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Association between Vaccination with the BNT162b2 mRNA Coronavirus Disease 2019 Vaccine and Noninfectious Uveitis

A Population-Based Study

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Purpose: To assess the association between BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine and the risk of active noninfectious uveitis (NIU).

Design: Retrospective, population-based study.

Participants: Two million six hundred two thousand five hundred fifty-seven people who received the first vaccine dose between December 20, 2020, and April 30, 2021, and 2 441 719 people who received the second vaccine dose between January 10, 2021, and April 30, 2021.

Methods: Events of active NIU were included if they occurred within 21 days after either vaccine dose. Active NIU was defined as newly active or worsening ocular inflammation requiring initiation or increase in local or systemic corticosteroids. Observed cases were compared with the expected number, based on the experience of the population in 2019.

Main Outcome Measures: Age- and sex-adjusted standardized incidence ratios (SIRs) and attributable risks after BNT126b2 vaccination.

Results: Overall, 100 and 88 events of active NIU were recorded within 21 days after the first and second vaccine doses, respectively. Using the experience of the population in 2019 as a reference, after the first dose, the estimated age- and sex-adjusted SIR was 1.41 (95% confidence interval [CI], 1.15−1.71) along with a 21-day attributable risk of 1.12 cases per 100 000 vaccinees. After the second dose, the SIR was 1.31 (95% CI, 1.05−1.62), with an estimated attributable risk of 0.86 cases per 100 000 vaccinees. Anterior uveitis was the most common site of inflammation, occurring in 90.96% of eyes, and idiopathic uveitis was the most common cause (56.38%).

Conclusions: This study suggests that the BNT162b2 mRNA COVID-19 vaccine may be associated with an increased risk of active NIU. However, considering the small effect size and study limitations, this study does not provide proof for a cause-and-effect relationship. The small estimated attributable risks suggest that the impact on public health is relatively minor. *Ophthalmology 2022;129:1087-1095 © 2022 by the American Academy of Ophthalmology*

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Prevention and treatment of coronavirus disease 2019 (COVID-19) is the leading issue in current global health care. The BNT162b2 mRNA vaccine demonstrated high efficacy in preventing severe acute respiratory syndrome coronavirus 2 infection, hospitalization, and related death.[1−4] Large population-based studies demonstrated that the vaccine has a good safety profile, although some increased risk of incident systemic complications was noted, including varicella zoster infection, lymphadenopathy, Guillain−Barré syndrome, and myocarditis.[1,4−12] In many countries, 2 doses of the vaccine and a booster dose are currently recommended for the general population older than 12 years and 2 doses for children between 5 and 12 years of age.[9,13]

Previous associations between vaccines and ocular complications have been suggested, including uveitis.[14−16] After the COVID-19 global vaccination campaign, cases are now reported of possible vaccine-related ocular complications.[17] Most are single or small case reports and include acute macular neuroretinopathy,[17] central serous retinopathy,[18] corneal graft rejection,[19−21] cranial nerve palsies, and particularly incident and relapses of uveitis.[22−24] Most uveitis cases are related to anterior uveitis, although several reports include cases of multiple evanescent white dot syndrome, Vogt−Koyanagi−Harada syndrome, and idiopathic panuveitis.[10,17,25−32] In all these reports, the association to the vaccine is related to temporal proximity and developed between 1 and 30 days after

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receiving a vaccine dose. However, it remains unclear whether the vaccine is related to an increase in the incidence of uveitis and whether any populations are at higher risk. In this study, we examined a large, population-based database of individuals who received the BNT162b2 vaccine and compared the rates of active noninfectious uveitis (NIU) requiring treatment with rates both before and after the COVID-19 pandemic.

Methods

A retrospective cohort study was conducted using deidentified health care records from the Clalit Health Services (CHS) database. The CHS is 1 of 4 national health maintenance organizations in Israel that insure and provide health care according to governmental guidelines. It insures > 4.7 million people constituting approximately 52% of the population of Israel and is representative of the entire population at large. The CHS information systems are fully digitized and generated from both outpatient facilities and all national hospitals, including records of primary care physicians, community specialty clinics, hospitalizations, laboratories, and pharmacies. Information regarding COVID-19 infections and vaccinations are collected centrally. The study was approved by the CHS institutional review board (identifier: CMC-022-21) and was exempt from the requirement for informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Study Design

We performed a retrospective cohort study with a nonconcurrent historic comparative group. In this approach, the observed cases of active NIU appearing after COVID-19 vaccination were compared with the expected cases of active NIU as estimated based on the experience of the CHS population during 2 periods: (1) 2019 before the COVID-19 pandemic and vaccine introduction in Israel and (2) 2020 during the COVID-19 pandemic but before introduction of the vaccine.

Study Population

The study included all patients who received at least 1 dose of the BNT162b2 vaccine. To estimate the observed cases of NIU after the first vaccine dose, we identified all CHS members 16 years of age or older who received the first dose of the vaccine starting from December 20, 2020, the start date of the mass COVID-19 vaccination campaign in Israel, until April 30, 2021. Identified participants constituted the population for the estimation of the standardized incidence ratio (SIR) of active NIU after the first vaccine dose. Among them, those who received the second vaccine dose by April 30, 2021, constituted the population for the estimation of SIR after the second vaccine dose. The first historic comparative group included the CHS members 16 years of age or older on January 1, 2019, and the second comparative historic group included CHS members 16 years of age or older on September 1, 2020.

Events were defined as suspected for active NIU if a medical record documented a diagnosis of NIU, according to International Classification of Diseases, Ninth Revision, definitions (Table S1, available at www.aaojournal.org), with a concomitant prescription of topical, regional, or systemic corticosteroids (Table S2, available at www.aaojournal.org). All case records meeting this definition were then reviewed by an investigator (O.T.-N.). Suspected events were confirmed and thus included in the study as active NIU if in the case review an ophthalmic examination by an ophthalmologist documented newly active or worsening inflammation (according to the Standardization of Uveitis Nomenclature criteria)[33] and local or systemic corticosteroids were initiated or increased. Otherwise, suspected events were excluded if they not documented by an ophthalmologist, a full ophthalmic examination was not performed, no signs of active inflammation were documented, the patient had a documented medical history of any infectious uveitis (including herpetic uveitis or toxoplasmosis), or local or systemic corticosteroids were not initiated or increased. After the manual review, we rejected 38.38% of cases of uveitis from the 2019 reference population, 37.59% of cases of uveitis from the 2020 reference population, and 38.82% of cases of uveitis documented in those who received the vaccine. The main reasons for case rejection were no documented evidence of signs of active uveitis, an infectious uveitis diagnosis, or misdiagnosis of uveitis. Vaccine-related events were recoded if they occurred during a 21-day window after either the first or second BNT162b2 vaccine dose administration. A 21-day window was chosen because, according to local guidelines, the second dose was administered 21 days after the first dose. For the 2019 historic reference population (before the COVID-19 pandemic), events were recorded if they occurred during a matched observation period in 2019 (January−May). Whereas for the 2020 reference population (after the COVID-19 pandemic began and before the vaccination period), events were recorded if they occurred between September 1, 2020, and December 18, 2020 (before vaccination). For the 2020 reference population, the period was chosen to account for changes in patient health care behavior during the first months of the pandemic. For all people identified, only the first event of active NIU during the follow-up period was included. If a second event was recorded after the second dose, it was considered a continuation of the first event. A record review of previous diagnoses of uveitis since January 1, 1999, was conducted to identify all individuals with previously known NIU (Table S1).

Additional variables were recorded for vaccine-related events, including time (days) after vaccination, anatomic site of inflammation, best-corrected visual acuity (BCVA), and uveitis definition according to the International Classification of Diseases, Ninth Revision. The BCVA measurement was converted to logarithm of the minimum angle of resolution (logMAR). For BCVA of counting fingers or worse, the following conversion was used: counting fingers, 2.0 logMAR; hand movements, 2.3 logMAR; light perception, 2.6 logMAR; and no light perception, 2.9 logMAR.[34]

Statistical Methods

The observed number of cases of active NIU occurring within 21 days after each vaccine dose (first and second) was compared with the expected number of cases, based on estimation from historic data. Observed cases after the first vaccine dose were assessed in those who received the first dose between December 20, 2020, and April 30, 2021, and the observed cases after the second vaccine dose were assessed in those who received the second dose between January 10, 2021, and April 30, 2021. Both cohorts were followed up retrospectively for 21 days for active NIU ascertainment. The expected incidence rate of active NIU was estimated based on the experience of the CHS population in 2019 during the same period (January−May) and in 2020 between September 1 and December 18. We used the same criteria for identifying cases among these reference populations as those for the cases occurring after vaccination. These rates were applied to estimate the number of active NIU cases that were expected to occur within 21 days after each of the first and the second vaccine doses. Standardized incidence ratios were computed by dividing the observed by the expected

number of active NIU cases for each vaccine dose; for each sex; for age groups 16 to 44 years, 45 to 64 years, and 65 years or older; and for the total population (adjusted for sex and age), along with the Poisson-based 95% confidence intervals (CIs). We calculated the attributable risk (AR) fraction among vaccinated as (SIR − 1) / SIR, and the AR for 100 000 vaccinees was calculated by multiplying the risk after each vaccine dose by the AR fraction. Cumulative incidence by time from vaccine dose (first and second separately) was estimated using the Kaplan−Meier method.

Subgroup analysis by past history of uveitis (no or yes) was performed. To calculate the SIRs for the first and second vaccine dose among participants with previous history of NIU, we used as reference the 2019 and 2020 populations with previous history of NIU. Similarly, for participants with no history of NIU, the reference populations were the 2019 and 2020 populations with no history of NIU. In the subgroup analysis, we conducted only age- and sex-adjusted estimates because the number of cases in each age group was small.

A statistically significant SIR was determined when its 95% CI entirely excluded the value 1. No adjustment for multiple comparisons was performed. All analyses were performed using SAS software version 9/4 (SAS Institute, Inc.).

Results

Overall, 2 602 557 people with an average age of 46.8 ± 19.6 years (51.5% female) received the first dose of BNT162b2 mRNA COVID-19 vaccine between December 20, 2020, and April 30, 2021. Of them, 2 441 719 people received the second vaccine dose between January 10, 2021, and April 30, 2021. A previous diagnosis of NIU was documented for 18 236 people (0.7%) who received the first dose and 17 250 people (0.7%) who received the second dose (Table S3, available at www.aaojournal.org).

Noninfectious Uveitis after Vaccination

After vaccination, 188 people experienced a confirmed event of active NIU that met the inclusion and exclusion criteria; of them, 100 people experienced an event during the 21 days after the first dose, and 88 people experienced an event during the 21 days after the second dose, reflecting a 21-day overall risk of 3.85 and 3.61 per 100 000 vaccinated individuals, respectively (Table 1). The cumulative incidence of active NIU by time from vaccination is presented in Figure 1 for each of the doses. Among those individuals who experienced the event, the median time to active NIU was 8.5 days (interquartile range [IQR], 3−16 days) after the first dose and 10 days (IQR, 6.5−15 days) after the second dose, with 68 events (68.0%) and 59 events (67.0%) occurring during the first 14 days after the first and second doses, respectively.

Comparison with Historical Cohorts

Total time (person-years) at risk and incidence rates for people after vaccination and for the reference populations in 2019 and 2020 are shown in Table 2. The overall incidence rate of active NIU was 66.8 cases per 100 000 person-years after the first dose and 62.7 cases per 100 000 person-years after the second vaccine dose. The corresponding rate in the reference populations was 45.7 cases per 100 000 person-years in 2019 and 45.1 cases per 100 000 person-years in 2020 (Table 2).

Using the experience of the population in 2019 as a reference, the age- and sex-adjusted SIRs were 1.41 (95% CI, 1.15−1.71) and

Table 1. Standardized Incidence Ratios of Active Noninfectious Uveitis after First or Second Vaccine Dose Stratified by Sex and Age Groups Using 2019 as the Reference Population

Gender	Age Group (yrs)	No. of Vaccines	No. of Observed Events	Risk (per 100 000 Vaccines)	No. of Expected Events	Standardized Incidence Ratio (95% Confidence Interval)	Attributable Risk per 100 000 Vaccines
First dose							
All	Age and sex adjusted	2 602 557	100	3.85	70.97	1.41 (1.15−1.71)	1.12
Male participants	16−44	655 658	21	3.21	9.48	2.22 (1.37−3.39)	1.76
	45−64	341 289	5	1.47	11.44	0.44 (0.14−1.02)	−1.89
	65+	264 191	19	7.20	9.45	2.01 (1.21−3.14)	3.62
	Age adjusted	1 261 138	45	3.57	30.36	1.48 (1.08−1.98)	1.16
Female participants	16−44	661 032	10	1.51	11.64	0.86 (0.41−1.58)	−0.25
	45−64	355 666	18	5.06	13.64	1.32 (0.78−2.09)	1.23
	65+	324 721	27	8.32	15.34	1.76 (1.16−2.56)	3.59
	Age adjusted	1 341 419	55	4.10	40.61	1.35 (1.02−1.76)	1.07
Second dose							
All	Age and sex adjusted	2 441 719	88	3.61	67.10	1.31 (1.05−1.62)	0.86
Male participants	16−44	603 921	7	1.16	8.73	0.80 (0.32−1.65)	−0.29
	45−64	323 337	26	8.05	10.83	2.40 (1.57−3.52)	4.69
	65+	254 712	9	3.54	9.11	0.99 (0.45−1.88)	−0.04
	Age adjusted	1 181 970	42	3.56	28.67	1.46 (1.06−1.98)	1.13
Female participants	16−44	610 436	18	2.95	10.74	1.68 (0.99−2.65)	1.19
	45−64	336 112	16	4.76	12.89	1.24 (0.71−2.02)	0.93
	65+	313 201	12	3.83	14.79	0.81 (0.42−1.42)	−0.89
	Age adjusted	1 259 749	46	3.65	38.43	1.20 (0.88−1.60)	0.60

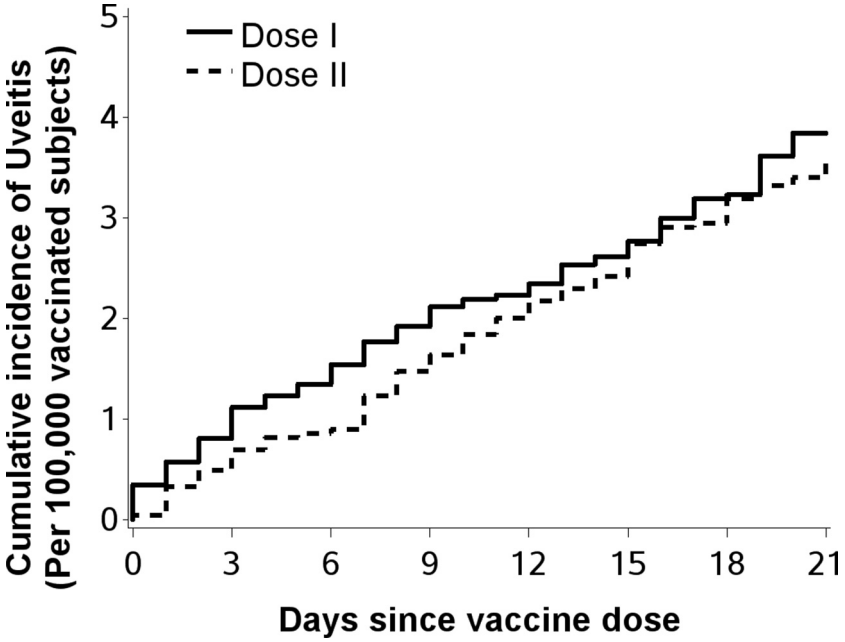

Figure 1. The cumulative incidence of active noninfectious uveitis by dose.

1.31 (95% CI, 1.05−1.62) after the first and the second doses, respectively (Table 1). This accounted for an AR of 1.12 events per 100 000 vaccinees after the first dose and 0.86 events per 100 000 vaccines after the second dose. Stratified analysis by sex and age revealed that, after the first dose, the age-adjusted SIRs were 1.48 (95% CI, 1.08−1.98) for male participants and 1.35 (95% CI, 1.02−1.76) for female participants, resulting in an AR of 1.16 and 1.07 per 100 000 vaccinees, respectively. After the second dose, the age-adjusted SIR among male participants was 1.46 (95% CI, 1.06−1.98) with an AR of 1.13 events per 100 000 vaccinees. Among female participants after the second dose, the age-adjusted SIR was 1.20 (95% CI, 0.88−1.60). Similar results were found when 2020 was used as the reference population (Table S4, available at www.aaojournal.org).

Subgroup Analysis by Past History of Uveitis

Table S5 (available at www.aaojournal.org) shows the total time (person-years) at risk and incidence rates after vaccination with each dose and for the reference populations 2019 and 2020, stratified by previous history of uveitis (people without a history of uveitis vs. people with previously known uveitis). Among people without a history of uveitis, the overall risk of new-onset NIU was 1.63 and 1.98 events per 100 000 vaccinated individuals after the first and the second vaccine doses, respectively (Table 3). Compared with the reference 2019 population with no history of uveitis, the age- and sex-adjusted SIRs for new-onset NIU were 1.3 (95% CI, 0.94−1.76) and 1.57 (95% CI, 1.16−2.08) after the first and the second vaccine doses, respectively. The corresponding ARs were 0.38 and 0.72 events per 100 000 vaccinees (Table 3). Our data show that people with a history of uveitis have a high risk of a recurrent active NIU event during the observation period (Table 3). After the first dose, the age- and sex-adjusted SIR for NIU relapse was 1.58 (95% CI, 1.20−2.04), which accounted for an AR of 116.94 per 100 000 vaccinees. After the second dose, the age- and sex-adjusted SIR for NIU relapse was 1.16 (95% CI, 0.83−1.57), which accounted for an AR of 31.27 per 100 000 vaccinees (Table 3). The results of subgroup analysis using 2020 as the reference population were comparable to the analysis using the 2019 reference population (Table S6, available at www.aaojournal.org).

Among patients with uveitis with no history of uveitis, the median time to active NIU was 8.5 days (IQR, 6−18 days) and 11 days (IQR, 5.5−16 days) after the first vaccine dose (n = 42) and the second vaccine dose (n = 48), respectively. Among patients with a history of uveitis, the median time to active NIU was 8.5 days (IQR, 3−15 days) and 10 days (IQR, 6.5−15 days) after the first vaccine dose (n = 58) and the second vaccine dose (n = 40), respectively.

Clinical Characteristics of Active NIU after Vaccination

Overall, events of active NIU involved 188 people, of which 166 were unilateral (88.3%; Table 4), with 76 events involving the right eye (45.78%) and 22 events being bilateral (11.7%). Anterior uveitis was the most common site of inflammation, occurring in 171 eyes (90.96%). Average BCVA at time of the event was 0.3 ± 0.44 logMAR. Clinical investigations were complete for 127 events (67.55%), with idiopathic uveitis being the most common cause (n = 106 [56.38%]), followed by patients with HLA-B27-associated uveitis (n = 12 [6.38%]) and patients with Behçet disease (n = 2 [1.06%]).

Discussion

The introduction of the BNT162b2 mRNA COVID-19 vaccine was a turning point in managing the COVID-19 pandemic. The vaccine is highly effective in preventing severe infection with severe acute respiratory syndrome

Table 2. Incidence Rates of Active Noninfectious Uveitis after the First and Second Vaccine Dose and in Reference Populations (2019 and 2020)

Sex	Age Group (yrs)	2019 Reference Population			2020 Reference Population			First Vaccine Dose (within 21 Days After)			Second Vaccine Dose (within 21 Days After)		
		Person-Years	*Events*	*Incidence Rate (per 100 000 Person-Years)*	*Person-Years*	*Events*	*Incidence Rate (per 100 000 Person-Years)*	*Person-Years*	*Events*	*Incidence Rate (per 100 000 Person-Years)*	*Person-Years*	*Events*	*Incidence Rate (per 100 000 Person-Years)*
All	16–44	720 499	201	27.9	527 533	162	30.7	75 702	31	41.0	69 819	25	35.8
	45–64	330 499	207	62.6	242 573	128	52.8	40 071	23	57.4	37 914	42	110.8
	65+	260 218	191	73.4	194 265	145	74.6	33 858	46	135.9	32 651	21	64.3
	Total	1 311 216	599	45.7	964 372	435	45.1	149 631	100	66.8	140 384	88	62.7
Female	16–44	362 576	111	30.6	265 541	95	35.8	38 006	10	26.3	35 096	18	51.3
	45–64	170 940	114	66.7	124 661	77	61.8	20 448	18	88.0	19 324	16	82.8
	65+	146 055	120	82.2	108 885	89	81.7	18 669	27	144.6	18 007	12	66.6
	Total	679 571	345	50.8	499 088	261	52.3	77 123	55	71.3	72 428	46	63.5
Male	16–44	357 923	90	25.1	261 992	67	25.6	37 696	21	55.7	34 722	7	20.2
	45–64	159 559	93	58.3	117 912	51	43.3	19 622	5	25.5	18 589	26	139.9
	65+	114 163	71	62.2	85 380	56	65.6	15 189	19	125.1	14 644	9	61.5
	Total	631 645	254	40.2	465 284	174	37.4	72 508	45	62.1	67 956	42	61.8

coronavirus 2 and hospitalizations and reduces morbidity rates.[1–4] Concerns regarding possible systemic adverse effects of the vaccine were raised, including ocular morbidity. Clinical trials and population-based studies that examined the incidence rates of systemic adverse effects demonstrated an increased risk of some complications, particularly myocarditis among young male recipients, but no increased risk of uveitis was found.[1,8]

Previous reports relate vaccines to events of uveitis, most commonly vaccines for the hepatitis B virus, human papillomavirus, and influenza virus.[16,35–37] Reports were mainly of anterior uveitis, but other cases included acute posterior multifocal placoid pigment epitheliopathy, Vogt–Koyanagi–Harada syndrome, or multiple evanescent white dot syndrome.[14,38–42]

Currently, reports suggest correlations between the BNT162b2 mRNA COVID-19 vaccine and cases of new onset or relapse of uveitis, ranging from reactivations of herpes-related uveitis to new episodes of NIU. In most of these reports, the correlation to the vaccine is based only on its occurrence within 30 days after vaccination.[10,17,25,26] The current global vaccination initiative includes large populations receiving a single vaccine over a short period, creating a unique opportunity to address the question of correlations between the vaccine and uveitis. Interestingly, a large population-based study using the same CHS database failed to show an increase in uveitis incidence after BNT162b2 vaccination.[8] Despite the disparities in the findings of the 2 studies, the results are not contradictory. Differences between the studies in population size, definition of active uveitis, and inclusion of people with a previous history of uveitis suggest that the populations and results are not comparable. In our study, we took particular care to identify events of active NIU by manually examining each case and confirming that an ophthalmologist reported signs of active inflammation. Our results suggest that, for the general population, an association may exist between the incidence of active NIU and the BNT162b2 vaccine compared with 2019 and 2020, with a small AR. This risk is outweighed by the impact of the vaccine on reducing the significant morbidity and mortality posed by COVID-19 infection.

Possible associations between vaccines and uveitis are of particular interest to ophthalmologists and patients with known uveitis. Many patients with NIU are treated with immunosuppression drugs and have concerns regarding the efficacy of the vaccine and potential disease reactivation. Our results suggest an increased incidence of active NIU among patients with a history of uveitis, accounting for an overall AR of approximately 1 case per 1000 vaccinated people and up to 3 cases per 1000 vaccinated people in certain age groups. More than 90% of cases were anterior uveitis and were treated topically. Studies examined patients with other systemic autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus, also demonstrated few cases of disease relapse.[43–46] Ophthalmologists should be aware of this potential increased risk of relapse to patients with a history of uveitis and should counsel them to be vigilant during the weeks after vaccination.

Table 3. Adjusted Standardized Incidence Ratios of Active Noninfectious Uveitis after First or Second Vaccine Dose Stratified by Past History of Uveitis Using 2019 as the Reference Population

Past History of Noninfectious Uveitis	Sex	Adjustment	No. of Vaccines	No. of Observed Events	Risk (per 100 000 Vaccines)	No. of Expected Events	Standardized Incidence Ratio (95% Confidence Interval)	Attributable Risk per 100 000 Vaccines
First dose								
No	All	Age and sex adjusted	258 4321	42	1.63	32.31	1.30 (0.94–1.76)	0.38
	Male	Age adjusted	1 252 498	21	1.68	14.22	1.48 (0.91–2.26)	0.54
	Female	Age adjusted	1 331 823	21	1.58	18.09	1.16 (0.72–1.77)	0.22
Yes	All	Age and sex adjusted	18 236	58	318.87	36.73	1.58 (1.20–2.04)	116.94
	Male	Age adjusted	8640	24	278.39	15.12	1.59 (1.02–2.36)	103.03
	Female	Age adjusted	9596	34	355.33	21.61	1.57 (1.09–2.20)	129.48
Second dose								
No	All	Age and sex adjusted	2 424 469	48	1.98	30.61	1.57 (1.16–2.08)	0.72
	Male	Age adjusted	1 173 811	25	2.13	13.45	1.86 (1.20–2.74)	0.98
	Female	Age adjusted	1 250 658	23	1.84	17.16	1.34 (0.85–2.01)	0.47
Yes	All	Age and sex adjusted	17 250	40	232.32	34.62	1.16 (0.83–1.57)	31.27
	Male	Age adjusted	8159	17	208.68	14.24	1.19 (0.70–1.91)	33.92
	Female	Age adjusted	9091	23	253.55	20.38	1.13 (0.72–1.69)	28.88

Although our results suggest an increased risk of uveitis among certain patient populations, it is important to address the overall excess morbidity that can be attributed to the vaccine. Based on evidence gained this far, the impact of this additional morbidity is outweighed by the reduced systemic COVID-19 morbidity achieved through vaccination. Similar to other reports, the results of this study do not support preventing patients from receiving the vaccination,[6,8,47] but they should be advised of the symptoms of active uveitis, particularly during the first 14 days after each dose, and should be advised to seek immediate ophthalmic care if they occur.

Table 4. Clinical Characteristics of Active Noninfectious Uveitis Cases Occurring after BNT162b2 mRNA Coronavirus Disease 2019 Vaccine Administration

Characteristic	Data
Unilateral disease	166 (88.3)
Right eye	76 (45.78)
Anatomic site	
Anterior uveitis	171 (90.96)
Intermediate uveitis	9 (4.79)
Posterior uveitis	1 (0.53)
Panuveitis	7 (3.72)
Cause	
Idiopathic	106 (56.38)
HLA B27	12 (6.38)
Behçet disease	2 (1.06)
Fuchs heterochromic iridocyclitis	2 (1.06)
Multifocal choroiditis	2 (1.06)
Posner Schlossman syndrome	1 (0.53)
BCVA (logMAR)	0.3 ± 0.44

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.
Data are presented as no. (%) or mean ± standard deviation.

In this study, we chose to examine the incidence of active NIU during the first 21 days after each of the first 2 doses. This window is deemed to be sufficient for short-term complications, without being too long to dilute the effect, and is in line with the window used by several studies to examine short-term complications of a COVID-19 vaccine.[6,8] This time frame limits the effect of other potential factors that could lead to active disease, unrelated to the vaccine. Other studies of vaccines used longer time frames, which increases the chance of other unrelated factors influencing new cases.[25]

Our study has several limitations related to its retrospective observational nature and having relied on data originally collected for purpose of administrative and clinical management and not specifically designed for the current study. As such, data extraction in our study may be subject to errors and lack of data, most likely leading to nondifferential misclassification. To identify events of active uveitis, we included only patients seen by an ophthalmologist. Although this might have resulted in loss of some cases, in Israel, good access to ophthalmologists exists, and most patients with ocular symptoms would not be treated by general practitioners. Patients with a diagnosis of uveitis related to an infectious cause were excluded from this study, but some patients with incident acute cases did not complete their systemic investigations, and we cannot exclude that some may represent uveitis resulting from an infective cause. Additionally, the cohort included a relatively large group with a previous diagnosis of uveitis (0.7%), which would include patients with single events of ocular inflammation who were not treated and followed up regularly by ophthalmologists. However, we tried to minimize this misclassification by manually reviewing all cases and only including events of active uveitis with no known

infective cause. Furthermore, this study examined only the risk of active uveitis developing, and we were unable to follow up patients and ascertain their final clinical and visual outcomes after treatment for uveitis. Another potential limitation is surveillance bias resulting from differences in terms of seeking medical care. However, generally, active uveitis is symptomatic, and therefore, it is unlikely that a patient is not seen by a physician, regardless of vaccination status; hence, we assume that the influence of this bias is minimal. Although our large sample size allowed us to conduct a stratified analysis, adjustment was limited only to age and sex. Hence, residual confounding remains a major concern of the current study because we did not control for other risk factors for NIU that may differ between vaccinated participants and the general population. Based on the limitations inherent in the study design, this study should be considered to be a signal detection hypothesis-generating study. Furthermore, it is important to note that causality involves much more than temporal association. Considering the small effect size and the inherent limitations, our study does not provide a proof for cause and effect. Further studies are needed to examine this association and to determine the visual burden of this excess morbidity.

In conclusion, our study suggests that the BNT162b2 mRNA COVID-19 vaccine may be associated with increased risk of NIU. The small estimated ARs suggest that the impact on public health is relatively minor. However, considering the small effect size and study limitations, this study does not provide proof for a cause-and-effect relationship. Future studies are needed to explore the association. The benefits of vaccination outweigh the possible link to active uveitis and support the continued use of the vaccine, although patients with known uveitis should be aware of the symptoms of relapse.

Footnotes and Disclosures

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Tomkins-Netzer, Sar, Barnett-Griness, Friedman, Shyriaieva, Saliba

Analysis and interpretation: Tomkins-Netzer, Sar, Barnett-Griness, Friedman, Shyriaieva, Saliba

Data collection: Tomkins-Netzer, Sar, Barnett-Griness, Friedman, Shyriaieva, Saliba

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Overall responsibility: Tomkins-Netzer, Sar, Barnett-Griness, Friedman, Shyriaieva, Saliba

Abbreviations and Acronyms:
AR = attributable risk; **BCVA** = best-corrected visual acuity; **CHS** = Clalit Health Services; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **NIU** = noninfectious uveitis; **SIR** = standardized incidence ratio.

Keywords:
BNT162b2, Coronavirus disease 2019, Noninfectious uveitis.

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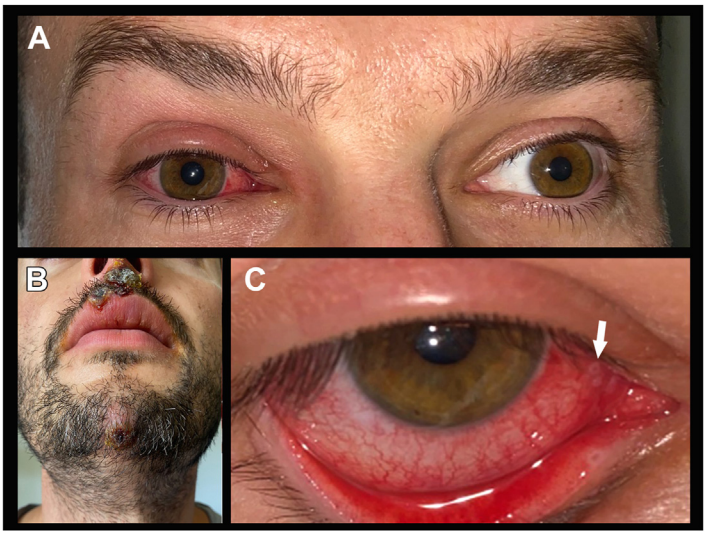
Pictures & Perspectives



Conjunctivitis with Monkeypox Virus Positive Conjunctival Swabs

A 39-year-old man consulted for unilateral red eye and itchiness (Fig **A**, **C**) 5 days after positive monkeypox virus (MPOX) cutaneous polymerase chain reaction (PCR) swab from chin and lip lesions (Fig **B**). Slit-lap examination showed conjunctival follicular reaction and the presence of small white vesicles on the nasal bulbar conjunctiva (Fig **C**, arrow). The rest of the anterior and posterior segment were normal, and the fellow eye remained uninvolved during follow up. Two separate conjunctival PCR swabs were positive for MPOX, confirming indirectly similar loads of the virus on conjunctival and eye secretions compared with cutaneous lesions (26.7 vs 24.8 [cycle threshold] respectively), raising the possibility of transmission via eye contact, i.e., during ophthalmologic examination. Healthcare professionals should be aware of this fact and employ adequate personal protection (Magnified version of Fig **A**-**C** is available online at www.aaojournal.org).

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