JAMA Ophthalmology | Original Investigation

Risk of Herpes Zoster Ophthalmicus Recurrence After Recombinant Zoster Vaccination

Anushka Walia, BS; Yuwei Sun, MS; Nisha R. Acharya, MD

IMPORTANCE The recombinant zoster vaccine (RZV) is currently recommended for immunocompetent adults aged 50 years or older and immunocompromised adults aged 19 years or older and is effective in preventing herpes zoster ophthalmicus (HZO). However, questions about the safety of RZV in patients with a history of HZO remain.

OBJECTIVE To evaluate whether there is an increased risk of HZO recurrence after RZV in patients with a history of HZO.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used medical and outpatient pharmacy claims data for commercial and Medicare Advantage enrollees from the Optum Labs Data Warehouse. Patients with incident HZO from January 1, 2010, to December 31, 2021, were identified; the study period ended on March 31, 2022. The vaccinated group consisted of patients with at least 1 dose of RZV more than 90 days following the initial HZO diagnosis. The unvaccinated group consisted of patients without any record of RZV in the study period. Vaccinated and unvaccinated patients were matched using exact k:1 matching without replacement.

EXPOSURE Recombinant zoster vaccination.

MAIN OUTCOMES AND MEASURES The main outcome was the number of HZO recurrences with and without RZV exposure.

RESULTS A total of 16 408 patients were included in the matched analysis, of whom 12 762 were unvaccinated (7806 [61.2%] female; mean [SD] age at diagnosis, 68.8 [10.3] years) and 3646 were vaccinated (2268 [62.2%] female; mean [SD] age at diagnosis, 67.4 [9.8] years). Within the primary risk period of 56 days after the index date (ie, the start of follow-up for the outcome), the incidence of HZO recurrence after any RZV exposure was 37.7 per 1000 person-years compared with 26.2 per 1000 person-years in the unexposed group. After controlling for race and ethnicity, inpatient stays, emergency department visits, concomitant vaccines, and eye care practitioner visits, the association between vaccination status and HZO exacerbation in the primary risk period had an adjusted hazard ratio for any RZV exposure of 1.64 (95% CI, 1.01-2.67; $P = .04$).

CONCLUSIONS AND RELEVANCE In this study, RZV exposure was associated with a higher likelihood of HZO recurrence in patients with a history of HZO compared with no RZV exposure. These findings support consideration that patients with a history of HZO may benefit from monitoring after receiving RZV in case of HZO recurrence.

Supplemental content

Author Affiliations: School of Medicine, University of California, San Francisco (Walia); F.I. Proctor Foundation, University of California, San Francisco (Sun, Acharya); Department of Ophthalmology, University of California, San Francisco (Acharya); Department of Epidemiology and Biostatistics, University of California, San Francisco (Acharya).

Corresponding Author: Nisha Acharya, MD, MS, F.I. Proctor Foundation, University of California, San Francisco, 490 Illinois St, 2nd Floor, San Francisco, CA 94158 (nisha.acharya@ucsf.edu).

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2023.6830
Published online February 15, 2024.

Herpes zoster (HZ), also known as shingles, is an infection caused by reactivation of varicella zoster virus (VZV) and affects more than 1 million individuals in the US per year.[1] Herpes zoster ophthalmicus (HZO), occurring in 10% to 25% of HZ cases, arises when VZV involves the ophthalmic division of the fifth cranial nerve. While HZO typically presents as a dermatomal rash on the forehead and eyelid, ocular involvement may occur in some patients. Ocular manifestations of HZO include conjunctivitis, scleritis, keratitis, uveitis, and acute retinal necrosis. Vision loss may result from HZO-related glaucoma, cataracts, keratitis, and retinal scarring. Patients with HZO may also have an increased risk of heart attack and stroke.[2] HZO may be chronic or recurrent in some cases and require ongoing treatment with antivirals and topical corticosteroids. The 5-year recurrence rate of HZO with or without eye involvement has been estimated to be 25%.[3]

Two vaccines directed toward HZ have been approved by the US Food and Drug Administration: zoster vaccine live (ZVL), which was licensed in 2006 and discontinued in 2020, and recombinant zoster vaccine (RZV), which was licensed near the end of 2017. RZV has been found to be effective in preventing HZ and HZO in patients aged 50 years or older in clinical trials and clinical settings.[4,5] These studies on vaccine effectiveness, however, excluded individuals with a prior diagnosis of HZO, and to our knowledge, no published data on RZV safety and effectiveness in these patients currently exists. Several case reports have described reactivation of HZO after RZV and ZVL in patients with a history of HZO.[6-9] The primary manifestation of HZO reactivation in individuals who had received RZV was keratitis and began 1 to 3 weeks after either the first or the second dose of the vaccine. Based on these case reports, the American Academy of Ophthalmology suggests that patients with HZO receive the vaccine only after infection has been well controlled.[10] The US Centers for Disease Control and Prevention currently recommends RZV in immunocompetent adults aged 50 years or older and immunocompromised adults aged 19 years or older, including those with a history of HZ as long as they are not experiencing an acute episode.[11] Further data on the safety of RZV in patients with a history of HZO would be helpful in informing vaccination recommendations for this patient population. This study aimed to evaluate whether there is an increased risk of reactivation of HZO following RZV in patients with a history of HZO.

Key Points

Question Is there an increased risk of reactivation of herpes zoster ophthalmicus (HZO) following administration of recombinant zoster vaccine (RZV) in patients with a history of HZO?

Findings In this cohort study of 16 408 patients, RZV exposure was associated with increased risk of HZO recurrence in patients with prior HZO compared with no RZV exposure.

Meaning These results support consideration that patients with a history of HZO undergo monitoring by an eye care practitioner after receiving RZV in case of HZO recurrence.

Methods

Data Source

This retrospective cohort study used data from the Optum Labs Data Warehouse, a deidentified administrative claims and electronic health record database that includes enrollment information, medical claims, and outpatient pharmacy claims for commercial and Medicare Advantage enrollees of all ages.[12] The Optum Labs Data Warehouse contains detailed longitudinal health information for over 200 million enrollees in the US across a spectrum of ages, genders, and geographic locations. Around 26 million individuals were enrolled in the database in 2020, accounting for 8% of the US population and 12% of the US privately insured population.[13] We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was approved by the institutional review board of the University of California, San Francisco, with informed consent waived due to use of deidentified claims data. This study was conducted in adherence with the tenets of the Declaration of Helsinki.[14]

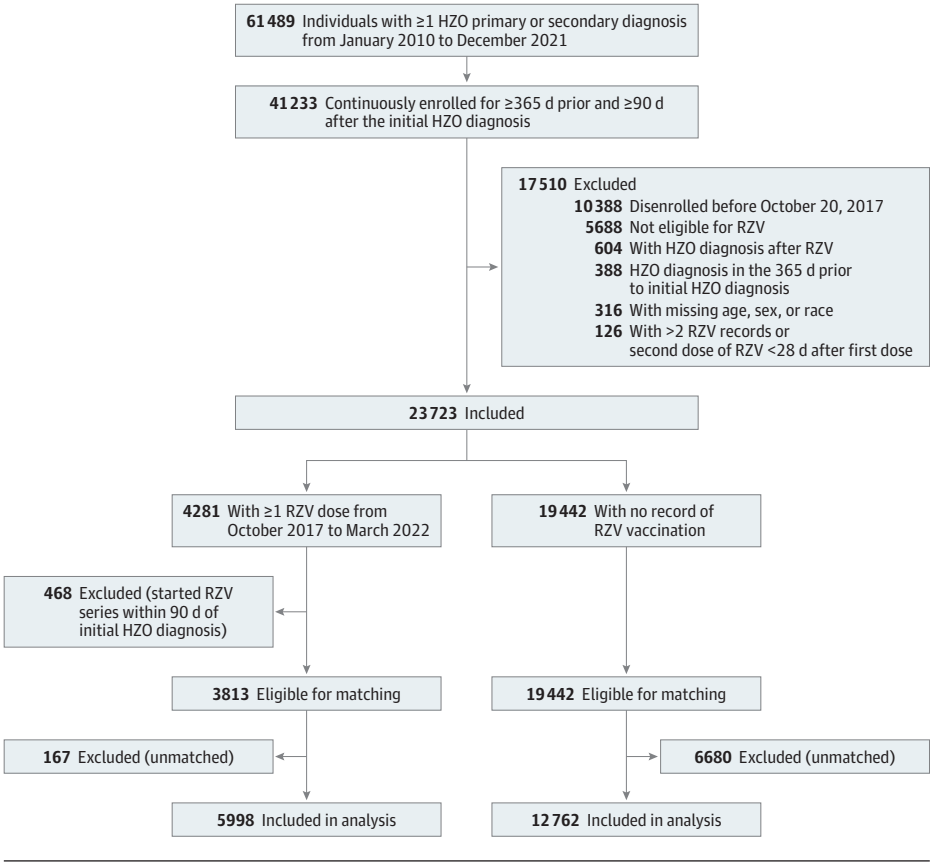
Inclusion and Exclusion Criteria

Patients with incident HZO from January 1, 2010, to December 31, 2021, were identified (eMethods 1 in Supplement 1). The 90-day period following the initial HZO diagnosis was considered part of the initial HZO episode. Patients whose initial HZO diagnosis was before October 20, 2017, had to be aged 50 years or older in 2017 to be eligible, and patients whose initial HZO diagnosis was on or after October 20, 2017, had to be aged 50 years or older at the time of initial HZO diagnosis to be eligible. This was done to avoid RZV exposure misclassification since RZV was approved on October 20, 2017, for people aged 50 years or older. Note that a patient's age was estimated by their year of birth, as the exact date of birth is unavailable to researchers to maintain patient confidentiality. RZV records were extracted from October 20, 2017, to March 31, 2022. The vaccinated group consisted of patients who had received at least 1 dose of RZV more than 90 days following the initial HZO diagnosis. The unvaccinated group consisted of patients without any record of RZV in the study period. **Figure 1** describes the selection process for the cohort.

Matching Scheme

Vaccinated and unvaccinated patients were matched using exact k:1 matching without replacement.[15] Each vaccinated patient was matched to up to 10 unvaccinated control individuals. Matching variables were the following: age at initial HZO diagnosis (40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, or ≥85 years), year of initial HZO diagnosis (each year from 2010 to 2021), and probable ocular involvement at initial HZO episode (yes or no), defined by an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis code indicating HZO ocular involvement or ophthalmic corticosteroid prescription during the initial HZO episode (eTables 2 and 3 in Supplement 1). Those matching variables were chosen since they are related to the

Figure 1. Cohort Selection



HZO indicates herpes zoster ophthalmicus; RZV, recombinant zoster vaccine.

outcome. In a cohort with a history of HZO, the longer the time since the initial HZO episode, the less likely a flare-up occurs. To avoid immortal time bias, the unvaccinated and vaccinated individuals were matched on time so that a patient who received RZV was matched to a nonvaccinated patient who had the same length of follow-up.[16] In addition, since the 2 RZV doses are recommended to be 2 to 6 months apart, matching was performed at the dose level. For example, if patient A received their first RZV dose 200 days after initial HZO diagnosis, this patient was matched to a patient B who had not received RZV 200 days after their initial HZO diagnosis, and both were followed up from that time onward. If patient A received a second dose 300 days after their initial HZO diagnosis, the patient was matched to another patient C who had not received RZV 300 days after their initial HZO diagnosis, and both were followed up from that time onward (eMethods 2 in Supplement 1). For each vaccinated patient, day 0 was the vaccination date and day 1 was the index date (the start of follow-up for the outcome). The index date was assigned to unvaccinated patients so that they had the same time interval (days) between their initial HZO date and index date as the matched vaccinated patients. Those with a resulting index date after March 31, 2022, or before October 20, 2017, were excluded. Matching was implemented by using the MatchIt package in R, version 4.1.0 (R Project for Statistical Computing).

Outcome and Follow-Up

Patients were evaluated for HZO recurrence or exacerbation in 3 biologically plausible and evidence-based risk intervals: 1 to 28 days, 1 to 42 days, and 1 to 56 days after the index date.[6-9,17,18] The period from days 1 through 56 was chosen as the primary risk window to allow enough time for patients with HZO to schedule an appointment with an eye specialist and fill new prescriptions. To qualify as an outcome event, a medication change including dose escalation of previous medications or new prescriptions and an HZO visit (HZO diagnosis at any diagnosis code position) with an optometrist or ophthalmologist within 7 days of the medication change were required. Medications included systemic antivirals, ophthalmic corticosteroids, and systemic corticosteroids (eTables 3 and 4 in Supplement 1). Prescription fills for those medications were identified by text search of drug names in outpatient pharmacy claims. Details on how pharmacy claims were processed and how medication changes were identified are described in eMethods 3 and 4 in Supplement 1. Patients were followed up from the index date until the first occurrence of outcome, disenrollment from the insurance plan, or end of the study period on March 31, 2022. Person-time after dose 2 was censored in the analysis if an outcome event occurred after dose 1. Unexposed person-time (control interval) was contributed by unvaccinated patients only.

Confounders

Demographics included age at initial HZO diagnosis, sex (female, male), race and ethnicity (Asian, Black, Hispanic, White, and unknown), and insurance type (commercial, Medicare Advantage) at the index date. In the Optum Labs Data Warehouse, race and ethnicity are ascertained by a marketing vendor using an algorithm based on names and geographic locations. Race and ethnicity were included as covariates in the analysis to account for variation in HZO recurrence patterns between racial and ethnic groups. HZO disease characteristics in the initial episode included probable ocular involvement, number of eye care practitioner (ophthalmologist or optometrist) visits with an HZ or HZO diagnosis, and prescription for ophthalmic steroids (binary), systemic antivirals (binary), and systemic corticosteroids (binary). These characteristics also served as a surrogate for HZO disease severity. Baseline characteristics in the 180 days prior to the index date included use of immunosuppressive medications (binary) (eTable 6 in Supplement 1), Charlson Comorbidity Index score, and health care utilization categorized by the number of ambulatory visits (office visits, outpatient hospital visits), any inpatient visit (hospital admission and long-term care; binary), and any emergency department visit (binary). An active prescription for systemic antivirals at the index date (binary) was also assessed. Receipt of influenza; pneumococcal; tetanus, diphtheria, and pertussis or tetanus and diphtheria; ZVL; or COVID-19 vaccine within 28 days of the index date was considered to be concomitant vaccination and was categorized as a binary variable (eTable 1 in Supplement 1). COVID-19 diagnosis (binary) in the baseline period was captured by diagnosis code in any type of encounter (eTable 7 in Supplement 1) or a positive polymerase chain reaction test result.

Statistical Analysis

Standardized mean differences (SMDs) were calculated to assess covariate balance in the original analytic sample and matched analytic sample by RZV exposure status. The analytic sample contains dose-level data, as matching was performed by dose level. Dose 1 and dose 2 were analyzed as the same exposure levels (ignoring dose number) and different exposure levels. Cox proportional hazards regression models were used to calculate the unadjusted and adjusted hazards of HZO outcome among exposed person-time compared with the unexposed person-time. Cox proportional hazards regression models were adjusted for covariates with an SMD greater than 0.1 in the matched sample. Since each treated unit could be matched to different numbers of control units, a weight equal to the reciprocal of the matching ratio (*weight* = 1/*k*) was assigned to each control observation in the SMD calculations and Cox proportional hazards regression models.[15] Cluster-robust SEs were used to account for nonuniform weights and dependence between observations within matched strata.[19]

Statistical analyses were performed in R, version 4.1.0. *P* values were 2-sided but were not adjusted for multiple analysis. $P < .05$ was considered statistically significant.

Results

A total of 16 408 patients with initial HZO diagnoses between January 1, 2010, and December 31, 2021, were included in the matched analysis. Of these patients, 12 762 were unvaccinated and 3646 had received RZV, contributing 3492 first doses and 2506 second doses. The distribution of matching ratios is summarized in eTable 8 in Supplement 1. Individual-level demographic characteristics, baseline health characteristics, and HZO disease severity in the initial episode by RZV exposure status are summarized in **Table 1**. Age at initial HZO diagnosis and sex were similar between vaccinated (2268 [62.2%] female; 1378 [37.8%] male; mean [SD] age at diagnosis, 67.4 [9.8] years) and unvaccinated (7806 [61.2%] female; 4956 [38.8%] male; mean [SD] age at diagnosis, 68.8 [10.3] years) patients. Of vaccinated patients, 106 (2.9%) were Asian; 257 (7.0%), Black; 212 (5.8%), Hispanic; and 2992 (82.1%), White; 79 (2.2%) had unknown race and ethnicity. Of unvaccinated patients, 423 (3.3%) were Asian; 1265 (9.9%), Black; 1117 (8.8%), Hispanic; and 9619 (75.4%), White; 338 (2.6%) had unknown race and ethnicity. Disease severity of the initial HZO episode was similar between cohorts. General health status, as measured by the Charlson Comorbidity Index, was also similar between vaccinated and unvaccinated patients, while inpatient stays and emergency department visits were less likely among vaccinated patients. A total of 1183 vaccinated patients (32.4%) received influenza; pneumococcal; tetanus, diphtheria, and pertussis or tetanus and diphtheria; or COVID-19 vaccine within 28 days of RZV receipt. Of unvaccinated patients, 1377 (10.8%) received other vaccines within 28 days of the index date. Standardized mean differences in the original analytic sample and matched analytic sample are summarized in eTable 9 in Supplement 1.

Within the primary risk period of 56 days after the index date, 84 total outcome events consistent with a recurrence of HZO were identified; 36 events (42.9%) were defined by a new prescription of ophthalmic steroids, 28 (33.3%) by a new prescription of systemic antivirals, and 20 (23.8%) by an escalation of systemic antivirals, ophthalmic steroids, or systemic steroids or a new prescription of systemic steroids. **Table 2** summarizes the number of HZO recurrences classified by RZV exposure, risk period, and dose number, with 2 doses of RZV analyzed without distinction of dose level or as different exposure levels. The median time between initial HZO diagnosis and first RZV dose was 661 days (IQR, 292-1500 days). When considering risk periods ranging from 28 to 56 days, the outcome event rate in the unexposed group ranged from 26.2 to 28.4 per 1000 person-years and the outcome event rate after any RZV exposure ranged from 37.7 to 39.7 per 1000 person-years. During the 56-day risk period, there were 34 exacerbations of HZO after any RZV exposure compared with 50 in unexposed person-time. The unadjusted hazard ratio (HR) of HZO recurrence after any exposure to RZV compared with no exposure was 1.93 (95% Cl, 1.20-3.11). The unadjusted HRs corresponding to risk periods of 28 and 42 days after vaccination were 1.91 (95% CI, 1.02-3.58) and 1.85 (95% Cl, 1.10-3.11), respectively.

Table 1. Individual-Level Characteristics by RZV Exposure Status in the Matched Cohort[a]

Characteristic	Vaccinated patients (n = 3 646)	Unvaccinated patients (n = 12 762)
Age at initial HZO diagnosis, y		
Mean (SD)	67.4 (9.8)	68.8 (10.3)
Median (IQR)	68 (59-75)	70 (61-77)
Year of initial HZO diagnosis, No. (%)		
2010	127 (3.5)	414 (3.2)
2011	157 (4.3)	486 (3.8)
2012	128 (3.5)	576 (4.5)
2013	177 (4.9)	601 (4.7)
2014	166 (4.6)	639 (5.0)
2015	267 (7.3)	824 (6.5)
2016	396 (10.9)	1106 (8.7)
2017	548 (15.0)	1549 (12.1)
2018	701 (19.2)	1834 (14.4)
2019	635 (17.4)	2113 (16.6)
2020	288 (7.9)	2099 (16.4)
2021	56 (1.5)	521 (4.1)
Sex, No. (%)		
Female	2268 (62.2)	7806 (61.2)
Male	1378 (37.8)	4956 (38.8)
Race and ethnicity, No. (%)		
Asian	106 (2.9)	423 (3.3)
Black	257 (7.0)	1265 (9.9)
Hispanic	212 (5.8)	1117 (8.8)
White	2992 (82.1)	9619 (75.4)
Unknown	79 (2.2)	338 (2.6)
HZO disease severity in initial episode		
Probable ocular involvement, No. (%)	1595 (43.7)	5375 (42.1)
Eye care practitioner visit, median (IQR)	1 (1-3)	1(1-2)
Systemic antivirals, No. (%)	2247 (61.6)	7958 (62.4)
Systemic corticosteroids, No. (%)	640 (17.6)	2308 (18.1)
Ophthalmic corticosteroids, No. (%)	1110 (30.4)	3500 (27.4)
Time from initial HZO diagnosis to vaccination or index date, median (IQR), d	661 (292-1500)	535 (257-1480)
Insurance type at index date, No. (%)		
Medicare Advantage	2287 (62.7)	8691 (68.1)
Commercial	1359 (37.3)	4071 (31.9)
Health care utilization at baseline		
Inpatient stay or long-term care stay, No. (%)	195 (5.3)	1065 (8.3)
Emergency department, No. (%)	484 (13.3)	2287 (17.9)
Ambulatory visit, median (IQR)	8 (4-14)	7 (3-14)
Charlson Comorbidity Index score at baseline, median (IQR)	3 (2-4)	3 (2-5)
Immunosuppressive medication use at baseline, No. (%)	720 (19.7)	2498 (19.6)
Systemic antivirals active on index date, No. (%)	190 (5.2)	476 (3.7)
Concomitant vaccines, No. (%)	1183 (32.4)	1377 (10.8)
COVID-19 at baseline, No. (%)	21 (0.6)	174 (1.4)

Abbreviations: HZO, herpes zoster ophthalmicus; RZV, recombinant zoster vaccine.

[a] The baseline period for the vaccinated subgroup was the 180 days before RZV dose 1 (or dose 2 if dose 1 was not matched and thus excluded from the matched analysis). The analytic sample was by dose level.

Adjusted HRs of HZO recurrences associated with any RZV dose, dose 1, and dose 2 are reported in **Figure 2**. After adjusting for race and ethnicity, inpatient stays, emergency department visits, concomitant vaccines, and eye care practitioner visits, the association between RZV and HZO exacerbation in the primary risk period had an adjusted HR for any RZV expo-

Table 2. Herpes Zoster Ophthalmicus Outcome Event Rate by Recombinant Zoster Vaccine Exposure and Unadjusted Hazard Ratio

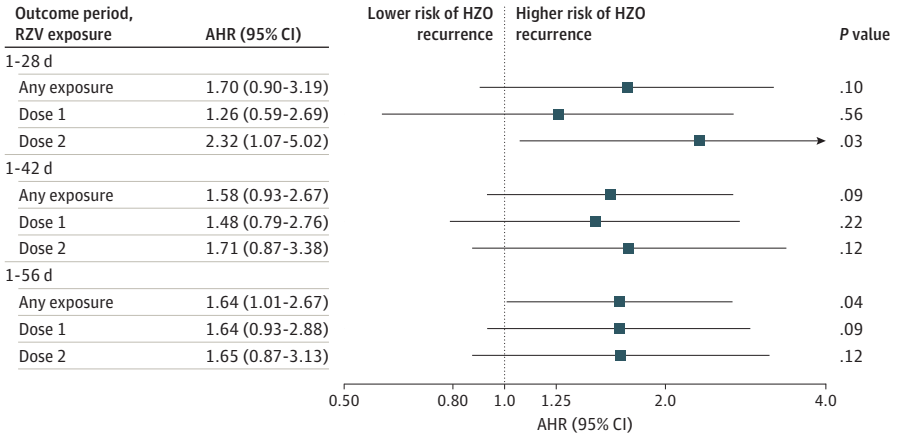
Outcome period, exposure status	Events, No.[a]	Person-years	Outcome event rate, per 1000 person-years	Unadjusted HR (95% CI)[b]
1-28 d				
Unexposed	27	967	27.9	1 [Reference]
Any exposure	18	456	39.5	1.91 (1.02-3.58)
Dose 1	<11	266	<41.4	1.45 (0.65-3.25)
Dose 2	<11	190	<57.8	2.54 (1.19-5.43)
1-42 d				
Unexposed	41	1442	28.4	1 [Reference]
Any exposure	27	680	39.7	1.85 (1.10-3.11)
Dose 1	15	397	37.7	1.76 (0.95-3.26)
Dose 2	12	283	42.4	1.98 (1.01-3.87)
1-56 d				
Unexposed	50	1910	26.2	1 [Reference]
Any exposure	34	901	37.7	1.93 (1.20-3.11)
Dose 1	20	527	37.9	1.95 (1.12-3.37)
Dose 2	14	375	37.4	1.92 (1.03-3.58)

Abbreviation: HR, hazard ratio.

[a] To protect patient privacy, Optum Labs does not allow reporting of the true value of a count if it is less than 11.

[b] Unexposed person-time served as reference group to calculate the HRs of herpes zoster ophthalmicus outcome after any recombinant zoster vaccine exposure (ignoring dose number) after dose 1 and after dose 2.

Figure 2. Adjusted Hazard Ratios (AHRs) of Herpes Zoster Ophthalmicus (HZO) Recurrence Associated With Recombinant Zoster Vaccine (RZV) Exposure



sure of 1.64 (95% CI, 1.01-2.67; P = .04). The association between vaccination and HZO recurrence in the 28-day and 42-day risk periods had adjusted HRs of 1.70 (95% CI, 0.90-3.19; P = .10) and 1.58 (95% CI, 0.93-2.67; P = .09), respectively.

Discussion

This analysis of nationwide insurance claims data suggests that there may be a risk of HZO exacerbation after vaccination associated with RZV in individuals with a history of HZO. Concerns about the safety of ZVL in patients with previous diagnoses of HZO have raised similar safety concerns regarding RZV. A number of case reports[8,9] describe a reactivation of HZO keratitis and keratouveitis after vaccination with ZVL, although an association between ZVL and HZO reactivation was not established by a retrospective cohort study examining vaccine safety.[20] A 2010 survey of the Cornea Society showed that the majority of practitioners were hesitant about recommending ZVL for patients with a history of HZO.[21] Vaccine hesitancy also exists for RZV, as suggested by a recent unpublished survey of Kera-net and the American Uveitis Society by our group. An unpublished survey of cornea and uveitis specialists conducted by our group in 2020 found that 33% of respondents believed it was not safe to administer RZV to patients with HZO with ocular involvement that has resolved, but no studies were available to inform risks. The Centers for Disease Control and Prevention recommends that individuals with a history of HZ receive RZV as long as they are not experiencing an acute episode.[11] However, there has been a lack of data available about the safety of RZV in patients with prior HZO. HZO is different from HZ in that recurrences are more common; thus, it is not surprising that there is some concern about RZV in patients with prior HZO.

The overall safety of RZV has been examined by prelicensure clinical trials and post licensure monitoring using the Vac-

cine Adverse Event Reporting System (VAERS). An analysis of reports to VAERS between October 2017 and June 2018 documented several cases of inflammatory eye disease following RZV vaccination.[22] Of the 14 reports of inflammatory eye disease, 1 patient was noted to have preexisting HZO. A vaccine safety study on RZV recipients found that among 292 individuals with a confirmed past HZ episode, only 1 experienced a recurrence within 30 days after vaccination.[23] To our knowledge, no studies specifically examining the risk of HZO recurrence after receipt of RZV have been published.

In our study, HZO recurrence within the 56-day risk period was found to be 37.7 per 1000 person-years after RZV exposure and 26.2 per 1000 person-years in the unexposed group. There are currently variable data on the incidence of recurrent HZO, with 1 retrospective medical record review of 90 patients with HZO reporting a recurrence rate of 17% within a 3-year follow-up period, equivalent to 57 per 1000 person-years.[3] A retrospective cohort study conducted in South Korea found the HZO recurrence rate to be 14.6%, with a mean time to recurrence of around 6 months.[24] Another study of an Italian cohort of 45 patients with HZO reported a recurrence rate of 51.1%, with an mean follow-up period of around 2 years.[25] Recurrence rates may vary between studies depending on characteristics of the cohorts analyzed, such as the number of patients that received treatment for HZO. Recurrence rates may also be influenced by the use of long-term systemic antiviral prophylaxis.[21] Although most patients received systemic antivirals at the time of initial diagnosis of HZO, antiviral use at the index date was 5.2% in the vaccinated cohort and 3.7% in the unvaccinated cohort. The Zoster Eye Disease Study will provide important information on the usefulness of antiviral prophylaxis in preventing recurrences of HZO.[26]

The etiology of VZV reactivation is not entirely clear, but this reactivation may be due to an immune response to VZV or active viral infection, which may be triggered by suppressed cell-mediated immunity. A study[27] showed that viral DNA is present in the cornea of individuals with HZO during periods of latency, suggesting that infection may not be fully resolved even when clinical signs are not present. As RZV does not contain live virus, the mechanism of vaccine-related HZO reactivation is likely not reinfection by VZV but may be an immune response to 1 or more components of the vaccine resulting in upregulation of transcription of viral DNA already present. RZV is effective for preventing HZ and HZO and encouraging vaccination is important, especially given the rising incidence of HZ in the US and its potential complications.[4,5,28]

Limitations

This study has several potential limitations. First, the lower bound of the 95% CI of the adjusted HR for HZO recurrence during the primary risk period approached 1.0. Adjusted HRs for HZO recurrence in the 28-day and 42-day risk periods were not statistically significant. In addition, because recurrent and new cases of HZO cannot be distinguished based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes, new medications and medication changes were used as surrogate measures of HZO exacerbation. Patients were also required to have an eye care practitioner visit within a week of their medication change to qualify as having an HZO recurrence. This conservative outcome definition was intended to reduce misclassification of HZO but may have underestimated the true rate of HZO recurrence, as patients who had an HZO exacerbation but did not seek treatment or visit an eye care practitioner would not be captured in our outcome definition. In addition, the relatively rare outcome of recurrent HZO precluded subgroup analysis by time since HZO diagnosis or by severity of disease, but the adjusted analysis accounted for these potential confounders. There were also some differences between vaccinated and unvaccinated cohorts, particularly regarding race and ethnicity, eye care practitioner visits, baseline health care utilization, and concomitant vaccines, but we accounted for this in the Cox proportional hazards regression models. While 32.4% of patients in the RZV group received concomitant vaccines, 10.8% of patients who did not receive RZV received other vaccines within 28 days of the index data. Whether other vaccines are linked to ocular inflammation warrants further investigation. Lastly, since the Optum Labs Data Warehouse only includes patients with commercial insurance, Medicare Part D, and Medicare Advantage plans, data may not be generalizable to individuals with other insurance plans or without insurance.

Conclusions

In this retrospective cohort study, RZV was associated with an increased risk of HZO exacerbation in patients with a history of HZO compared with no RZV exposure. These results support consideration that patients with a history of HZO undergo monitoring by an eye care practitioner after receiving RZV in case of HZO recurrence.

ARTICLE INFORMATION

Accepted for Publication: December 10, 2023.

Published Online: February 15, 2024. doi:10.1001/jamaophthalmol.2023.6830

Author Contributions: Ms Sun and Dr Acharya had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtained funding: Acharya.
Administrative, technical, or material support: Acharya.
Supervision: Acharya.

Conflict of Interest Disclosures: Dr Acharya reported being an adviser for Roche outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by grant R01 EY028739 from the National Eye Institute and Office of Research on Women's Health, National Institutes of Health (PI Acharya) and an Optum Labs Data Warehouse research credit. The Department of Ophthalmology at University of California, San Francisco, is supported by core grant EY06190 from the National Eye Institute and an unrestricted grant from the Research to Prevent Blindness Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study;

collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Rimland D, Moanna A. Increasing incidence of herpes zoster among veterans. *Clin Infect Dis*. 2010; 50(7):1000-1005. doi:10.1086/651078

2. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. *Neurology*. 2010;74(10):792-797. doi:10.1212/WNL.0b013e3181d31e5c

3. Tran KD, Falcone MM, Choi DS, et al. Epidemiology of herpes zoster ophthalmicus: recurrence and chronicity. *Ophthalmology*. 2016; 123(7):1469-1475. doi:10.1016/j.ophtha.2016.03.005

4. Lu A, Sun Y, Porco TC, Arnold BF, Acharya NR. Effectiveness of the recombinant zoster vaccine for herpes zoster ophthalmicus in the United States. *Ophthalmology*. 2021;128(12):1699-1707. doi:10.1016/j.ophtha.2021.04.017

5. Sun Y, Kim E, Kong CL, Arnold BF, Porco TC, Acharya NR. Effectiveness of the recombinant zoster vaccine in adults aged 50 and older in the United States: a claims-based cohort study. *Clin Infect Dis*. 2021;73(6):949-956. doi:10.1093/cid/ciab121

6. Lu TJ, Ta CN. Reactivation of herpes zoster keratitis following Shingrix vaccine. *Case Rep Ophthalmol*. 2022;13(1):104-108. doi:10.1159/000522272

7. Jabbour S, Shekhawat NS, Chen A, Woreta FA. Presumed herpes zoster ophthalmicus reactivation following recombinant zoster vaccination. *Cornea*. 2021;40(2):248-250. doi:10.1097/ICO.0000000000002537

8. Khalifa YM, Jacoby RM, Margolis TP. Exacerbation of zoster interstitial keratitis after zoster vaccination in an adult. *Arch Ophthalmol*. 2010;128(8):1079-1080. doi:10.1001/archophthalmol.2010.142

9. Jastrzebski A, Brownstein S, Ziai S, Saleh S, Lam K, Jackson WB. Reactivation of herpes zoster keratitis with corneal perforation after zoster vaccination. *Cornea*. 2017;36(6):740-742. doi:10.1097/ICO.0000000000001203

10. American Academy of Ophthalmology. Recommendations for herpes zoster vaccine for patients 50 years of age and older—2018. Accessed June 3, 2023. https://www.aao.org/education/clinical-statement/recommendations-herpes-zoster-vaccine-patients-50-

11. US Centers for Disease Control and Prevention. Herpes zoster Shingrix vaccine recommendations. May 6, 2022. Accessed June 10, 2022. https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html

12. Optum Labs and Optum Labs Data Warehouse. Descriptions and citation. March 2022. Accessed November 29, 2023. https://www.optumlabs.com/

13. Keisler-Starkey K, Bunch LN. Health insurance coverage in the United States: 2019.

14. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

15. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci*. 2010;25(1):1-21. doi:10.1214/09-STS313

16. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. doi:10.1136/bmj.b5087

17. Lehmann A, Matoba A. Reactivation of herpes zoster stromal keratitis after HZ/su adjuvanted herpes zoster subunit vaccine. *Ophthalmology*. 2018;125(11):1682. doi:10.1016/j.ophtha.2018.08.030

18. Rowhani-Rahbar A, Klein NP, Dekker CL, et al; Risk Interval Working Group of the Clinical Immunization Safety Assessment Network. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine*. 2012;31(1):271-277. doi:10.1016/j.vaccine.2012.07.024

19. Greifer N. Estimating effects after matching. estimating effects after matching. Accessed April 21, 2022. https://cran.r-project.org/web/packages/MatchIt/vignettes/estimating-effects.html

20. Liu RT, Yeung SN, Carleton B, Etminan M. Risk of anterior segment complications associated with the live herpes zoster vaccine: evidence from a health-claim database. *Cornea*. 2018;37(8):952-956. doi:10.1097/ICO.0000000000001595

21. Sy A, McLeod SD, Cohen EJ, et al. Practice patterns and opinions in the management of recurrent or chronic herpes zoster ophthalmicus. *Cornea*. 2012;31(7):786-790. doi:10.1097/ICO.0b013e31823cbe6a

22. Hesse EM, Shimabukuro TT, Su JR, et al. Postlicensure safety surveillance of recombinant zoster vaccine (Shingrix)—United States, October 2017–June 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(4):91-94. doi:10.15585/mmwr.mm6804a4

23. Ocran-Appiah J, Boutry C, Hervé C, Soni J, Schuind A; ZOSTER-056 Study Group. Safety of the adjuvanted recombinant zoster vaccine in adults aged 50 years or older: a phase IIIB, non-randomized, multinational, open-label study in previous ZOE-50 and ZOE-70 placebo recipients. *Vaccine*. 2021;39(1):6-10. doi:10.1016/j.vaccine.2020.10.029

24. Lee SM, Han J, Yang CM, et al. Chronic and recurrent herpes zoster ophthalmicus. *Medicina (Kaunas)*. 2021;57(10):999. doi:10.3390/medicina57100999

25. Miserocchi E, Fogliato G, Bianchi I, Bandello F, Modorati G. Clinical features of ocular herpetic infection in an italian referral center. *Cornea*. 2014; 33(6):565-570. doi:10.1097/ICO.0000000000000129

26. Cohen EJ, Hochman JS, Troxel AB, Colby KA, Jeng BH; ZEDS Trial Research Group. Zoster Eye Disease Study: rationale and design. *Cornea*. 2022; 41(5):562-571. doi:10.1097/ICO.0000000000002743

27. Wenkel H, Rummelt V, Fleckenstein B, Naumann GOH. Detection of varicella zoster virus DNA and viral antigen in human eyes after herpes zoster ophthalmicus. *Ophthalmology*. 1998;105(7): 1323-1330. doi:10.1016/S0161-6420(98)97042-7

28. Thompson RR, Kong CL, Porco TC, Kim E, Ebert CD, Acharya NR. Herpes Zoster and postherpetic neuralgia: changing incidence rates from 1994 to 2018 in the United States. *Clin Infect Dis*. 2021;73 (9):e3210-e3217. doi:10.1093/cid/ciaa1185