was available free of charge to nearly all age-eligible members of the 4 participating health plans. The study was approved by the institutional review board at each participating VSD site.

Study Population

The study began on 1 January 2018 with VSD members aged 50 years or older who were eligible for RZV vaccination. Additional members entered the study later when they reached age 50 years. We required at least 12 months of continuous membership before study entry. We excluded members who had already received RZV and those with an HZ diagnosis in the year before study entry. We followed participants until they were diagnosed with HZ, disenrolled from the health plan, or died or until the end of the study on 31 December 2022.

Study Outcome

The outcome was incident HZ, defined as an HZ diagnosis based on International Classification of Diseases, 10th Revision (ICD-10) code B02, together with a prescription for an antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days of diagnosis. In this study, 86% of all first HZ diagnoses received an antiviral prescription and were considered incident HZ cases. The positive predictive value of this incident case definition was estimated to be 96.7%, based on chart review of a sample of 400 cases (50 vaccinated and 50 unvaccinated sampled randomly from each site).

Exposure

The exposure of interest was RZV vaccination status, which was a time-varying variable. All participants started follow-up unvaccinated. The vaccination status of each participant was

monitored over time, and at each time point, participants were categorized as unvaccinated, 1 to 29 days after the first dose, 30 or more days after the first dose, 1 to 29 days after the second dose, or 30 or more days after the second dose. We defined participants as "fully vaccinated" 30 or more days after they received the second dose and as "partially vaccinated" 30 or more days after they received the first dose (protection was expected to begin ≥30 days after vaccination to allow time for the immune response). To assess the effectiveness of RZV in relation to time since vaccination, we further refined our time-varying measure of RZV status based on the interval since receipt of the last dose (30 days to <1 year, 1 to <2 years, 2 to <3 years, or ≥3 years).

To examine whether VE was lower in fully vaccinated persons who were immunocompromised when vaccinated, we subdivided fully vaccinated persons on the basis of whether they used corticosteroids during the 3-month period before the first or second RZV dose. It should be noted that this measure of corticosteroid use is anchored to the time of vaccination and is distinct from the time-varying measure of corticosteroid use at the time of HZ risk. Also, to examine whether VE was lower in fully vaccinated persons who received their second dose after more than the recommended 6 months, we subdivided fully vaccinated persons on the basis of the length of time between the first and second doses (28 days to 6 months [recommended], >6 months to <1 year, and ≥1 year).

Covariates

Estimates of VE were conditioned on calendar time and VSD site and adjusted for time-fixed covariates (sex and race or ethnic group) and time-varying covariates (age, ZVL status, corticosteroid use, influenza vaccination, hospital admission, outpatient visit frequency, and 5 health conditions). Age was specified as 5-year groups from 50 to 89 years and 90 years or older. Zoster vaccine live status was specified as a 5-level indicator (unvaccinated, probably unvaccinated, unknown status, vaccinated <5 years, and vaccinated ≥5 years) and was updated when time since ZVL vaccination reached 5 years. The other 9 time-varying covariates were binary indicators (yes or no). These other covariates were updated quarterly based on a lookback period before the start of each quarter. For 7 of these 9 time-varying covariates, the lookback period was 1 year. For influenza vaccination, the lookback extended to the prior influenza season, and for corticosteroid use, the lookback was 3 months. Corticosteroid use was defined as prior receipt of oral or intravenous corticosteroids. Outpatient visit frequency was calculated as the number of weeks during the prior year in which a person had at least 1 outpatient visit. This measure was dichotomized (after each quarterly update) according to whether the person was above or below the median for their age-sex group. We used diagnoses from outpatient visits during the prior year to adjust for 5 health conditions: diabetes (ICD-10 codes E10 and E11), chronic obstructive pulmonary disease (ICD-10 code J44), coronary heart disease (ICD-10 codes I20 to I25), obesity (ICD-10 code E66), and hypertension (ICD-10 code I10).

We measured corticosteroid use as an incomplete proxy for immunocompromise status that was feasible to measure across all study sites. In a prior study of ZVL effectiveness, we developed an algorithm to identify immunocompromise status, based on a comprehensive set of medications and diagnoses (15). Notably, corticosteroid use identified about 60% of

persons classified as immunocompromised at the time of ZVL vaccination. It is important to note that many immunocompromised persons are not identified by the proxy measure used in this multisite study.

Statistical Analysis

We conducted a descriptive analysis of the study population and vaccine coverage. Among those who received the first dose by 30 September 2022, we used the Kaplan-Meier method to estimate the percentage who received a second dose within the recommended 6 months (183 days) and also within 1 and 2 years after the first dose. We also calculated crude incidence rates of HZ by RZV vaccination status.

We used Cox regression to compare risk for HZ in persons who were vaccinated with risk in otherwise similar persons who were unvaccinated. We fitted several Cox models. Each model was specified with a calendar timeline and stratified by site. Each model included the time-fixed and time-varying covariates described earlier. Thus, vaccine recipients were compared with unvaccinated participants in risk sets that comprised persons at risk for HZ on the same day at the same site. The first model included a 5-level measure of RZV vaccination status: unvaccinated, 1 to 29 days after the first dose, 30 or more days after the first dose, 1 to 29 days after the second dose, and 30 or more days after the second dose. Unvaccinated persons were the reference group. We estimated the HZ hazard ratio for persons who were fully vaccinated and those who were partially vaccinated. We estimated VE as 1 minus the hazard ratio, scaled as a percentage. The second model included an 11-level measure of RZV vaccination status: unvaccinated persons and, for vaccine recipients, 5 groups based on time since receipt of each dose (1 to 29 days, 30 days to <1 year, 1 to <2 years, 2 to <3 years, or ≥3 years). This 11-level measure was used to examine whether VE varied by time since the last dose.

A third set of Cox models was used to examine whether risk for HZ in fully vaccinated persons varied by 3 factors: age at the first dose (50 to 64 and ≥65 years), immunocompromise status at the time of vaccination, and length of time between the first and second doses. Each model was similar to the first model, except that fully vaccinated persons were divided into subgroups based on these 3 factors. In addition, we examined the period before the COVID-19 pandemic (January 2018 through February 2020) using the same Cox model with the 5-level measure of RZV vaccination status described earlier. Finally, we conducted sensitivity analyses without the covariates that could bias VE estimates due to vaccination-confounder feedback. These sensitivity analyses omitted all time-varying covariates except age and ZVL status.

We used SAS, version 9.4 (SAS Institute), to conduct all analyses.

Role of the Funding Source

This study was funded by the Centers for Disease Control and Prevention through contracts with participating sites. The authors had complete control over design, analysis, and the decision to submit the manuscript for publication.

Results

From 2018 through 2022, 1 996 885 persons entered the study population and contributed more than 7.6 million person-years of follow-up. At study entry, 38% of the participants were aged 65 years or older, 53% were female, and 59% were White (Table). During the study period, 761 042 persons (38%) received at least 1 dose of RZV and 576 483 (29%) received 2 doses. The average duration of follow-up was 3.8 years per person. The average duration of follow-up in unvaccinated persons was 3.2 years, which included follow-up before vaccination as well as follow-up of never-vaccinated persons. The average duration of follow-up after vaccination was 1.6 years after the first dose and 1.4 years after the second dose.

Vaccine coverage increased slowly from 2018 through 2020 and more rapidly from 2021 through 2022 (Supplement Figure 1). Among the 1 419 944 persons still in follow-up as of 31 December 2022, 50.4% were unvaccinated, 11.5% had received 1 dose only, and 38.1% had received 2 doses. Among recipients of the first dose, an estimated 68% received the second dose within the recommended 6 months, 81% received the second dose within 1 year, and 90% received the second dose within 2 years (Supplement Figure 2). Throughout the study period, coverage was higher among persons aged 65 years or older compared with those aged 50 to 64 years (Supplement Figure 1).

During follow-up, 45 333 new HZ cases were identified, of which 42 798 (94%) were in unvaccinated persons. The unadjusted incidence of HZ per 1000 person-years was 6.7 among unvaccinated persons, 2.5 among partially vaccinated persons (1 dose only), and 1.7 among fully vaccinated persons (2 doses) (Figure 1).

After adjustment for covariates, VE against HZ was 64% for partially vaccinated persons and 76% for fully vaccinated persons (Figure 1). The analysis that was restricted to the prepandemic period yielded results similar to those for the overall study period; VE was 65% for partially vaccinated persons and 77% for fully vaccinated persons (Supplement Figure 3). The sensitivity analysis that omitted time-varying covariates also yielded similar results (Supplement Tables 1a and 1b).

Among fully vaccinated persons, VE waned very little with time since vaccination; VE was 79% during the first year, 75% during the second year, and 73% both during and after the third year. However, among partially vaccinated persons, VE decreased substantially, from 70% during the first year to 45% during the second year, 48% during the third year, and 52% after the third year (Figure 2).

Among fully vaccinated persons, VE was higher in those who were vaccinated before age 65 years (81%) than in those vaccinated at age 65 years or older (74%) (Figure 3). Vaccine effectiveness was lower in persons who were immunocompromised (defined on the basis of corticosteroid use) when they were vaccinated (65%) compared with those who were not immunocompromised when they were vaccinated (77%). However, VE was similar in persons who received the second dose later than recommended; it was 76% when the interval between doses was within the recommended 6 months, 78% when it was more than 6 months to less than 1 year, and 75% when it was 1 or more years.

Finally, among the covariates, older age, female sex, corticosteroid use, and higher outpatient visit frequency were associated with substantially higher risk for HZ. Risk for HZ was substantially lower in Black persons (vs. White persons and those in other races or ethnic groups) and in persons who had previously received ZVL (Supplement Table 2).

Discussion

This large cohort study found that 2 doses of RZV had effectiveness of 76% against HZ. Effectiveness for fully vaccinated persons waned very little during the 4 years after vaccination. In contrast, although VE for partially vaccinated persons was 70% initially, effectiveness decreased substantially after the first year. Effectiveness for fully vaccinated persons did not differ by whether the second dose was given after the recommended 6 months. Effectiveness was slightly higher in persons vaccinated before age 65 years and somewhat lower in those who were immunocompromised due to corticosteroid use when they were vaccinated.

Our VE estimate of 76% was lower than the estimates from the 2 clinical trials, where VE was 97% among persons aged 50 years or older (7) and 90% among those aged 70 years or older (8). Our findings are generally consistent with those of 3 observational studies that reported VE estimates ranging from 70% to 86% (10–12). One reason our VE estimate was lower than the estimates in the trials may be that our case ascertainment was less specific than in the trials, where cases were confirmed by polymerase chain reaction (PCR) testing. Izurieta and colleagues reexamined data from the clinical trial and found that the VE estimate for persons aged 50 years or older would have been approximately 76%–which is similar to our VE estimate–if it had been based on clinically “suspected cases” before PCR confirmation (10).

We found that the effectiveness of 2 RZV doses waned very little during the 4 years of follow-up. This is broadly consistent with the long-term follow-up of the available trial participants, which found that VE waned only modestly during the 8 years, from 98% in year 1 to 90% in year 4 and 84% in year 8 (13).

Recombinant zoster vaccine is recommended as a 2-dose vaccine series. Although 1-dose VE was 70% in the first year, it decreased to 45% to 52% in the next 3 years, which supports the importance of the second dose. Notably, VE increased after the second dose regardless of whether it was administered within the recommended 6 months after the first dose. This finding provides reassurance about the effectiveness of the second dose even if receipt of it was delayed due to vaccine shortage or other factors.

Subgroup analyses found that VE was lower but still substantial among persons who might have been immunocompromised at the time of vaccination due to recent use of corticosteroids. A recent clinical trial among patients who were immunocompromised after an autologous stem cell transplant similarly reported substantial VE (68%) (16). Additional studies found VE of 87% for patients with hematologic cancer and 91% for those with potential immune-mediated diseases (16–18). Although we found that VE was lower in the subgroup who used corticosteroids in the 3 months before vaccination, we also found that

corticosteroid users were at higher risk for HZ. Taken together, these findings suggest that the number of HZ cases prevented per 100 vaccine recipients in our study population was similar in corticosteroid users and nonusers.

Our study was strengthened by the large size, demographic diversity, and high vaccine coverage of the study population at the 4 VSD sites. Nearly 50% of the study population had received at least 1 dose of RZV by the end of the study period. In addition, our research design and analytic approach facilitated estimation of VE by time since vaccination, age at vaccination, immunocompromise status at vaccination, and time between the first and second doses. We were able to assess vaccine protection for 4 years after vaccination; previous real-world studies included only 1 to 2 years of follow-up (10, 11). The specification of Cox regression with a calendar timeline reduced the potential for confounding arising from the effects of the COVID-19 pandemic on seeking care for shingles; analyses were stratified by “risk sets” comprising persons who were at risk for HZ on the same date at the same VSD site.

The study also had limitations. First, our case ascertainment required an HZ diagnosis code together with an antiviral prescription. With this approach, HZ status was not identified as specifically as in the clinical trials, which required PCR confirmation. This may have lowered our VE estimates. Second, our case ascertainment likely missed some persons with relatively mild cases who did not seek care or presented too late for an antiviral prescription. If RZV was less likely to prevent these undetected milder cases, our VE estimate would be biased upward. Third, our study population was limited to people with health insurance and may not be representative of other populations. Fourth, approximately 27% of the study population was lost to follow-up before the end of the study–7% due to death and another 20% due to disenrollment from their health plan. Fifth, some potential confounders were measured imperfectly or not at all. Although many factors can contribute to immunocompromise, we only measured use of corticosteroids and thereby missed a substantial proportion of immunocompromised persons. However, in our study population, the prevalence of corticosteroid use during follow-up was similar in fully vaccinated and unvaccinated persons. If the prevalence of unmeasured immunocompromise was also similar in fully vaccinated persons and unvaccinated persons, it is unlikely that unmeasured immunocompromise biased our estimate of the effectiveness of full vaccination in the overall study population. On the other hand, if unmeasured immunocompromise was actually more prevalent in vaccinated persons than in unvaccinated persons, this would likely bias the VE estimate downward.

In conclusion, 2 doses of RZV showed high effectiveness that waned very little over 4 years. Our finding of substantial VE among corticosteroid recipients underscores the value of vaccination for these persons, who are at increased risk for HZ. Our finding that the effectiveness of 1 dose decreased after a year further supports the current recommendation for a second dose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer:

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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RZV Vaccination Status	HZ Cases	Person-Years	Unadjusted Rate per 1000 Person-Years	Adjusted VE (95% CI), %
Unvaccinated (reference group)	42 798	6 419 704	6.7	
1–29 d after first dose	314	59 736	5.3	23 (14–31)
≥30 d after first dose (partially vaccinated)	805	321 052	2.5	64 (62–67)
1–29 d after second dose	83	44 943	1.8	74 (68–79)
≥30 d after second dose (fully vaccinated)	1333	768 761	1.7	76 (75–78)

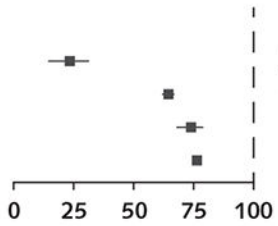

Figure 1. Effectiveness of RZV against HZ, January 2018 to December 2022.

The figure shows the VE estimates obtained from the first model with a 5-level measure of RZV vaccination status. The model was conditioned on Vaccine Safety Datalink site and calendar time and adjusted for age; sex; racial or ethnic group; zoster vaccine live status; corticosteroid use; influenza vaccination; hospital admission; outpatient visit frequency; and diagnoses of diabetes, chronic obstructive pulmonary disease, coronary heart disease, obesity, and hypertension. HZ = herpes zoster; RZV = recombinant zoster vaccine; VE = vaccine effectiveness.

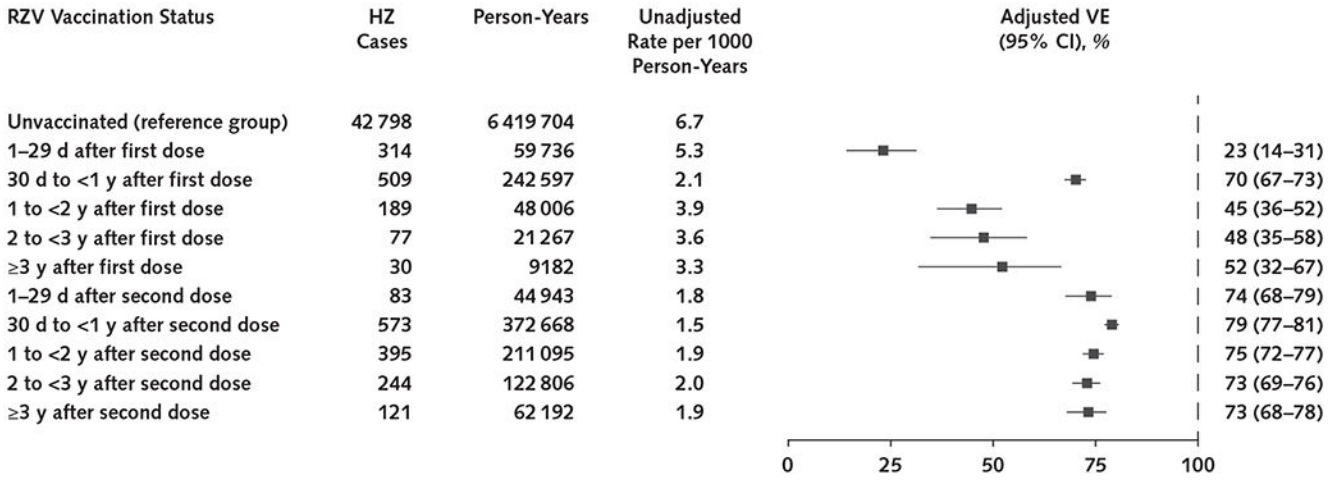

Figure 2. Effectiveness of RZV against HZ, January 2018 to December 2022, by vaccine dose and time since vaccination.

The figure shows the VE estimates obtained from the second model with an 11-level measure of RZV vaccination status. The model was conditioned on Vaccine Safety Datalink site and calendar time and adjusted for age; sex; racial or ethnic group; zoster vaccine live status; corticosteroid use; influenza vaccination; hospital admission; outpatient visit frequency; and diagnoses of diabetes, chronic obstructive pulmonary disease, coronary heart disease, obesity, and hypertension. HZ = herpes zoster; RZV = recombinant zoster vaccine; VE = vaccine effectiveness.

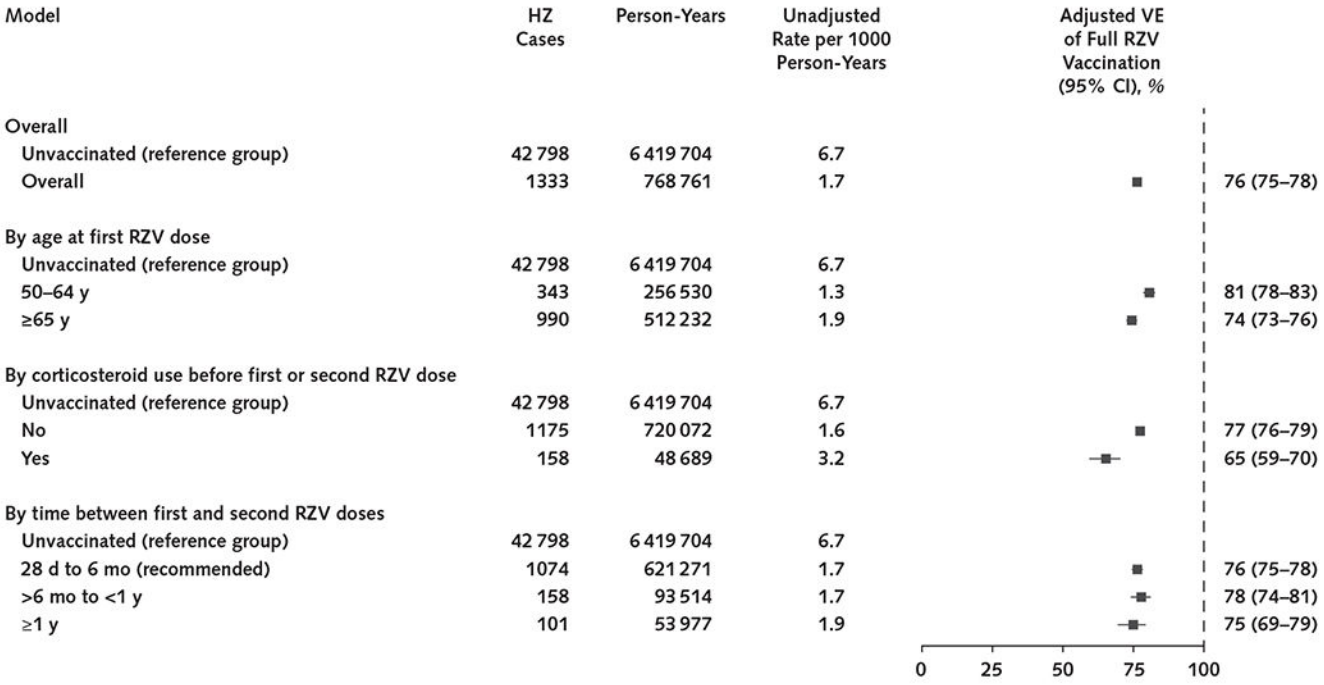

Figure 3. Effectiveness of full vaccination with RZV (≥30 days after second dose) against HZ overall, by age at first dose, by corticosteroid use before vaccination, and by time between doses, January 2018 to December 2022.

The figure summarizes the VE estimates for fully vaccinated persons obtained from 4 models: 1 with a 5-level measure of RZV vaccination status (results shown in Figure 2), and the other 3 similar to the first model except that fully vaccinated persons were divided into subgroups based on age at the first dose, corticosteroid use before vaccination, and time between doses. All models were conditioned on Vaccine Safety Datalink site and calendar time and adjusted for age; sex; racial or ethnic group; zoster vaccine live status; corticosteroid use; influenza vaccination; hospital admission; outpatient visit frequency; and diagnoses of diabetes, chronic obstructive pulmonary disease, coronary heart disease, obesity, and hypertension. HZ = herpes zoster; RZV = recombinant zoster vaccine; VE = vaccine effectiveness.

Table.

Characteristics of the Study Population, January 2018 to December 2022

Characteristic	Participants (*n* = 1 996 885)
Age at study entry, *n (%)*	
50-54 y	620 218 (31.1)
55-59 y	314 032 (15.7)
60-64 y	295 286 (14.8)
65-69 y	257 025 (12.9)
70-74 y	205 031 (10.3)
75-79 y	132 240 (6.6)
80-84 y	88 355 (4.4)
85-89 y	53 520 (2.7)
≥90 y	31 178 (1.6)
Sex, *n* (%)	
Female	1 065 434 (53.4)
Male	931 451 (46.6)
Race or ethnicity, *n* (%)	
White	1 179 399 (59.1)
Black	116 274 (5.8)
Asian	274 858 (13.8)
Hawaiian or Pacific Islander	11 151 (0.6)
Native American or Alaska Native	7496 (0.4)
Other/multiple	57 510 (2.9)
Hispanic (regardless of race)	292 962 (14.7)
Unknown	57 235 (2.9)
ZVL status at study entry, *n* (%) *	
Unvaccinated (known)	963 078 (48.2)
Unvaccinated (probable)	198 489 (9.9)
Unknown	104 935 (5.3)
Vaccinated <5 y	468 268 (23.4)

Characteristic	Participants (*n* = 1 996 885)
Vaccinated ≥5 y	262 115 (13.1)
VSD site, *n* (%)	
A	1 493 318 (74.8)
B	218 231 (10.9)
C	83 868 (4.2)
D	201 468 (10.1)

VSD = Vaccine Safety Datalink; ZVL = zoster vaccine live.

* Recipients of ZVL were categorized as being <5 or ≥5 years since vaccination on the day they entered the study. Among persons with no documented ZVL, those who were VSD members since becoming eligible for ZVL on the basis of age and licensure dates (May 2006 for those aged ≥60 years and March 2011 for those aged 50 to 59 years) were considered to be unvaccinated (known); those who joined the VSD at age ≥60 years after May 2006 were considered to have unknown vaccination status; and those who joined the VSD at age 50 to 59 years after March 2011 were considered to be unvaccinated (probable). (ZVL uptake was very low at ages 50 to 59 years when there was licensure but no Advisory Committee on Immunization Practices recommendation.)