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Herpetic Eye Disease After SARS-CoV-2 Vaccination: A CDC-VAERS Database Analysis

Rohan Bir Singh, MD,†‡ Uday Pratap Singh Parmar,§ Parul Ichhpujani, MBBS, MS,§ Bennie H. Jeng, MD, MS,¶ and Vishal Jhanji, MD,‖*

Purpose: The aim of this study was to evaluate the cases of herpes simplex and zoster ophthalmicus after SARS-CoV-2 vaccination and assess the clinical presentations in patients.

Methods: A retrospective analysis of cases reported to the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS) between December 11, 2020, and July 1, 2022. Patients diagnosed with herpes simplex ophthalmicus (HSO) and herpes zoster ophthalmicus (HZO) after vaccination with BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen) were included in the study. We performed a descriptive analysis of patient demographics, history, and ophthalmic and systemic clinical presentations. The correlations between vaccine type and continuous variables were assessed by the one-way analysis of variance test. In addition, we used the Pearson χ^2 test to assess the association between 3 vaccines and categorical variables. A post hoc analysis was performed between HSO and HZO onset intervals after vaccination, dose, and vaccine type. The 30-day risk analysis was also performed for HSO and HZO onset postvaccination using the reverse Kaplan–Meier analysis.

Results: A total of 1180 cases of HZO (983, 83.30%) and HSO (180, 15.25%) were reported. The mean age of patients with HZO and HSO was 59.02 ± 19.05 and 52.68 ± 17.83 years, respectively. Most of the cases of HZO (795, 80.87%) and HSO (131, 72.78%) were reported in patients who received BNT162b2. In the cohort, 63.28% and 65.56% diagnosed with HZO and HSO were women. About one third of HZO (36.52%) and HSO (35.56%) cases were reported after the first dose. More than half of the cases of HZO (61.34%) and HSO (64.45%) were reported within the first 2 weeks after vaccination. The estimated crude reporting rate (per million doses) in the United States was 0.25, 0.22, and 0.47 for BNT162b2, mRNA-1273, and Ad26.COV2.S, respectively. The onset interval for HZO was significantly shorter in patients who received BNT162b2 (20.51 ± 56.20 days, $P = 0.030$) compared with patients who received mRNA-1273 (36.56 ± 108.67 days) and Ad26.COV2.S (39.66 ± 60.15 days) vaccines. The 30-day risk analysis showed a significantly higher risk of HZO after BNT162b2 than the other 2 vaccines ($P = 0.011$).

Conclusions: The low crude reporting rate suggests that HZO and HSO after SARS-CoV-2 vaccination occur rarely. This study provides insights into the possible temporal association between reported HSO and HZO after SARS-CoV-2 vaccines; however, further investigations are required to delineate the possible underlying immunological mechanisms.

Key Words: herpetic eye disease, SARS-CoV-2 vaccine, herpes zoster ophthalmicus, herpes simplex ophthalmicus, COVID-19

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Since the outbreak of the COVID-19 pandemic, global efforts to mitigate the clinical effects and spread of severe acute respiratory syndrome coronavirus (SARS-CoV-2) have primarily focused on rapid development and administration of vaccines. Over the past 2 years, development of 336 vaccines using different platforms was initiated and 32 vaccines have received emergency use authorization (EUA) worldwide.[1] In the United States, the first vaccine, BNT162b2 (Pfizer Inc./BioNTech SE, Mainz, Germany), received EUA on December 11, 2020, from the United States Food and Drug Administration (FDA).[2] Since then, 2 other vaccines, mRNA-1273 (Moderna Therapeutics Inc, Cambridge, MA) and Ad26.COV2.S (Janssen Pharmaceuticals, Beerse, Belgium), have received EUAs. The BNT162b2 and mRNA-1273 consist of nucleoside-modified mRNA (formulated in lipid nanoparticles), which encodes for membrane-anchored, full-length SARS-CoV-2 spike protein. The transient expression of the spike protein antigen induces neutralizing antibodies and cellular immune responses against it, thus conferring protection to the recipient against SARS-CoV-2.[3,4] The Ad26.COV2.S vaccine uses a recombinant replication-incompetent adenovirus type 26 as a vector for delivering the SARS-CoV-2 spike protein genetic code, generating an immune response against the virus.[5–7] In 1990, the Centers for Disease Control and Prevention (CDC) established the Vaccine Adverse Event Reporting System (VAERS) that acts as an early warning system for potential vaccine-related adverse events for FDA-approved vaccines.[8] VAERS records clinical data for several ophthalmic disorders, including

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From the *Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston †Department of Ophthalmology, Leiden University Medical Center, Leiden, the Netherlands; ‡Discipline of Ophthalmology and Visual Sciences, Faculty of Health and Medical Sciences, Adelaide Medical School, University of Adelaide, Australia; §Department of Ophthalmology, Government Medical College and Hospital, Chandigarh, India; ¶Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA ‖Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, PA

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Correspondence: Vishal Jhanji, MD, Professor of Ophthalmology, University of Pittsburgh School of Medicine 203 Lothrop St, Room 833, Pittsburgh, PA 15213 (e-mail: jhanjiv@upmc.edu)

herpes simplex and zoster ophthalmicus (HSO and HZO), as possible adverse events after vaccination.[9] Although the precise underlying mechanism that causes herpetic eye disease after vaccination has not been elucidated yet, cases of herpetic eye disease have been reported after BNT162b2, AZD1222, mRNA-1273, and CoronaVac vaccine administration highlighting a possible association.[10]

For deeper insights into the temporal association between herpetic eye disease and the 3 FDA emergency-use–authorized SARS-CoV-2 vaccines, we analyzed a large cohort of these cases reported to the VAERS over the past 20 months. In this article, we determine the crude reporting rate of HSO and HZO in the United States since the initiation of the vaccination program. We also report the clinical characteristics of patients diagnosed with HSO and HZO and assess the association between demographics and disease onset duration after vaccination.

METHODS

Data Source

We conducted this retrospective database analysis using the data obtained from the CDC-VAERS database (Centers for Disease Control and Prevention, Atlanta, GA). The clinical adverse event data after administration of FDA-approved vaccines reported to VAERS are publicly available, deidentified, and anonymized, and it is reported by patients, parents (for minor patients), clinicians, vaccine manufacturers, and regulatory bodies globally. These data are accessible through the Wide-ranging Online Data for Epidemiologic Research (WONDER) interface operated by the CDC.[11] The data collected in VAERS include patient demographic information, vaccination and adverse event onset date, brief medical history, comorbidities, previous adverse events, and a detailed report of the clinical signs and symptoms and diagnoses of the adverse events after vaccination. The CDC and FDA review the adverse event reports that seem to be false or fabricated before listing them on the database. A false VAERS report violates federal law (18 U.S. Code § 1001) and is punishable by a fine and imprisonment. The submitted reports are stratified and coded by third party coders and assigned appropriate medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) terms.[12] On requesting the appropriate authorities for permission to analyze and publish these data, we were informed that the CDC WONDER allows access to the information freely for use, copy, distribution, or publication of this information without additional or explicit permission.[13] This study was conducted in compliance with the tenets of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research 2007. Since this study includes publicly available, deidentified, anonymous data, the University of Adelaide Human Research Ethics Committee exempted it from ethical review (Reference No. 36126).

STUDY POPULATION

This study cohort includes patients with adverse events categorized as HSO, HZO, and ophthalmic herpes who had received BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines between December 11, 2020, and July 1, 2022. The data were organized into symptoms, age, sex, location, and onset interval. The data included adverse event descriptions, laboratory data, current illness, adverse events after previous vaccinations, medications at the time of vaccination, and allergies. The data points of interest were manually extracted (by RBS and UP) from the unstructured adverse event descriptions for analysis.

Statistical Analysis

The statistical analysis was performed using R Studio (R Foundation for Statistical Computing, Vienna, Austria). The crude reporting rates were estimated using frequency of HSO and HZO cases reported (by vaccine type) per million doses of SARS-CoV-2 vaccine. A descriptive analysis of the demographic characteristics and vaccination data was performed. The association between the onset interval of HSO and HZO and vaccine type, age (by decade), sex, and dosage were evaluated using the one-way analysis of variance test. As the history of COVID-19 and ocular and systemic presentations are categorical variables, the Pearson χ^2 test of association was used to assess the risk associated with the 3 vaccines. A post hoc analysis was performed to evaluate the variability in HSO and HZO onset duration with dose and vaccine type. A 30-day reverse Kaplan–Meier risk analysis for the 3 vaccines was also performed. The Na.rm code accounted for the missing data in the analysis. The value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 2,715,605,142 doses of BNT162b2 (2,009,774,448), mRNA-1273 (641,160,920), and Ad26.COV2.S (64,669,774) were administered between December 11, 2020, and July 1, 2022. During this period, 1180 cases of herpes ophthalmicus [including 983 (83.30%) and 180 (15.25%) cases of HSO and HZO, respectively] were reported to the CDC-VAERS. The causative organism was not identified in 17 cases. The mean ages of the patients diagnosed with HZO and HSO were 59.02 ± 19.05 and 52.68 ± 17.83 years, respectively. A similar proportion of patients with HZO (622, 63.28%) and HSO (118, 65.56%) were women. The demographic data of the patients are summarized in Table 1. Most of the patients had received BNT162b2 vaccine (HZO: 80.87%, HSO: 72.78%), followed by mRNA-1273 (HZO: 17.40%, HSO: 25.56%). Only 13 patients (1.32%) with HZO and 3 with HSO (1.67%) had received Ad26.COV2.S vaccine. A comparable proportion of HZO and HSO cases were reported after all vaccine doses. Approximately half of the cases of HZO (47.10%) and HSO (51.67%) were diagnosed in the first week after vaccination. These included 139 (14.14%) HZO and 16 (8.89%) HSO cases reported on the day of vaccination.

As the adverse event data recorded by VAERS are only limited to the 3 FDA-approved vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S), a higher proportion of HZO and HSO cases were reported from Europe (HZO: 84.44%, HSO: 77.22%) and North America (HZO: 12.21%, HSO: 17.78%) where these vaccines are primarily in use,

TABLE 1. Demographics and Vaccine Data of Patients Who Were Diagnosed With Herpes Zoster and Herpes Simplex Ophthalmicus After SARS-CoV-2 Vaccinations

	Herpes Zoster Ophthalmicus		Herpes Simplex Ophthalmicus			
	N = 983	%	N = 180	%	χ^2	*P*
Mean age (in yr)*	59.02 ± 19.05	52.68 ± 17.83				
Age**						
0–10	4	0.41	0	0.00	18.151	<0.0001
11–20	20	2.03	3	1.67		
21–30	41	4.17	12	6.67		
31–40	99	10.07	21	11.67		
41–50	122	12.41	34	18.89		
51–60	149	15.16	38	21.11		
61–70	200	20.35	14	7.78		
71–80	148	15.06	14	7.78		
81–90	122	12.41	12	6.67		
91–100	25	2.54	3	1.67		
Unknown	53	5.39	29	16.11		
Sex**						
Female	622	63.28	118	65.56	0.3054	0.305
Male	347	35.30	57	31.67		
Unknown	14	1.42	5	2.78		
Origin**						
Europe	830	84.44	139	77.22	43.217	<0.0001
North America	120	12.21	32	17.78		
Asia	17	1.73	5	2.78		
South America	4	0.41	0	0.00		
Australasia	6	0.61	1	0.56		
Unknown	6	0.61	3	1.67		
Type of vaccine**						
BNT162b2	795	80.87	131	72.78	10.022	<0.0001
mRNA-1273	171	17.40	46	25.56		
Ad26.COV2.S	13	1.32	3	1.67		
Unknown	4	0.41	0	0.00		
Dosage**						
1	359	36.52	64	35.56	0.763	0.092
2	326	33.16	57	31.67		
3	124	12.61	20	11.11		
4	7	0.71	0	0.00		
Unknown	167	16.99	39	21.67		
Onset interval postvaccination**						
Day 0	139	14.14	16	8.89	0.6875	0.872
Days 1–7	324	32.96	77	42.78		
Days 8–14	140	14.24	23	12.78		
Days 15–21	85	8.65	5	2.78		
Days 22–28	45	4.58	10	5.56		
Days >28	175	17.80	22	12.22		
Unknown	75	7.63	27	15.00		

*One-way analysis of variance test performed.
**Chi-square test performed.

compared with Asia (HZO: 1.73%, HSO: 2.78%), Australasia (HZO: 0.61%, HSO: 0.56%), and South America (HZO: 0.41%), where other vaccines are more commonly administered. In the United States, the crude reporting rate (per million doses) was 0.25, 0.22, and 0.47 for BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines, respectively. The crude reporting rate for each country could not be calculated because of the lack of stratified data for the 3 vaccine types.

The mean onset interval was significantly shorter in patients who presented with HSO (15.25 ± 28.63 days) compared with those with HZO (23.26 ± 67.74 days, $P = 0.013$) (Table 2). The HZO onset interval was significantly

shorter in patients who received BNT162b2 (20.51 ± 56.20 days, $P = 0.030$) compared with those who received mRNA-1273 (36.56 ± 108.67 days) and Ad26.COV2.S (39.66 ± 60.15 days). The onset interval was significantly shorter in both women and men who were diagnosed with HSO compared with those with HZO (women: 12.67 ± 23.90 days vs. 27.68 ± 83.49 days, $P = 0.027$; men: 16.53 ± 26.08 vs. 21.2 ± 36.40, $P = 0.044$). The onset interval was significantly shorter in patients diagnosed with HSO compared with those diagnosed with HZO in their third and seventh to 10th decades. The intragroup analysis also showed that HSO and HZO onset intervals were comparable for all vaccine doses.

In the cohort, very few patients with HZO (3.46%) and HSO (1.11%) had a history of COVID-19. In the cohort, only 13.63% of patients with HZO and 5% of patients with HSO had a history of hypertension, and 3.43% of patients with HZO and 1.67% of patients with HSO had a history of diabetes mellitus. A significantly higher proportion of patients diagnosed with HSO (20.00%, $P = 0.001$) had reduced vision compared with patients with HZO (7.22%). Expectedly, a significantly higher proportion of patients with HSO (26.67%, $P = 0.049$) presented with keratitis (4.68%) compared with patients with HZO. However, a comparable proportion of patients with HZO (34.49%) and HSO (30.56%) reported ocular pain. A significantly higher proportion of patients with HSO (6.11%, $P = 0.038$) presented with dendritic ulcers compared with patients with HZO (1.22%). Interestingly, only a moderately higher proportion of patients with HZO (20.24%, $P = 0.099$) presented with painful rash (shingles) compared with patients with HSO (6.67%). The systemic presentations were comparable in both groups and are summarized in Table 3.

The post hoc analysis revealed a significant difference in HSO ($P = 0.045$) and HZO ($P = 0.036$) onset after vaccination with BNT162b2 compared with mRNA-1273 (Table 4). We observed that the time interval was significantly shorter in patients diagnosed with HZO after the first dose compared with the second and fourth doses (Table 5). Similarly, the duration of HZO onset after the fourth dose was significantly longer compared with the first and third doses. However, it should be noted that very few patients have received the fourth booster dose of the BNT162b2 and mRNA-1273 vaccines. Finally, the 30-day risk analysis showed no significant difference in HSO onset between BNT162b2 and mRNA-1273 vaccines (Fig. 1). However, the risk of HZO onset was significantly higher in the 30-day period after vaccination with BNT162b2 compared with mRNA-1273 and Ad26.COV2.S vaccines ($P = 0.011$). (Fig. 2).

DISCUSSION

Global vaccination efforts were critical to abate the spread of SARS-CoV-2 and reduce the morbidity and

TABLE 2. Analysis to Assess the Factors Associated With the Onset Interval of Herpes Zoster and Herpes Simplex Ophthalmicus After SARS-CoV-2 Vaccinations

	Herpes Zoster Ophthalmicus		Herpes Simplex Ophthalmicus		Herpes Zoster versus Herpes Simplex Ophthalmicus
	Mean Onset Interval (in d)	*P*	Mean Onset Interval (in d)	*P*	*P*
	23.26 ± 67.74		15.25 ± 28.63		**0.013**
Vaccine*					
BNT162b2	20.51 ± 56.20	**0.030**	12.18 ± 22.99	0.0501	0.072
mRNA-1273	36.56 ± 108.67		24.54 ± 39.11		0.688
Ad26.COV2.S	39.66 ± 60.15		4.5 ± 0.71		**0.021**
Sex*					
Female	27.68 ± 83.49	0.059	12.67 ± 23.90	0.228	**0.027**
Male	16.53 ± 26.08		21.2 ± 36.40		**0.044**
Age group*					
0–10	136 ± 0	0.882	0	0.289	1
11–20	9.72 ± 10.15		1 ± 0		1
21–30	18.29 ± 32.67		9 ± 18.98		**0.048**
31–40	24.58 ± 46.82		15.88 ± 35.19		0.072
41–50	18.82 ± 32.77		11.35 ± 16.45		0.091
51–60	27.87 ± 107.32		20.5 ± 33.44		0.211
61–70	30.54 ± 97.82		13.25 ± 14.68		**0.036**
71–80	20.83 ± 33.20		4.9 ± 4.43		**0.023**
81–90	21.51 ± 52.89		8.91± 12.42		**0.043**
91–100	14.37 ± 32.47		81 ± 0		**0.002**
Dose*					
1	15.07 ± 27.09	0.166	10.64 ± 25.51	0.52	0.211
2	33.06 ± 81.27		18.94 ± 34.84		0.109
3	17.15 ± 37.45		20.11 ± 29.16		0.762
4	92.5 ± 171.27		0		1

*One-way analysis of variance test.

TABLE 3. Comparative Analysis of the Clinical History, Ocular and Systemic Presentations in Patients Diagnosed With Herpes Simplex and Zoster Ophthalmicus After SARS-CoV-2 Vaccinations

	Herpes Zoster Ophthalmicus	Herpes Simplex Ophthalmicus	$\chi 2$	*P*
History*				
COVID-19	34/983 (3.46%)	2/180 (1.11%)	1.3932	0.707
Hypertension	134/983 (13.63%)	9/180 (5%)	2.184	0.535
Diabetes mellitus	34/983 (3.43%)	3/180 (1.67%)	2.522	0.471
Ocular presentation*				
Eye pain	339/983 (34.49%)	55/180 (30.56%)	1.440	0.781
Reduced vision	71/983 (7.22%)	36/180 (20.00%)	11.045	0.001
Ptosis	3/983 (0.31%)	0		1
Eyelid edema	131/983 (13.33%)	16/180 (8.89%)	0.2994	0.584
Lacrimation	15/983 (1.53%)	4/180 (2.22%)	0.1845	0.667
Keratitis	46/983 (4.68%)	48/180 (26.67%)	5.112	0.049
Dendritic ulcers	12/983 (1.22%)	11/180 (6.11%)	5.071	0.038
Systemic presentation*				
Fever	83/983 (8.44%)	19/180 (10.56%)	1.9213	0.589
Headache	126/983 (12.82%)	17/180 (9.44%)	2.522	0.471
Malaise	21/983 (2.14%)	4/180 (2.22%)		1
Arthritis	15/983 (1.53%)	4/180 (2.22%)	1.440	0.781
Fatigue	60/983 (6.10%)	12/180 (6.67%)	0.3271	0.955
Adenopathy	34/983 (3.46%)	4/180 (2.22%)	1.440	0.696
Painful rash (shingles)	199/983 (20.24%)	12/180 (6.67%)	6.272	0.099

*Chi-square test performed.

mortality associated with it. The 3 FDA-authorized vaccines have played a significant role in stemming the impact of SARS-CoV-2 in the United States and several other countries.[3,14,15] As the development of these vaccines was completed in record time and received the requisite emergency authorization, concerns were raised about rare, short, and long-term systemic effects, including ocular disorders. In the past, ocular adverse events such as uveitis, keratitis, and optic neuritis have been reported after vaccinations.[9,16–18]

Herpetic eye disease is the most common cause of infectious and inflammatory keratitis, primarily caused by HSV and VZV.[19–21] The causative viruses typically infect humans during the early years and remain dormant for decades in the neurons of dorsal root ganglia, cranial nerve ganglia, and autonomic ganglia until reactivation due to trauma, stress-related triggers or due to an immune compromised state.[22–25] Recently, Wang et al[26] evaluated the data from global pharmacovigilance surveillance systems and reported HZO cases from the European Union (117 cases), United Kingdom (13 cases), and Australia (6 cases) after vaccination with BNT162b2 (60 cases), mRNA-1273 (23 cases), ChAdOx1 nCoV-19 (51 cases), and Ad25.COV2.S (2 cases). They also reported HSO cases from the United Kingdom (2 cases) and Australia (1 case) after vaccination with mRNA-1273 (1 case) and ChAdOx1 nCoV-19 (2 cases).

TABLE 4. Post hoc Analysis Comparing the Onset Interval After Different Vaccine types in Patients Diagnosed With Herpes Zoster and Herpes Simplex Ophthalmicus

Herpes Zoster Ophthalmicus	BNT162b2	mRNA-1273	Ad26.COV2.s
BNT162b2	1		
mRNA-1273	0.036	1	
Ad26.COV2.S	0.838	0.999	1
Herpes simplex ophthalmicus			
BNT162b2	1		
mRNA-1273	0.045	1	
Ad26.COV2.S	0.923	0.591	

Although the causal mechanism that may cause HSV and VZV reactivation after SARS-CoV-2 vaccination is unclear, it has been speculated that the viral mRNA delivered through these vaccines may trigger an immunomodulatory response, leading to the reactivation of dormant virus. The spike protein transcribed by the viral mRNA generates a strong T-cell–mediated immune response, resulting in increased spike protein-specific $CD8^+$ T cells and T-helper type 1 $CD4^+$ T cells during the subsequent vaccine doses.[27] Another hypothesis suggests a reduction in VZV-specific $CD8^+$ T cells due to a massive shift of naive $CD8^+$ T cells after SARS-CoV-2 vaccination, resulting in a subdued immune response against latent viruses leading to their reactivation.[28]

In addition to case reports of HZO and HSO after vaccination with BNT162b2 and mRNA-1273 vaccines, 2 case series (Rallis et al and Cohen et al) have reported HZO and HSO cases in 10 and 5 patients, respectively.[10,29] As advancing age is a risk factor for HZO and HSO reactivation, most of the patients in this study were in their sixth and eighth decades. Almost all patients with HSO and HZO reactivation in the above mentioned case series were also in similar age groups. The speculative mechanisms of HZO and HSO reactivation in the cases series were primarily associated with mRNA-based vaccines. We also observed that the crude reporting rates for the mRNA-based BNT162b2 and mRNA-1273 vaccines were comparatively higher than the adenoviral vector-based Ad26.COV2.S vaccine. However, fewer cases after the

TABLE 5. Post hoc Analysis Comparing the Onset Interval After Different Doses in Patients Diagnosed with Herpes Zoster and Herpes Simplex Ophthalmicus

Herpes Zoster Ophthalmicus	1st Dose	2nd Dose	3rd Dose	4th Dose
1st dose	1			
2nd dose	0.008	1		
3rd dose	0.999	0.198	1	
4th dose	0.013	0.106	0.021	1
Herpes simplex ophthalmicus				
1st dose	1			
2nd dose	0.442	1		
3rd dose	0.620	0.999	1	

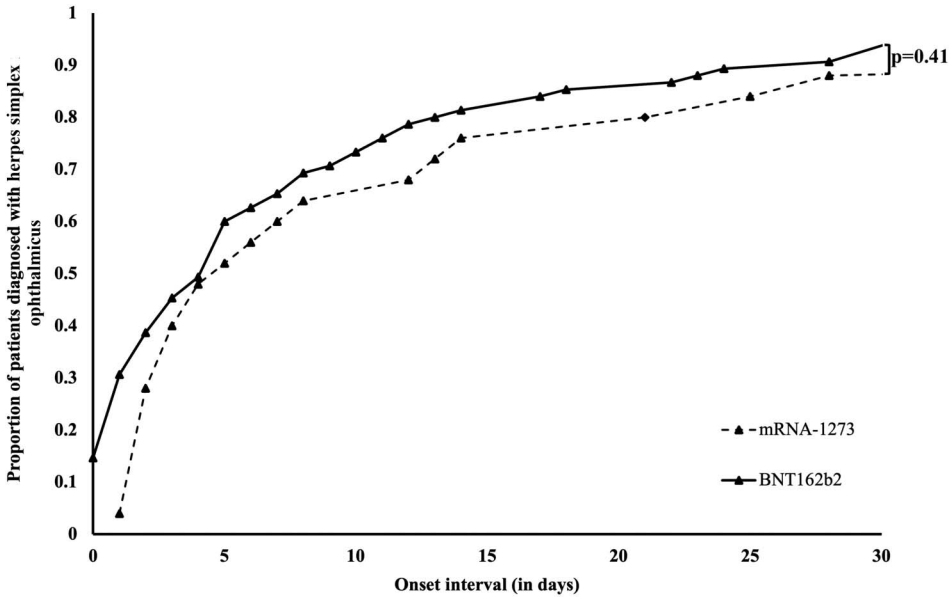

FIGURE 1. Reverse Kaplan–Meier 30-day risk analysis for herpes simplex ophthalmicus case reports after administration of BNT162b2 and mRNA-1273 vaccines. No cases of HSO were reported after vaccination with Ad26.COV2.S.

administration of Ad26.COV2.S vaccine can also be attributed to fewer doses of the vaccine delivered in the United States and other countries and its single-shot protocol compared with the multidose protocol for the other vaccines. Overall, an almost equal proportion of patients were diagnosed with HZO and HSO after the first and second doses. These data are contrary to the shifting naive $CD8^+$ T-cell hypothesis because a higher proportion of cases were expected after the subsequent vaccinations due to preexisting spike protein-specific $CD8^+$ T cells and T-helper type 1 $CD4^+$ T cells.

Approximately 60% of the cases of HZO and HSO were diagnosed within the first 2 weeks of vaccination, including ~10% of the cases on the day of vaccination, underlining the temporal relationship between the adverse events and vaccination. Rallis et al[10] reported an average onset duration of 12.3 ± 10.3 days in their patient cohort, whereas 4 of the 5 cases reported by Cohen and colleagues presented with symptoms within the first week of vaccination. The onset interval was significantly shorter in patients with HZO and moderately shorter in patients with HSO after administration of BNT162b2 vaccines compared with mRNA-1273 and Ad26.COV2.S, thus highlighting the need for additional caution in high-risk patients who receive BNT162b2 in the short term. These data were further corroborated by the 30-day risk analysis evaluation in patients who received BNT162b2. Notably, the onset interval was shorter in most age groups with HSV reactivation compared with those with VZV reactivation.

The clinical manifestations in patients with HSV and VZV reactivation were in line with the established clinical

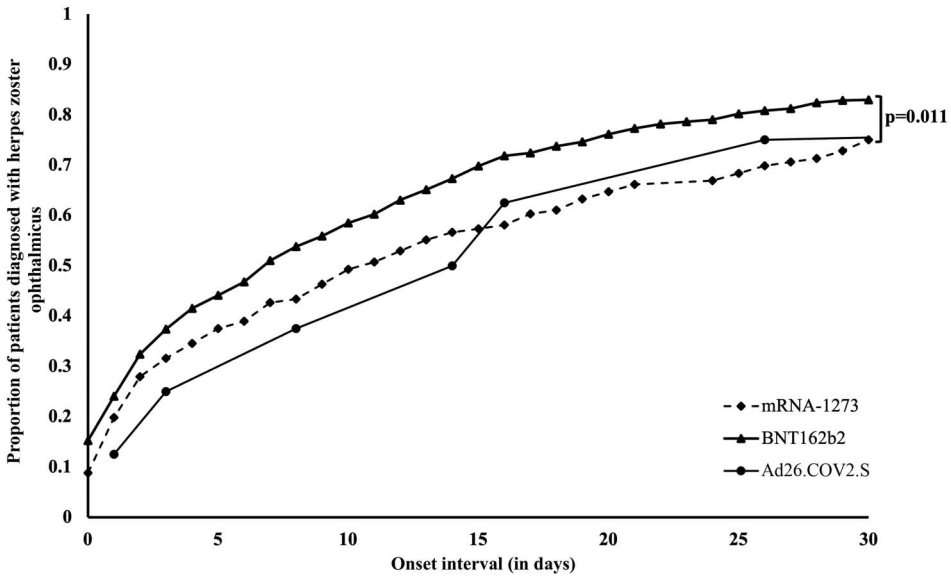

FIGURE 2. Reverse Kaplan–Meier 30-day risk analysis for herpes zoster ophthalmicus case reports after administration of BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines.

presentations. Dendritic corneal ulcers were more common in patients with HSO, whereas patients with HZO more commonly presented with a painful rash, a hallmark of VZV reactivation. A third of the patients with HSO and HZO presented with ocular pain. Expectedly, reduced vision was more common in patients with HSO compared with patients with HZO. The adnexal disorders, including ptosis and eyelid edema, were more common in patients with HZO and rarely seen in patients who presented with HSO. Systemic presentations such as fever, headache, and malaise were observed in both groups.

LIMITATIONS

This retrospective database analysis has several limitations. The CDC-VAERS is a global passive surveillance system recording vaccine-associated adverse events. Despite the mandatory requirement to report some of the vaccine-associated adverse events, under reporting and delayed reporting are very common. A few cases submitted to VAERS were incomplete and lacked uniformly reported data. Moreover, VAERS does not include all data points that may aid in assessing the risk of HSV and VZV reactivation in patients. The temporal association of the cases was primarily established based on the history reported by the patients to the physicians and pharmacovigilance bodies. In this study, 11.96% patients reported with herpetic eye disease on the day of vaccination. Considering the probable underlying immunological mechanisms, it is highly unlikely that the vaccine induced reactivation of the herpes simplex and varicella-zoster viruses in such a short span of time. However, there is a possibility that these patients had undiagnosed HSO and HZO which were aggravated on exposure to the vaccination. Moreover, the data pertaining to previous diagnosis of herpetic eye diseases were not available for most patients; hence, we could not assess the risk of vaccine-induced recurrence.

An unvaccinated control group is required for a more rigorous relative risk analysis, which could not be conducted for this study. The data reported in this study only suggest a temporal relationship between HSO and HZO onset and SARS-CoV-2 vaccination and does not demonstrate a causal relationship. Therefore, further investigations are required to establish a causal relationship. Moreover, the cases reported to VAERS are limited to the countries where the 3 FDA-authorized vaccines, BNT162b2, mRNA-1273, and Ad26.COV2.S, are approved for use, and therefore, the HZO and HSO cases after vaccination with ChAdOx1 nCoV-19, ZyCoV-D, Sputnik, Convidecia, Sinopharm, Abdala, Soberana, Zifivax, and Novavax could not be evaluated; several cases of herpetic eye disease after administration of these vaccines have been reported in the literature. Moreover, the pharmacovigilance associated with SARS-CoV-2 vaccines is limited to the European Union, the United States, Australia, Canada, and a few Asian countries. Hence, adverse events have not been reported from several developing countries where a large proportion of SARS-CoV-2 vaccines were administered.

In conclusion, this analysis of the largest global adverse event database suggests that the 3 vaccines BNT162b2, mRNA-1273, and Ad26.COV2.S rarely causes HZO and HSO. Most of the patients diagnosed with HSO and HZO received the BNT162b2 vaccine. The cases of HSO and HZO typically present in the first 2 weeks after vaccination, more commonly in the older age groups. Although the benefits of vaccination outweigh the risk of HSO and HZO, ophthalmologists and corneal specialists should be aware of a possibility of reactivation of HSV and VZV after vaccination and should ensure that the patients at risk should be made aware of it.

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