

Risk of herpes zoster ophthalmicus following COVID-19 vaccination in a large US claims database

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Purpose

- Herpes zoster ophthalmicus (HZO) after COVID-19 vaccination has been reported in multiple case studies. It is unknown whether an association exists, or if the case studies represent increased reporting in a time of great attention on COVID-19 vaccine adverse events.
- This uncertainty contributes to vaccine hesitancy, particularly in patients with pre-existing disease, and highlights the need for evidence-based guidelines.
- Aim:** To determine whether there is an increased risk of HZO following COVID-19 vaccination.

Methods

Data source

Retrospective observational study utilizing Optum Labs Data Warehouse, a US longitudinal, real-world data asset with de-identified administrative claims and electronic health record data.

Main outcome

HZO following vaccination was defined by an ICD-10 diagnosis code within 30 days after vaccine administration (or up to the second dose if a second dose was administered), plus a new prescription or dose escalation of antivirals within 5 days of HZO diagnosis.

Study populations & analyses

Cohort study design: COVID-19 vaccinated individuals from 12/11/2020- 6/30/2021 were compared to two influenza-vaccinated cohorts: a pre-pandemic group (1/1/2018-12/13/2019) and an early pandemic group (3/1/2020-11/1/2020). Cox proportional hazard models were used to calculate unadjusted and adjusted hazard ratios for HZO.

Self-controlled design: The incidence rate ratio comparing the risk of HZO in the risk intervals following COVID-19 vaccination to a control interval 60 to 90 days prior to first dose was estimated using conditional Poisson regression.

Table 1. Characteristics of patients included in cohort study by vaccine type

Characteristic	COVID-19 vaccinated	Influenza vaccinated pre-pandemic	Influenza vaccinated early pandemic
Total patients	1 959 157 (100.0%)	4 545 838 (100.0%)	3 623 307 (100%)
Age			
Mean (SD)	43.4 (16.3)	56.6 (20.6)	58.8 (20.0)
Median [Q1, Q3]	44.0 [31.0, 57.0]	62.0 [41.0, 73.0]	65.0 [46.0, 74.0]
Gender			
Female	991 089 (50.6%)	2 550 645 (56.1%)	2 047 282 (56.5%)
Male	967 916 (49.4%)	1 994 794 (43.9%)	1 575 789 (43.5%)
Race/ethnicity			
White	1 297 664 (66.2%)	3 246 964 (71.4%)	2 567 990 (70.9%)
Asian	134 706 (6.9%)	216 652 (4.8%)	173 341 (4.8%)
Black	135 837 (6.9%)	446 078 (9.8%)	330 927 (9.1%)
Hispanic	197 620 (10.1%)	413 970 (9.1%)	320 115 (8.8%)
Healthcare utilization			
Ambulatory visit count			
Mean (SD)	10.4 (14.3)	18.5 (23.7)	17.3 (22.7)
Median [Q1, Q3]	6.00 [2.00, 13.0]	11.0 [5.00, 23.0]	11.0 [5.00, 21.0]
Inpatient visit ever	269240 (13.7%)	1119523 (24.6%)	769475 (21.2%)
Medical history			
HZO history	924 (0.0%)	4350 (0.1%)	3444 (0.1%)
Asthma	97806 (5.0%)	350132 (7.7%)	262905 (7.3%)
Autoimmune disease	116777 (6.0%)	478283 (10.5%)	378259 (10.4%)
Cancer	55594 (2.8%)	347600 (7.6%)	286321 (7.9%)
Cardiovascular disease	70312 (3.6%)	684424 (15.1%)	552103 (15.2%)
Chronic kidney disease	43393 (2.2%)	493125 (10.8%)	423539 (11.7%)
Chronic lung disease	39733 (2.0%)	506530 (11.1%)	370803 (10.2%)
Diabetes (any type)	157715 (8.1%)	960966 (21.1%)	769311 (21.2%)
HIV/AIDS	5134 (0.3%)	17836 (0.4%)	12277 (0.3%)
Solid organ transplantation	4094 (0.2%)	21876 (0.5%)	17457 (0.5%)
Recent COVID-19 infection	19538 (1.0%)	N/A	51577 (1.4%)
Received zoster vaccine	158494 (8.1%)	579596 (12.8%)	709668 (19.6%)
Medication use			
Systemic corticosteroids	10559 (0.5%)	84836 (1.9%)	57986 (1.6%)
Other immunosuppressants	36103 (1.8%)	142048 (3.1%)	120841 (3.3%)
Antivirals	14071 (0.7%)	44313 (1.0%)	34115 (0.9%)

- Compared to COVID-19 vaccinated cohorts, the influenza vaccinated cohorts were older and had a higher prevalence of comorbid disease.

Table 2. Descriptive analysis of HZO cases in the 30 days following diagnosis by vaccine type

Characteristic	COVID-19 vaccine (N=57)	Influenza vaccine pre-pandemic (N=181)	Influenza vaccine early pandemic (N=124)
ICD-10 code for ocular involvement	13 (22.8%)	56 (30.9%)	44 (35.5%)
Treated with ophthalmic steroids	<11 (<19.3%)	53 (29.3%)	50 (40.3%)
Still on antivirals at 30 days	<11 (<19.3%)	29 (16.0%)	31 (25.0%)
Number of visits to eye care provider			
Mean (SD)	1.54 (1.31)	1.63 (1.41)	1.87 (1.39)
Median [Min, Max]	1.00 [0, 6.00]	1.00 [0, 8.00]	2.00 [0, 6.00]

- HZO cases following influenza vaccination were more likely to have intraocular involvement.

Table 3. Risk of HZO following COVID-19 vaccine vs influenza vaccine pre-pandemic

Characteristic	HZO cases	Person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p
Vaccine type					
Influenza 2018-2019	181	373367.4	Reference	Reference	
COVID-19	57	257608.7	0.45 (0.33, 0.61)	0.84 (0.60, 1.17)	0.297
Age (years)	--	--	1.04 (1.03, 1.05)	1.03 (1.02, 1.04)	<0.001
Healthcare utilization					
Ambulatory visit count	--	--	1.010 (1.008, 1.011)	1.004 (1.001, 1.007)	0.013
Medical history					
HZO	44	476.7	300.7 (216.7, 417.2)	157.5 (110.7, 224.2)	<0.001
Autoimmune disease	47	54723.2	2.60 (1.89, 3.57)	1.50 (1.05, 2.14)	0.025
HIV/AIDS	<11	2139.3	3.76 (1.2, 11.74)	3.57 (1.13, 11.28)	0.030
Received RZV or ZVL vaccine	26	68829.6	1.00 (0.67, 1.51)	0.57 (0.38, 0.86)	0.007
Medication use					
Antivirals	19	5500.3	9.88 (6.18, 15.78)	2.94 (1.80, 4.79)	<0.001

Adjusted models include all variables in Table 1. Main results and significant results after adjustment are shown here.

- There was no increase in risk of HZO following COVID-19 vaccination compared to influenza vaccination in a pre-pandemic period.
- History of HZO, autoimmune disease, HIV/AIDS, and antivirals were significantly associated with an increased risk of HZO, while zoster vaccination was protective.

Table 4. Risk of HZO following COVID-19 vaccine vs influenza vaccine early pandemic

Characteristic	HZO cases	Person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p
Vaccine type					
Influenza 2020	124	297596.9	Reference	Reference	
COVID-19	57	257608.7	0.52 (0.38, 0.71)	0.93 (0.63, 1.36)	0.703
Age (years)	--	--	1.03 (1.02, 1.04)	1.02 (1.01, 1.03)	<0.001
Race/ethnicity					
White	>124	382083.5	Reference	Reference	
Hispanic	<11	52088	0.45 (0.22, 0.91)	0.47 (0.23, 0.97)	0.041
Medical history					
HZO	35	402.4	331.9 (229.2, 480.5)	185.8 (123.5, 279.4)	<0.001
Diabetes (any type)	23	35631.8	2.14 (1.38, 3.31)	1.47 (1.03, 2.1)	0.034
Received RZV or ZVL vaccine	<11	1971	4.75 (1.52, 14.88)	0.36 (0.22, 0.60)	<0.001
Medication use					
Antivirals	17	4662.6	12.26 (7.44, 20.21)	3.64 (2.11, 6.29)	<0.001

Adjusted models include all variables in Table 1. Main results and significant results after adjustment are shown here.

- There was no increase in risk of HZO following COVID-19 vaccination compared to influenza vaccination in an early pandemic period.
- History of HZO, diabetes, and antivirals were significantly associated with an increased risk of HZO, while zoster vaccination was significantly associated with a decreased risk of HZO.

Self-controlled design results

- Patients were not at an increased risk of HZO following COVID-19 vaccination compared to their control interval (IRR = 0.88; 95% CI: 0.58 – 1.33; p = 0.53).
- No signal of association was seen when analyses were stratified by type of COVID-19 vaccine administered.

Subgroup	Incidence Rate Ratio (95% CI)	p
BNT162b2	1.10 (0.63, 1.97)	0.737
mRNA-1273	0.70 (0.36, 1.36)	0.288
Ad26.COVS.2	0.50 (0.07, 2.56)	0.423

Conclusions

- This large retrospective observational study did not find an increased risk of HZO following COVID-19 vaccination.
- These results provide reassurance for the safety of the COVID-19 vaccine from an ophthalmic standpoint.
- As COVID-19 vaccine recommendations continue to evolve, further research is needed to determine the impact of additional doses and boosters on risk of HZO.

References

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