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Risk of non-infectious uveitis following COVID-19 vaccination in a US claims database

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Abstract

Purpose: To assess risk of non-infectious uveitis (NIU) following COVID-19 vaccination in patients without a prior history of uveitis.

Design: A retrospective matched cohort study and self-controlled case series (SCCS) analysis using a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data, Optum Labs Data Warehouse from December 11, 2020 to November 30, 2021.

Participants: In the matched cohort analysis, patients continuously enrolled with coverage 730 days before December 11, 2020 who received a COVID-19 vaccination during the study period were included. This COVID-vaccinated group was matched to a COVID-unvaccinated historical cohort of patients enrolled from 2018 and 2019. In the SCCS design, individuals from the vaccinated cohort who experienced a NIU event during the study period were included. Enrollees with prior uveitis history were excluded.

Methods: Hazard ratios for NIU were calculated using Cox proportional hazards models in the matched cohort design. Incidence rate ratios (IRR) comparing NIU incidence in exposed post-vaccine risk periods and unexposed control periods within an individual were calculated using conditional Poisson regression models in the SCCS design. Models were adjusted for age, recent receipt of non-COVID-19 vaccinations, corticosteroid or immunosuppressive use, and smoking history. Subgroup analyses were conducted by vaccination type and age group.

Main Outcome Measures: Rates of NIU identified with International Classification of Disease 10th revision codes.

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Supplemental Material: This article contains online-only material. The following should appear online only: Supplemental Tables 1–10, Supplemental Figures 1–2

Meeting Presentation: Part of the content of this research will be presented at the 2023 ARVO meeting.

Results: 4,611,378 patients were included in the matched cohort analysis, with 2,305,689 per cohort. The adjusted hazard ratio comparing NIU incidence in the COVID-19 vaccinated cohort to the unvaccinated cohort was 0.91 (95% CI: 0.75–1.10, p=0.33). In the SCCS analysis, 686 patients were included. The IRR comparing post-vaccine risk of NIU to risk during the control intervals was 1.05 (95% CI: 0.89–1.23, p=0.57). An increased risk was found in the subgroup aged 5–44 years (IRR = 1.40, 95% CI: 1.04–1.87, p=0.024).

Conclusions: Our matched cohort and SCCS analyses using a large claims database did not detect increased NIU risk following COVID-19 vaccination overall in individuals without history of the disease, providing reassurance about the overall safety of vaccination. The finding of increased risk in our youngest subgroup suggests potentially heightened immune responses in younger individuals and merits further investigation.

Keywords

COVID-19; COVID-19 vaccination; non-infectious uveitis; incidence

INTRODUCTION

Thus far, hundreds of millions of doses of COVID-19 vaccines have been administered in the United States as dose series and boosters, most notably the Pfizer-BioNTech mRNA BNT162b2 vaccine, Moderna mRNA 1273 vaccine, and Johnson & Johnson Janssen Ad26.COV2.S vaccine. While all three vaccines demonstrate high efficacy and have a favorable safety profile, reports of non-infectious uveitis (NIU) following vaccination have raised questions about whether there is an increased risk of ocular inflammation following COVID-19 vaccination.

Inflammation in the eye due to uveitis can cause irreversible damage, making it one of the leading causes of preventable blindness in developing countries.[1] While uveitis can be caused by direct infection, most cases are non-infectious and thought to be immune-mediated by unknown triggers. To date, there have been multiple case reports noting the onset of non-infectious uveitis following COVID-19 vaccinations. For example, several have highlighted instances of incident unilateral and bilateral anterior, posterior, and pan uveitis within 3 days and 30 days of receiving either dose of either mRNA vaccine.[2–5]

Concern about uveitis following vaccine administration is not new, as prior literature has reported ocular inflammation following the Bacille Calmette-Guerin, Hepatitis B, HPV, and influenza vaccinations, among others.[6–9] In a comprehensive review of the major adverse reaction reporting databases, it was determined that at least 289 cases of vaccine-associated uveitis occurred between 1984 and 2014.[10] However, despite the prevalence of vaccine-associated uveitis case reporting, no large-scale analytical or comparative studies have been conducted examining this potential association in the United States to date. The aim of our study was to assess the incidence of non-infectious uveitis following COVID-19 vaccination in patients without a prior history of the disease.

METHODS

Data Source

De-identified healthcare claims data from Optum Labs Data Warehouse (OLDW; Optum Labs, Eden Prairie, MN) was extracted to conduct this retrospective observational study.[11] OLDW contains detailed longitudinal health information for over 200 million enrollees in the United States across a spectrum of ages, genders, and geographies. The database contains patient claims data and electronic health record information from both private commercial and Medicare Advantage enrollees, including medical and pharmacy claims, laboratory results, and enrollment information.

Study Population

The COVID-19 vaccinated study population consisted of patients in OLDW age 5 and older with at least one recorded dose but no more than four recorded doses of a COVID-19 vaccine with emergency use authorization in the United States (Pfizer's BNT162b2, Moderna's mRNA-1273, or Johnson and Johnson's Ad26.COV2.S) from December 11, 2020 to November 30, 2021. Doses were identified based on Current Procedural Terminology (CPT) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and generic drug name text search in the pharmacy claims (Supplemental Table 1). Patients were required to have been continuously enrolled with medical and pharmacy coverage from 2 years (730 days) prior to their first vaccine record (index date). Given that individuals with and without a history of uveitis constitute different clinical populations, patients with a diagnosis of NIU in the 2 years before the index date were excluded (Supplemental Table 2). A look back period of 2 years was selected because it was thought that most patients with a uveitis history would have been seen for follow-up at least once within a 2-year period, even if their uveitis was inactive. Additionally, patients with a prior diagnosis of any infectious uveitis in the 2 years before the index date or during the observation period were excluded (Supplemental Table 2).

Outcome Assessment

A NIU outcome event was defined by the first occurrence of an International Classification of Disease 10th revision (ICD-10) diagnosis code for NIU in the first or second position in an encounter with either an ophthalmologist or optometrist (Supplemental Table 2 includes specific ICD-10 codes used). Additionally, at least one of the following prescription fills or procedure codes for a corticosteroid were required within seven days of the initial diagnosis to classify as an outcome event: 1) Topical (ophthalmic) corticosteroid prescription fill; 2) Local corticosteroid (ocular injection and implant) prescription fill or procedure code in a medical claim; 3) a new systemic corticosteroid prescription fill based on the pharmacy claims in the 30 days prior to the diagnosis, or 4) an escalated systemic corticosteroid prescription fill based on the pharmacy claims in the 30 days prior to the diagnosis, (Supplemental Table 3). Dose escalations among patients on systemic corticosteroids in the previous 30 days required an increase of the equivalent of 5mg of prednisone (Supplemental Table 4).

Matched Cohort Analysis

COVID-19 vaccination records are under-captured in US claims databases due to the nature of the vaccine rollout and how providers were instructed to bill insurance companies for the vaccines.[12,13] Patients without a record of COVID-19 vaccination may have been vaccinated without it being captured in OLDW. Therefore, in the first study design, the COVID-19 vaccinated cohort was compared to an unvaccinated historical comparison cohort of patients that were enrolled prior to the COVID-19 pandemic. Patients in the historical comparison group were required to be enrolled in OLDW with medical and pharmacy coverage during 2018 or 2019, before the COVID-19 pandemic began and COVID-19 vaccines were developed. After these patients were identified, they were each randomly assigned an index date from December 11, 2017 through November 30, 2019 based on the distribution of index calendar dates in the vaccinated population. Using this index date, the same exclusion criteria was applied as in the COVID-19-vaccinated group, described in the Study Population section.

The eligible vaccinated and unvaccinated patients were matched 1:1 on the following variables using exact matching: age (in 5 year categories), gender, race/ethnicity, US census region, insurance type (commercial or Medicare Advantage), Charlson Comorbidity Index (in 0, 1, 2, 3, 4, and >4 categories), history of autoimmune disease in the past 2 years (Supplemental Table 5), and receipt of an influenza vaccination in the past 2 years (Supplemental Table 6). Additionally, matching by healthcare utilization (in quartile categories of mean number of ambulatory visits per year in the past 2 years based on the vaccinated cohort) was done to account for potential differential utilization of healthcare during the pre-pandemic and pandemic eras, which the two different cohorts were drawn from.

For each patient, follow-up ended at the first occurrence of any of the following: occurrence of an NIU outcome event, disenrollment from the plan, or the end of the study period (1/31/2022 for the vaccinated group and 1/31/2020 for the unvaccinated group). Follow-up was split into multiple risk periods beginning at the index date and ending 60 days later or the next vaccination date, whichever came first. The next risk period began at the next vaccination date and continued up to 60 days or the next vaccination date, and so forth. The risk periods for each unvaccinated patient were designed to mirror the risk periods of their vaccinated match, so that the matched pairs have parallel risk periods based on the timing of the vaccinated patient's COVID-19 vaccination records. Risk periods were only included in the analysis if both the unvaccinated and vaccinated match were both at risk for the outcome at the beginning of the window, so if one of the pairs experienced an NIU event or disenrolled, no subsequent risk periods for the whole pair would be included (Supplemental Figure 1). To minimize bias, risk periods in both the vaccinated and unvaccinated groups were of equal length, 60 days. We used a 60-day timeframe to ensure that we did not miss patients who may have experienced delays in care due to the COVID-19 pandemic, or who delayed pursuing care themselves, especially given that these were patients who had not experienced NIU previously. Hazard ratios were additionally calculated using a 30-day timeframe instead as a sensitivity analysis.

Cox proportional hazards regression models with cluster-robust standard errors to account for the matched pairs were applied to estimate the marginal (unadjusted) and conditional (adjusted) effects of COVID-19 vaccination on NIU risk and corresponding 95% confidence intervals and p-values. Adjusted hazard ratios were adjusted for the following covariates: age as a continuous variable; administration of influenza, hepatitis B, human papillomavirus, varicella, measles/mumps/rubella, pneumococcal, or herpes zoster vaccinations within 30 days prior to the index date through the risk period, systemic corticosteroid use at the start of the risk period, immunomodulatory therapy use at the start of the risk period, and smoking history at baseline (Supplemental Table 3, 6, 7, 8). Subgroup analyses were conducted by age group (age 5–44, 45–64, >65 years) and COVID-19 vaccination type (BNT162b2, mRNA-1273, Ad26.COV2.S).

Self-Controlled Case Series Analysis

As an additional analysis, a self-controlled case series (SCCS) design was used to compare the incidence of non-infectious uveitis in unexposed control periods versus exposed post-vaccine risk periods within the same individual. This design inherently controls for time-invariant factors such as demographics, smoking history, chronic disease, and long-term medication use and has been applied extensively to study adverse vaccine events using observational data.[14,15] Individuals from the eligible pre-match vaccinated cohort who experienced a NIU event from their index date through the end of the study period (earliest of 1/31/2022 or disenrollment date) were included in the self-controlled case series analysis. Because patients in the SCCS design were selected from the pre-matched eligible vaccinated cohort, patients could be included in the SCCS analysis but not have been matched to an unvaccinated patient and thus not included in the matched cohort analysis.

Risk periods were defined as the 60 days following each COVID-19 vaccination and were censored early if the individual received another COVID-19 vaccination or if the study period ended prior to the full 60 days. Within the study period, a window of 30 days prior to a COVID-19 vaccine administration was excluded from the analysis to account for healthy vaccinee bias.[16] However, any period immediately following vaccination was preferentially designated as a risk period, even if the period was also within 30 days prior to the next COVID-19 vaccination. Any other time during the study period was considered to be an unexposed control period, remote from COVID-19 vaccination. Refer to Supplemental Figure 2 for a diagram of the SCCS design.

A fundamental assumption of the SCCS design is that the occurrence of an event does not change the probability of subsequent events occurring.[17] Because NIU sometimes may have a chronic or recurrent disease course, only the first occurrence of non-infectious uveitis during the study period was counted as an outcome event.[18] Conditional Poisson regression with an offset of the natural log of the length of the entire interval was used to estimate incidence rate ratios, 95% confidence intervals, and p-values for the risk of NIU following COVID-19 vaccination compared to unexposed periods. Subgroup analyses were conducted by age group and COVID-19 vaccination type, similar to the cohort analysis.

All statistical analyses were performed in R (Version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). P-values < 0.05 were considered

statistically significant. This study used de-identified data from an insurance claims database, so we were not required to obtain informed consent per our ethical board. This study was approved by the Institutional Review Board of the University of California, San Francisco and was conducted in adherence with the tenets of the Declaration of Helsinki.

RESULTS

Matched Cohort Design Results

Before matching, 8,166,608 unvaccinated individuals and 2,314,698 COVID-19 vaccinated individuals were eligible for the study (Supplemental Table 9). Following the 1:1 exact matching process, a total of 4,611,378 patients were included in the matched cohort analysis, with 2,305,689 patients in each cohort (mean age (SD) = 43.5 (17.7) years, 50.8% female, Table 1). 7.8% of patients in each cohort had a history of autoimmune disease. Among the historical unvaccinated cohort, 12.8% had a smoking history, 0.7% were on corticosteroids at their index date, 1.8% were on immunomodulatory therapy at their index date, and 5.9% had received a different vaccination 30 days prior to their index date. Among the COVID-19 vaccinated cohort, 13.1% had a smoking history, 0.6% were on corticosteroids at their index date, 2.0% were on immunomodulatory therapy at their index date, and 8.2% had received a different vaccination prior to their index date. A total of 4,219,633 COVID-19 vaccination doses (and corresponding matched unvaccinated risk periods) were included in the cohort analysis (Table 2).

In the vaccinated cohort, there were 254 cases of NIU in the risk periods following COVID-19 vaccination (519,752.1 person-years total), resulting in a crude incidence rate of 47.1 per 100,000 person-years. Among those who experienced an NIU event following the vaccine, the median time to the event from vaccination was 27 days (IQR=13–41 days). In the historical unvaccinated cohort, there were 266 cases of NIU in the risk periods (495,822.1 person-years total), resulting in a crude incidence rate of 50.6 per 100,000 person years. The unadjusted hazard ratio comparing NIU incidence in the vaccinated cohort to the unvaccinated cohort was 0.92 (95% CI: 0.76–1.11, p = 0.38). After adjustment for continuous age, history of other recent vaccinations, corticosteroid use, immunomodulatory therapy use, and smoking status, there was still not an increased risk of NIU in the vaccinated cohort as compared to the unvaccinated cohort (HR = 0.91; 95% CI: 0.75–1.10, p = 0.33, Table 3). Age was associated with an increased risk of post-vaccine NIU (HR = 1.02, 95% CI: 1.02–1.03, p < 0.001). Additionally, use of immunomodulatory therapy at the index date was associated with an increased risk of post-vaccine NIU (HR: 2.85, 95% CI = 1.91–4.24, p < 0.001). History of other recent vaccinations was associated with a decreased risk of post-vaccine NIU (HR = 0.66, 95% CI: 0.47–0.94, p = 0.02). No significant signals were detectable in subgroup analyses conducted by age or vaccination type (Figure 1). In our sensitivity analysis, the unadjusted hazard ratio using a 30-day timeframe was 0.82 (95% CI: 0.65–1.05, p = 0.11), and the adjusted hazard ratio using the 30-day timeframe was 0.83 (95% CI: 0.65–1.06, p = 0.14, Supplemental Table 10).

Subsequent characterization of the NIU cases within the two cohorts revealed that a similar percentage were treated with topical or local steroids (>95.6% in the unvaccinated cohort, >95.5% in the vaccinated cohort) and systemic steroids (5.6% in the unvaccinated cohort,

5.3% in the vaccinated cohort). The mean number of eye visits for NIU within 90 days of the diagnosis was higher in the unvaccinated group (2.71, [SD] = 1.86 visits) compared to the vaccinated group (2.49, [SD] = 1.44 visits). The distribution of anatomical locations involved in the NIU cases were similar across the cohorts, with anterior uveitis being the most common (Table 4).

Self-Controlled Case Series Results

Of all eligible vaccinated patients, 686 patients experienced an NIU event and were included in the self-controlled case series analysis (mean age (SD) = 52.9 (15.0) years, 56.7% female, Table 1). 16.6% of patients had a history of autoimmune disease. A total of 1,407 COVID-19 vaccine doses were identified in this population (Table 2).

There were 263 incident cases of NIU in the post-vaccine risk intervals, which spanned a cumulative 179 person-years throughout the study period. There were 423 incident cases of NIU in the unexposed control intervals, which spanned a cumulative time of 334 person-years throughout the study period. The incidence rate ratio (IRR) comparing the post-vaccine risk of NIU to the risk during the control intervals was 1.05 (95% CI: 0.89–1.23, p = 0.57). In a subgroup analysis by age, an increased risk of NIU post COVID-19 vaccination was found in the youngest subgroup, individuals between age 5 and 44 years (IRR = 1.40, 95% CI: 1.04–1.87, p = 0.02). No signal was detectable in the other age groups, or in the subgroup analyses by vaccination type (Figure 2).

DISCUSSION

In this study's population-based retrospective matched cohort analysis, there was not an increased risk of NIU following COVID-19 vaccination in the overall population of patients without prior history of the disease. The self-controlled case series analysis corroborated this finding. In the cohort analysis, the crude incidence rates of NIU were consistent with incidence rates of the disease in the United States as reported in the literature, which range from 24.9 to 52.4 cases per 100,000 person-years, adding validation to the study design.[19] In the matched cohort analysis, the detectable increased risk of post-vaccine NIU associated with age and immunomodulatory therapy use is consistent with these characteristics being known risk factors for development of the disease, most likely due to the immune dysregulation that accompanies older age, or a preexisting immune-mediated disease that would warrant the use of immunosuppressive drugs.[20,21]

In the self-controlled-case series analysis, there was a detectable increased risk of NIU following COVID-19 vaccination in the youngest subgroup of patients aged between 5 and 44 years old. Though still not significant, the hazard ratio in the matched cohort analysis comparing risk of NIU in the vaccinated cohort to the unvaccinated cohort also increased in the youngest subgroup. Though risk of non-infectious uveitis is known to increase with age, these results may indicate that younger age may be a risk factor for the development of vaccine-associated NIU.[22] This could be explained by the fact that younger individuals with heightened antibody responses have exaggerated immune reactions to the vaccination, a phenomena consistent with the finding of increased risk of other rare post-vaccination outcomes in specifically younger populations, such as myocarditis.[23]

However, the subgroup analysis is considered exploratory and should be interpreted with caution. Though this analysis provides preliminary insight into how risk may vary by age, division of the study populations into inevitably smaller subgroups resulted in sample sizes that were inadequate for making definitive conclusions, evidenced by the metrics' wide and overlapping confidence intervals and nonsignificant p-values in the subgroup analysis. Regardless, this finding is hypothesis-generating, and further exploration of post-vaccination risk of NIU in a larger sample size to allow for increased granularity in an age-based subgroup analysis could help elucidate this potential relationship.

Several hypotheses exist to potentially explain the connection between vaccination and the autoimmune etiology of non-infectious uveitis. One theory posits that the adjuvants included in the formulations of the vaccines activate endosolic or cytoplasmic Toll-like-receptors, triggering the inflammatory cascade and tissue damage characteristic of innate immunity.[24] Another theory is that vaccine peptide fragments engage in molecular mimicry, which leads to generation of antibodies against uveal self-peptides.[25] A third theory posits a Type 3 delayed hypersensitivity reaction in which antibodies against surface antigens of the vaccine form immune complexes that get deposited in ocular tissues and lead to inflammation and damage.[26]

Prior studies have sought to understand the potential association between COVID-19 vaccination and uveitis. In a retrospective analysis using the Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System between December 11, 2020 and May 29, 2022, a total of 1,094 cases of vaccine-associated uveitis were reported from 40 countries, with the highest number of reports following the BNT162b2 vaccine.[27] That study also found that most cases of vaccine-associated uveitis were reported after earlier doses, with 41.32% reported after the first dose, 34.1% after the second, and 8.87% after the third. Additionally, some comparative studies have been conducted, though none have been based in the United States. One Israel-based nationwide study of the risk of a variety of post-vaccine adverse events found no association between the BNT162b2 mRNA vaccine and uveitis in a similarly aged population to our study with mean (IQR) age of 38 (27–54) years.[28] Another Israel-based population study in a similarly aged population to our study with a mean (SD) age of 46.8 (19.6) years did find an association but noted that the small effect size implied that the minimal attributable risk should have minor public health impact.[29]

Also, a Japan-based study conducted a similar analysis of the association between COVID-19 vaccination and uveitis using both a matched cohort analysis and a self-controlled case series analysis and found no associated risk of uveitis with either study design. Of note, this was the only one of the four aforementioned studies that differentiated between incident and recurrent cases of NIU in their analyses and focused solely on those without a history of NIU. Though their study population was on average much older (mean age 69.3 years), restricted to a Japanese city, and underpowered in their matched cohort design, their results are overall consistent with our findings in a similar population without a NIU history.[30] Our study adds to the literature in being the first population-based retrospective comparative study examining the association between development of non-infectious uveitis and COVID-19 vaccination in the United States. It is strengthened

by the use of two separate analytical methodologies and a large sample size that each address confounding by different methods (cohort matching and self-controlled design), which allows rigorous evaluation surrounding this rare ocular event.

One potential limitation of this study is that the OLDW data source only includes patients with Medicare Advantage or commercial insurance, which may challenge the generalizability of this study to uninsured populations or those with basic Medicare or Medicaid plans. The COVID-19 vaccinated cohort was also on average younger and healthier than what would be expected of the vaccinated United States population as a whole, which also raises generalizability considerations. Additionally, smoking history is a known risk factor for uveitis, but it could not be determined for the majority of patients included in the analysis. Though it was adjusted for as a covariate in the final matched cohort analysis, the lack of available data limited the analysis. There may be other important confounders that are difficult or impossible to adjust for using claims data. For example, it is possible that patients on immunomodulatory therapies discontinued their medications around the time of immunization, which would not have been captured using claims data. However, it is unlikely that this phenomenon had considerable effect on these results given that only around 2% of the study population was on immunomodulatory therapy during the study period. This phenomenon may be of more significance in a study of a population with pre-existing NIU, where immunomodulatory therapy use is more common.

Finally, though a rigorous definition was used to identify non-infectious uveitis outcomes, it is possible that misclassifications could have occurred. For example, individuals newly diagnosed with NIU but previously on topical steroids for a different condition could have used accessible past prescriptions to treat their uveitis without getting a new prescription, and would not have been counted as an incident case. While the cohort design avoids the issue of misclassification of COVID-19 vaccination status by using a historical comparator group, vaccine misclassification could still occur in the self-controlled study design if some but not all of an individual’s vaccination records were captured as insurance claims. This would result in misclassifying exposed risk periods as unexposed control periods, which could bias toward not detecting a significant effect of the vaccine when in fact there is increased risk. However, the corroborating results from the cohort analyses suggest that COVID-19 vaccination does not significantly increase the risk of developing NIU. Another potential opportunity for misclassification was in identification of vaccine dose. Because dose number was sometimes not identifiable within the pharmacy claims data, doses were determined by the order in which they presented in the claims data, which may have resulted in the improper classification of subsequent doses as first doses if the true first doses were absent from the record. For this reason, dose-specific associations were not able to be determined in our study. Additionally, a patient with a remote history of NIU in extended remission may have been misclassified as an incident case if they were not seen in the 2-year look back period. However, it is unlikely that patients with a history of NIU would not be seen in any given two year period, and evaluating for NIU history prior to that 2-year look back period would require a longer continuous insurance enrollment requirement and thus limit generalizability by skewing the study population towards an older population.

In summary, this large epidemiological study did not detect an increased risk of NIU following COVID-19 vaccination in individuals without a history of the disease, providing reassurance about the overall safety of vaccination. Further research studying age-group-specific and dose-specific relationships and evaluating associations in uninsured populations will further strengthen the generalizability of these findings. Additionally, while this study has valuable implications on vaccine recommendations for the general public, future studies focused on the potential relationship between COVID-19 vaccination and NIU specifically in patients with a prior history of NIU will be important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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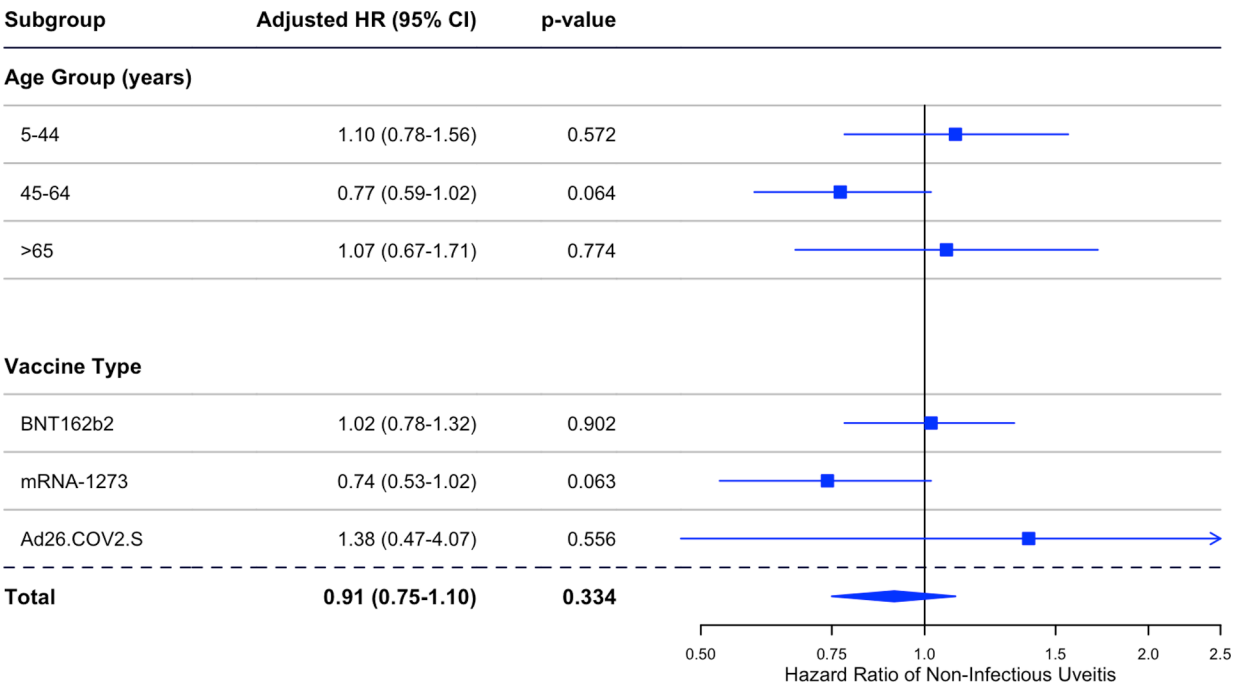

Figure 1.

Forest plot showing subgroup analyses conducted by age and vaccination type revealing no increased risk of non-infectious uveitis after vaccination in any subgroups. CI = confidence interval; HR = hazard ratio.

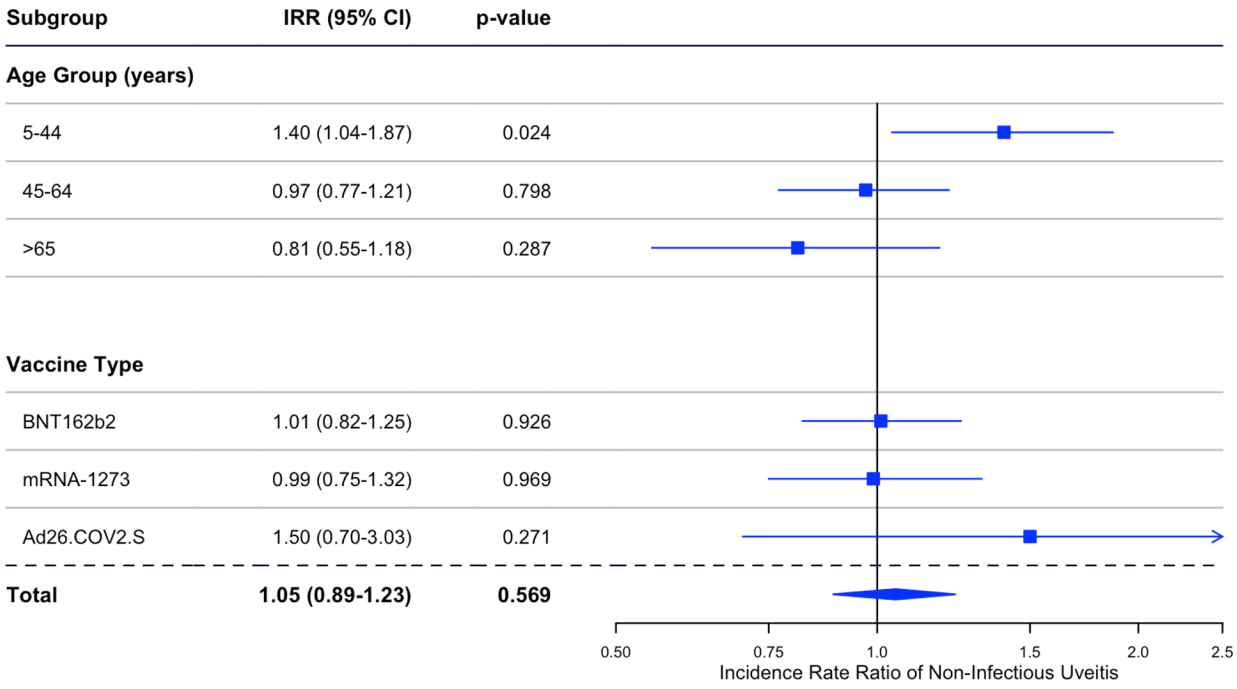

Figure 2.

Forest plot showing subgroup analysis by age and vaccination type revealing mildly increased risk of non-infectious uveitis in risk periods in subgroup aged 5–44 years with no increased risk in any other subgroups. Cl = confidence interval; IRR = incidence rate ratio.

Table 1.

Characteristics of matched cohort and self-controlled case series study populations

Characteristic	Cohort Population		SCCS Population[a]
	Unvaccinated N (%)	Vaccinated N (%)	N (%)
Total patients	2305689	2305689	686
Age (years)			
Mean (SD)	43.5 (17.7)	43.5 (17.7)	52.9 (15.0)
Median [Q1, Q3]	45.0 [31.0, 57.0]	45.0 [31.0, 57.0]	55.0 [43.0, 63.0]
Gender			
Female	1170225 (50.8%)	1170225 (50.8%)	389 (56.7%)
Male	1135464 (49.2%)	1135464 (49.2%)	297 (43.3%)
Race/ethnicity [b]			
Asian	151550 (6.6%)	151550 (6.6%)	42 (6.1%)
Black	182270 (7.9%)	182270 (7.9%)	77 (11.2%)
Hispanic	254070 (11.0%)	254070 (11.0%)	81 (11.8%)
White	1621803 (70.3%)	1621803 (70.3%)	461 (67.2%)
Unknown	95996 (4.2%)	95996 (4.2%)	25 (3.6%)
Region			
Midwest	682324 (29.6%)	682324 (29.6%)	216 (31.5%)
Northeast	247042 (10.7%)	247042 (10.7%)	73 (10.6%)
South	914945 (39.7%)	914945 (39.7%)	266 (38.8%)
West	458669 (19.9%)	458669 (19.9%)	131 (19.1%)
Other/Unknown	2709 (0.1%)	2709 (0.1%)	0 (0.0%)
Insurance Type			
Commercial	2201883 (95.5%)	2201883 (95.5%)	609 (88.8%)
Medicare Advantage	103806 (4.5%)	103806 (4.5%)	77 (11.2%)
Healthcare Utilization [c] **(ambulatory visits/year)**			
Mean (SD)	10.0 (13.0)	10.2 (12.9)	15.5 (16.0)
Median [Q1, Q3]	6.00 [2.5, 12.5]	6.00 [3.0, 12.5]	10.5 [5.0, 20.0]
Charlson Comorbidity Index [c]			
Mean (SD)	1.11 (1.66)	1.11 (1.64)	1.99 (2.20)
Median [Q1, Q3]	0 [0, 2.0]	0 [0, 2.0]	1.0 [0, 3.0]
Received Influenza Vaccine [c]	1047357 (45.4%)	1047357 (45.4%)	335 (48.8%)
History of Autoimmune Disease [c]	180637 (7.8%)	180637 (7.8%)	114 (16.6%)
Smoking Status			
Never smoker	181155 (7.9%)	414768 (18.0%)	
Current/former smoker	294801 (12.8%)	302736 (13.1%)	
Unknown	1829733 (79.4%)	1588185 (68.9%)	
Medication Use [d]			

Characteristic	Cohort Population		SCCS Population[a]
	Unvaccinated N (%)	Vaccinated N (%)	N (%)
Systemic Corticosteroids	17106 (0.7%)	13605 (0.6%)	
Immunomodulatory Therapy	41580 (1.8%)	45266 (2.0%)	
Received Other Vaccine [e]	137089 (5.9%)	188233 (8.2%)	

Abbreviations: SCCS=self-controlled case series; SD=standard deviation; Q1=1st quartile; Q3=3rd quartile.

[a]The SCCS (self-controlled case series) population includes patient who received a COVID-19 vaccination and experienced an outcome event during the study period.

[b]Ethnicity is assigned by an external vendor who uses a rule-based system that combines analysis of first names, middle names, surnames, and surname prefixes and suffixes with geographic criteria. Optum Labs then assigns these ethnicity values into one of five compliance-determined race/ethnicity code. *values: W (Non-Hispanic White), B (Non-Hispanic Black), H (Hispanic), A (Asian), and U (Unknown).*

[c]Measured in the two years (730 days) prior to the index date.

[d]Measured at the dose level at the time of vaccination or start of each risk period.

[e]Receipt of any of the following vaccines with or around the same time as the risk period (30 days before index date/dose up to event/censor): influenza, hepatitis B, human papillomavirus (HPV), varicella, measles/mumps/rubella (MMR), pneumococcal, or zoster vaccine.

Table 2.

Characteristics of COVID-19 vaccines doses included in each analysis

Characteristic	Cohort Design N doses (%)	SCCS Design[a] N doses (%)
Total doses	4219633	1407
Type of vaccination		
BNT162b2	2658488 (63.0%)	861 (61.2%)
mRNA-1273	1412335 (33.5%)	501 (35.6%)
Ad26.COV2.S	148810(3.5%)	45 (3.2%)
Dose administered		
1	2305689 (54.6%)	686 (48.8%)
2	1620699 (38.4%)	530 (37.7%)
3	291939 (6.9%)	191 (13.6%)
4	1306 (0.0%)	0 (0.0%)
Site of vaccination		
Mass immunization center	32919 (0.8%)	19 (1.4%)
Office	1152562 (27.3%)	425 (30.2%)
Outpatient hospital	333872 (7.9%)	148 (10.5%)
Pharmacy	2600127 (61.6%)	750 (53.3%)
Other	100153 (2.4%)	65 (4.6%)
Month of vaccination		
Dec 2020	13781 (0.3%)	<11 (<0.8%)
Jan 2021	131279 (3.1%)	75 (5.3%)
Feb 2021	227634 (5.4%)	138 (9.8%)
Mar 2021	689823 (16.3%)	298 (21.2%)
Apr 2021	932091 (22.1%)	>321 (>22.8%)
May 2021	524403 (12.4%)	134 (9.5%)
Jun 2021	247030 (5.9%)	52 (3.7%)
Jul 2021	161731 (3.8%)	35 (2.5%)
Aug 2021	252060 (6.0%)	43 (3.1%)
Sep 2021	197606 (4.7%)	44 (3.1%)
Sep 2021	213468 (5.1%)	68 (4.8%)
Nov 2021	408655 (9.7%)	98 (7.0%)
Dec 2021	220072 (5.2%)	90 (6.4%)

Abbreviations: SCCS=self-controlled case series.

[a]The SCCS population includes patient who received a COVID-19 vaccination and experienced an outcome event during the study period. To protect patient privacy, some counts cannot be displayed within small subgroups.

Table 3.

Matched Cohort Design Results: Risk of Non-infectious Uveitis among COVID-19 vaccinated versus historical unvaccinated cohorts

Characteristic	Adjusted HR (95% CI)[a]	*p*
Vaccination Status		
Unvaccinated	Reference[b]	
COVID-19 vaccinated	0.91 (0.75, 1.10)	0.333
Age (years)	1.02 (1.02, 1.03)	<0.001
Other Vaccine Received [c]		
Absent	Reference[b]	
Present	0.66 (0.47, 0.94)	0.022
Systemic Corticosteroid Use [d]		
Absent	Reference[b]	
Present	1.40 (0.68, 2.91)	0.365
Immunomodulatory Therapy Use [d]		
Absent	Reference[b]	
Present	2.85 (1.91, 4.24)	<0.001
Smoking Status		
Never smoker	Reference[b]	
Current/former smoker	0.96 (0.70, 1.32)	0.787
Unknown	0.80 (0.62, 1.05)	0.107

Abbreviations: HR=hazard ratio; CI=confidence interval, IMT=immunomodulatory therapy.

[a]Hazard ratios calculated using Cox proportional hazards regression. P-values displayed correspond to adjusted HRs. The adjusted models include all the variables listed in the table.

[b]Unvaccinated individuals served as the reference group to calculate the hazard ratios of NIU in the COVID-19 vaccinated group. For other vaccination, steroids, IMT, and smoking status, individuals without a history were used as the reference group for calculating the hazard ratios for those exposures.

[c]Receipt of any of the following vaccines with or around the same time as the risk period (30 days before index date/dose up to event/censor): influenza, hepatitis B, human papillomavirus (HPV), varicella, measles/mumps/rubella (MMR), pneumococcal, or zoster vaccine.

[d]Measured at the dose level at the time of vaccination or start of each risk period.

Table 4.

Matched Cohort Design: Characteristics of NIU Outcomes by COVID-19 vaccine exposure

Characteristic	Unvaccinated	Vaccinated
Total patients with NIU outcome	266	254
Received topical or local steroid within 7 days of diagnosis	>240 (>95.6%)	>234(>95.5%)
Received systemic steroids within 7 days of diagnosis	14 (5.6%)	13 (5.3%)
Number of eye visits for NIU within 90 days of diagnosis		
Mean (SD)	2.71 (1.86)	2.49 (1.44)
Median [Q1, Q3]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]
Uveitis anatomical location		
Anterior	>217(>86.5%)	220 (89.8%)
Intermediate/Posterior/Panuveitis	23 (9.2%)	25 (10.2%)
Unknown	<11 (<4.4%)	0 (0%)

Abbreviations: NIU=non-infectious uveitis.