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INVITED REVIEW

Ocular Adverse Events After COVID-19 Vaccination

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ABSTRACT

Purpose: The COVID-19 pandemic has galvanized the development of new vaccines at an unprecedented pace. Since the widespread implementation of vaccination campaigns, reports of ocular adverse effects after COVID-19 vaccinations have emerged. This review summarizes ocular adverse effects possibly associated with COVID-19 vaccination, and discusses their clinical characteristics and management.

Methods: Narrative Literature Review.

Results: Ocular adverse effects of COVID-19 vaccinations include facial nerve palsy, abducens nerve palsy, acute macular neuroretinopathy, central serous retinopathy, thrombosis, uveitis, multiple evanescent white dot syndrome, Vogt-Koyanagi-Harada disease reactivation, and new-onset Graves' Disease. Studies in current literature are primarily retrospective case series or isolated case reports – these are inherently weak in establishing association or causality. Nevertheless, the described presentations resemble the reported ocular manifestations of the COVID-19 disease itself. Hence, we hypothesize that the human body's immune response to COVID-19 vaccinations may be involved in the pathogenesis of the ocular adverse effects post-COVID-19 vaccination.

Conclusion: Ophthalmologists and generalists should be aware of the possible, albeit rare, ocular adverse effects after COVID-19 vaccination.

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COVID-19; vaccination; ocular inflammation; adverse effects; uveitis

Historically, vaccines have been known to be associated with ocular phenomena. For example, vaccinations against influenza, yellow fever, hepatitis B, and Neisseria meningitidis have been associated with uveitis, acute idiopathic maculopathy, acute macular neuroretinopathy (AMN), Vogt-Koyanagi-Harada disease (VKH), and multiple evanescent white dot syndrome (MEWDS).[1–7] The surge in the literature on COVID-19 and rapid development of vaccination regimens has produced reports on the ocular manifestations of COVID-19, as well as ocular adverse effects of COVID-19 vaccinations. Some of the reported ocular manifestations of COVID-19 infection include conjunctivitis, episcleritis, uveitis, vascular changes in the retina and cotton wool spots, optic neuritis, ocular motility deficits from cranial nerve palsies, and transient accommodation deficits.[8–13]

There are currently four types of COVID-19 vaccines. These include mRNA vaccines (BNT162b2, Pfizer-BioNTech[14]; mRNA-1273, Moderna[15]), protein subunit vaccines (NVX-CoV2373, Novavax[16]), vector vaccines (Ad26.COV2, Janssen Johnson & Johnson[17]; ChAdOx1 nCoV-19/ AZD1222, Oxford-AstraZeneca[18]), and whole virus vaccines (PiCoVacc, Sinovac[19]; BBIBP-CorV, Sinopharm[20]). While their respective trial reports on vaccine safety have shown that ocular adverse effects are rare, the possible manifestations are still a cause for concern, given the scale of the current vaccination campaign against COVID-19.

This review provides a comprehensive overview of COVID-19 vaccine-induced ocular adverse effects. A review of the incidence of such conditions is timely and would be beneficial to ophthalmologists and general physicians alike, in identifying patients who may be at a higher risk of ocular adverse events so that protocols for close monitoring of patients at risk can be designed and implemented.

Methodology

For this narrative review, relevant publications were identified through a computerized database search of MEDLINE, EMBASE and Google Scholar. The search comprised the following keywords: 'COVID,' 'COVID-19,' 'SARS-COV-2,' 'coronavirus,' 'vaccination,' 'ocular complications,' 'ocular manifestation,' 'thrombosis,' 'retinopathy,' 'maculopathy,' 'uveitis,' 'ocular inflammation.' Search results were screened for relevance. References cited within the identified articles

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Table 1. Summary of studies describing ocular adverse effects secondary to COVID-19 vaccination.

Study	Summary	Vaccine	Dose Involved	Time to onset of symptoms	Ocular Symptom and Number of Cases (n)
Bayas *et al.*[21] Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination.	A case report of bilateral superior ophthalmic vein thrombosis post-vaccination	AZD1222	1	10 days	Conjunctival congestion, retroorbital pain, diplopia n = 1
Bøhler *et al.*[22] Acute macular neuroretinopathy following COVID-19 vaccination.	A case report of acute macular neuroretinopathy (AMN) post-vaccination	AZD1222	1	2 days	Paracentral scotoma n = 1
Book *et al.*[23] Bilateral Acute Macular Neuroretinopathy After Vaccination Against SARS-CoV-2	A case report of Bilateral Acute Macular Neuroretinopathy post-vaccination	AZD1222	1	3 days	Bilateral paracentral scotoma n = 1
Collela *et al.*[24] Bell's palsy following COVID-19 vaccination	A case report of Bell's Palsy post-vaccination	BNT162b2	1	5 days	Left sided facial droop n = 1
Crnej *et al.*[25] Acute corneal endothelial graft rejection following COVID-19 vaccination	A case report of DMEK rejection post-vaccination	BNT162b2	1	7 days	Sudden painless decrease of vision n = 1
Elsheikh *et al.*[26] Acute Uveitis following COVID-19 Vaccination	A case report of juvenile idiopathic arthritis-associated anterior uveitis post-vaccination	BBIBP-CorV	2	5 days	Bilateral blurred vision, photophobia n = 1
Fowler *et al.*[27] Acute-onset central serous retinopathy after immunization with COVID-19 mRNA vaccine.	A case report of acute-onset central serous retinopathy (CSR) post-vaccination	BNT162b2	1	3 days	Blurring of vision, metamorphopsia n = 1
Goyal *et al.*[28] Bilateral Multifocal Choroiditis following COVID-19 Vaccination	A case report of bilateral multifocal choroiditis post-vaccination	AZD1222	2	9 days	Right eye floater that progressed gradually from the periphery toward the center n = 1
Mambretti *et al.*[29] Acute Macular Neuroretinopathy following Coronavirus Disease 2019 Vaccination.	A case report of acute macular neuroretinopathy (AMN) post-vaccination	AZD1222	1	2 days	Paracentral scotoma n = 2
Michel *et al.*[30] Acute Macular Neuroretinopathy After COVID-19 Vaccine.	A case report of acute macular neuroretinopathy (AMN) post-vaccination	AZD1222	1	2 days	Central scotoma n = 1
Mudie *et al.*[31] Panuveitis following Vaccination for COVID-19.	A case report of panuveitis post-vaccination	BNT162b2	2	3 days	Reduction in visual acuity, ocular pain, red eye, photophobia n = 1
Ozonoff *et al.*[32] Bell's palsy and SARS-CoV-2 vaccine.	A case series of numerical imbalance in incidences of Bell's palsy between vaccine and placebo arms during trials	BNT162b2, mRNA-1273	NA	NA	n = 7
Papasavvas *et al.*[33] Reactivation of Vogt-Koyanagi-Harada disease under control for more than 6 years, following anti-SARS-CoV-2 vaccination.	A case report of reactivation of Vogt-Koyanagi-Harada disease post-vaccination	BNT162b2	2	6 weeks	Photophobia, ocular pain n = 1
Phylactou *et al.*[34] Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine.	A case report of Descemet membrane endothelial keratoplasty (DMEK) patients with graft rejection post-vaccination	BNT162b2	1, 2	7 days to 3 weeks	Blurred vision, red eye, photophobia n = 2
Rabinovitch *et al.*[35] Uveitis following the BNT162b2 mRNA vaccination against SARS-CoV -2 infection	Multicentre, retrospective study describing vaccine-related uveitis and multiple evanescent white dot syndrome post-vaccination	BNT162b2	1, 2	1–30 days	Blurred vision, red eye, photophobia n = 23
Ravichandran *et al.*[36] Corneal graft rejection after COVID-19 vaccination.	A case report of PKP patient with graft rejection post-vaccination	AZD1222	1	3 weeks	Blurred vision, red eye n = 1
Renisi *et al.*[37] Anterior uveitis onset after BNT162b2 vaccination	A case report of anterior uveitis post-vaccination	BNT162b2	2	14 days	Blurred vision, red eye, photophobia n = 1
Repajic *et al.*[38] Bell's Palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell's palsy	A case report of Bell's palsy post-vaccination. This patient had a history of 3 episodes of Bell's palsy	BNT162b2	2	36 h	Facial droop n = 1
Reyes-Capo *et al.*[39] Acute Abducens Nerve Palsy Following COVID-19 Vaccination.	A case report of isolated abducens nerve palsy post-vaccination	BNT162b2	1	2 days	Painless, horizontal, binocular diplopia n = 1

(*Continued*)

Table 1. (Continued).

Study	Summary	Vaccine	Dose Involved	Time to onset of symptoms	Ocular Symptom and Number of Cases (n)
Santovito *et al.*[40] Acute reduction of visual acuity and visual field after Pfizer-BioNTech COVID-19 vaccine 2nd dose: a case report.	A case report of possible uveitis post-vaccination	BNT162b2	2	3 days	Reduction in visual acuity, visual distortion n = 1
Shemer *et al.*[41] Association of COVID-19 Vaccination and Facial Nerve Palsy: A Case-Control Study	A case-control study of association between facial nerve palsy between vaccinated and unvaccinated groups	BNT162b2	1, 2	9–14 days	n = 21
Vera-Lastra *et al.*[42] Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants.	A case report of Graves' disease activation post-vaccination	BNT162b2	1	2–3 days	n = 2
Wasser *et al.*[43] Keratoplasty Rejection After the BNT162b2 messenger RNA Vaccine.	A case report of penetrating keratoplasty (PKP) patients with graft rejection post-vaccination	BNT162b2	1	13–14 days	Blurred vision, ocular discomfort, red eye n = 2

were used to further augment the search. This review encompassed an international search, but only articles published in English were used. We restricted our search to articles published within the past decade, up till August 21, 2021.

Results

A total of 23 articles reported ocular findings associated with COVID-19 vaccinations (Table 1). Ocular complications were reported in 74 unique individuals – including facial nerve palsy/ Bell's palsy, abducens nerve palsy, AMN, superior ophthalmic vein (SOV) thrombosis, corneal graft rejection, uveitis, central serous chorioretinopathy, VKH reactivation, and onset of Graves' disease. The reported entities appear to overlap with the ocular manifestations of COVID-19 itself, suggesting a common pathway between virus and vaccine-mediated immune response in humans.

Facial Nerve Palsy

The Pfizer-BioNTech (BNT162b2)[14] and Moderna (mRNA-1273)[15] vaccine trials suggest an imbalance in the incidence of Bell's palsy following vaccination compared with the placebo arm of each trial. Among 36,901 vaccine arm participants in combined data, there were seven Bell's palsy cases (1:5272) compared with one Bell's palsy case among placebo arm participants (1:36,938). The United States Food and Drug Administration (FDA) initially reported that the observed frequency of reported Bell's palsy in the vaccine group was consistent with the expected background rate in the general population, providing no clear basis to conclude a causal relationship.[44,45] Ozonoff *et al.*[32] commented that such reporting was misconceived. Given the generally agreed incidence of Bell's palsy at 15–30 cases per 100,000 person-years,[46,47] the median 2-month observation period of the clinical trials translated to an observed incidence of 3.5–7 times higher in the vaccine arms than the general population. Cirillo *et al.*[46] provided an alternative interpretation – given that safety data were collected for 2 months after the second, not the first dose, the observed incidence might be 1.5–3 times higher than the general population. Collela *et al.*[24] and Repajic *et al.*[38] provided detailed expositions of the signs and symptoms that led to a diagnosis of Bell's palsy in COVID-19 BNT162b2 vaccine recipients. An Israeli case-control study[41] found that 21 of 37 individuals (56.8%) with facial nerve palsy were recently vaccinated with the first or second dose of the BNT162b2 vaccine, compared with 44 of 74 (59.5%) in the control group. After adjustment for pre-existing immune- or inflammatory-related disorders, diabetes, and a previous episode of peripheral nerve palsy, odds ratio (OR) for exposure to the vaccine among cases was insignificant at 0.84 (95%CI 0.37–1.90, p-value = 0.67). Based on the OR from different studies, it is highly unlikely that Bell's palsy is associated with COVID-19 vaccination and if at all, the pathophysiological process for facial nerve palsy post COVID-19 vaccination needs to be hypothesized and proven. While facial nerve palsy is a reported adverse event in other vaccinations,[32] such as influenza and meningococcal conjugate vaccinations, mRNA-based vaccines might follow a different immune mechanism.

Abducens Nerve Palsy

A healthy 59-year-old female presented with isolated abducens nerve palsy following a febrile episode two days after receiving the BNT162b2 vaccine.[39] No details on the persistence of the palsy were provided. Slit lamp, fundus examination, and non-contrast magnetic resonance imaging (MRI) of the brain and orbits were unremarkable.

AMN

AMN is a rare condition characterized by macular reddish-brown, wedge-shaped lesions, the apices of which are often directed toward the fovea.[48] This is often accompanied by paracentral scotomas and mild loss of vision at onset.[48] Four studies[22,23,29,30] reported cases of AMN. All patients were female and received the ChAdOx1 nCoV-19 vaccine. All were on oral contraceptive pills (OCP) and manifested symptoms two days after the first dose. Three reported fever, and one reported flu-like symptoms prior to the appearance of the scotoma. In two patients, the visual symptoms lasted <24 h. On optical coherence tomography (OCT), hyperreflectivity of the outer nuclear and plexiform layers was seen along with disruption of the ellipsoid zone. Subtle capillary dropout was also noted on OCT angiography.

AMN is a rare retinal disease, the pathophysiology of which is still unknown, although a microvascular abnormality in the deep capillary plexus of the retina is hypothesized.[48,49] Of the AMN cases reviewed, all subjects were confounded by OCP usage. OCP usage has been associated with structural changes to the macula, retinal nerve fiber layer, and choroidal thickness[50] and identified as a risk factor for AMN. However, the relative rarity of AMN and the temporal association between the vaccine administration and the onset of the disease should be taken into consideration. This is likely due to the presence of estrogen and progesterone receptors in ocular tissues of premenopausal women, including the choroid and retina.[51] It has been postulated that concurrent OCP usage may increase the susceptibility of ocular tissues to AMN.[48] Whether the potential thrombogenic role of COVID-19 vaccination played an additional role in the AMN pathogenesis of these patients has yet to be established.

Central Serous Chorioretinopathy

A 33-year-old male presented with blurring of vision and metamorphopsia 69 h after receiving the first dose of BNT162b2 and was diagnosed with central serous chorioretinopathy.[27] He had a previous ocular history of mild hyperopic refractive error. Dilated fundus examination revealed foveal reflex loss and a swollen macula without haemorrhage. OCT was performed, which showed macular serous detachment of the neurosensory retina, with OCT angiography showing general attenuation of choriocapillaris flow signal in the area of serous retinal detachment. Fundus fluorescein angiography showed point leakage. The patient was prescribed spironolactone, and all symptoms eventually resolved on follow up.

Ophthalmic Vein Thrombosis

Regarding post-vaccination thrombosis, rare cases of post vaccination immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST) after administration of the adenovirus vector vaccines ChAdOx1 nCoV-19 and Ad26.COV2 have been well described.[52–57] Anatomically, CVST post-COVID-19 vaccination has been reported to occur in virtually all the dural venous sinuses,[52] and a majority of patients are females.[52] This section focuses on superior ophthalmic vein thrombosis, as reported in two isolated cases.[21,58] Both patients received the ChAdOx1 nCoV-19 vaccine. Panovska-Stavridis *et al.*[58] describe a 29-year-old female who presented with severe headache, orbital swelling with proptosis, limited ocular motility, vertical diplopia, and reduced visual acuity 10 days after the first dose. Initial findings showed thrombocytopenia of 18×10^9/L and high D-dimer levels of 35712 µg/L. Antibody screening showed high levels of antibodies against Heparin/Platelet Factor 4 complex. Contrast-enhanced MRI demonstrated central filling defects and a widened and enhanced left SOV, revealing thrombosis. The patient was treated with intravenous immunoglobulin (IVIG) for two days followed with tapered oral prednisolone. All symptoms resolved within 5 days. Bayas *et al.*[21] described a 55-year-old female with bilateral SOV thrombosis on post-dose day 10, also definitively diagnosed on MRI showing filling defects and T2 enhancement of both SOV. Laboratory investigations supported a diagnosis of secondary immune thrombocytopenia. Despite therapeutic heparinization, the patient developed an ischemic stroke in the left parietal lobe, middle cerebral artery region on post-dose day 18. Healthcare professionals should be on the alert for possible cases of thromboembolism – CVST, pulmonary, deep vein thrombosis, or in the ophthalmic context – SOV thrombosis – after ChAdOx1 nCoV-19 or Ad26.COV2 administration.

Corneal Graft Rejection

Four articles described corneal graft rejection soon after receiving a COVID-19 vaccination.[25,34,36,43] Phylactou *et al.*[34] reported two cases of allograft rejection following Descemet's membrane endothelial keratoplasty (DMEK); both were female. A 66-year-old woman received the BNT162b2 vaccine 14 days after grafting and developed endothelial graft rejection 7 days later (day 21 post-transplant). She had a history of well-controlled human immunodeficiency virus infection with undetectable viral load. The other case, an 83-year-old woman, underwent DMEK 6 years before BNT162b2 administration. She developed symptoms 3 weeks after the second dose. For both DMEK cases, slit lamp examination and anterior segment optical coherence tomography (OCT) revealed moderate conjunctival injection, diffuse corneal oedema, and fine keratic precipitates limited to the donor endothelium with anterior chamber cells. Crnej *et al.*[25] reported the case of a 71-year old male that presented with acute endothelial rejection 7 days after receiving the first dose of BNT162b2, 5 months after DMEK surgery. Topical dexamethasone 1 mg/mL every two hours was initiated. BCVA improved to 20/25 with a clear cornea one week later. The patient opted to receive his second dose after being counselled for the possible association between the first dose of vaccination and the acute transplant rejection. The graft remained clear, and visual acuity remained stable 3 weeks after the second dose. Rejections were also reported following three penetrating keratoplasty (PKP) cases[36,43]; all three were male; 1 case had a previous re-graft. Two of the PKP rejections manifested 13 to 14 days after receiving the first dose[43] of the vaccine, while the third occurred after 21 days, also from the first dose.[36]

Regarding corneal graft rejection, any systemic immune dysregulation may compromise corneal ocular immune privilege and increase the patient's susceptibility for rejection.[59]There is a report about acute corneal endothelial graft rejection with coinciding COVID-19 infection.[60] Inflammation in COVID-19 patients is characterized by increased tumor necrosis factor–α (TNF–α) and interleukin-6 (IL-6) production.[61] Cells of the innate immune system can invade the cornea and result in the up regulation of cytokines (including TNF–α, chemokines) and other pro-inflammatory molecules, which can result in rejection of the corneal transplants. With activation of the immune system post-vaccination, these mechanisms may contribute to vaccine-related corneal graft rejection. Reports on graft rejection after other viral vaccinations are scarce.[62–64]

New Onset Uveitis

We identified five case reports[26,28,31,37,40] and one multicenter, retrospective case series[35] describing uveitis after COVID-19 vaccination. In one case report,[26] an 18-year-old female with a history of antinuclear antibody (ANA) positive oligoarticular juvenile idiopathic arthritis (JIA) presented with bilateral anterior uveitis 5 days after the second dose of BBIBP-CorV. HLA-B27 testing returned negative.

She was started on topical prednisolone acetate 1% every 2 h and cyclopentolate hydrochloride three times daily, with complete resolution and bilateral 6/6 visual acuity by 6 weeks. Goyal *et al.*[28] described bilateral choroiditis in a 34-year-old male 9 days after the second dose of AZD1222. The patient presented with a right eye floater that rapidly progressed to severe visual loss within 12 hours. OCT revealed massive subretinal fluid involving the macula in the right eye. The left eye had milder subretinal fluid not involving the macula. B-scan showed bilateral choroidal thickening. He was started on oral prednisolone 1 mg/kg/day. Visual acuity was reinstated to 6/6 bilaterally in eleven days. In the remaining four articles, all subjects received the BNT162b2 vaccine. Santovito *et al.*[40] described a male patient with a SARS-COV-2 infection several months earlier who developed transient visual field loss 3 days after a first dose of BNT162b2. The visual acuity deficit lasted less than a day and was associated with a plethora of systemic nonspecific symptoms, such as unilateral headache, nausea, asthenia, and mild confusion. No further investigations were performed. Mudie *et al.*[31] described a female subject who developed panuveitis three days after the second dose. Her vision improved on a tapering dose of 50 mg/day of oral prednisone and two hourly difluprednate lasting three weeks. At the end of three weeks, there was recurrence of choroidal thickening and systemic corticosteroid therapy was recommenced. OCT showed vitreous debris, retinal and choroidal thickening. Fluorescein angiography (FA) revealed mild peripheral vascular leakage. Rabinovitch *et al.*[35] described 21 cases of uveitis in Israel following COVID-

19 vaccination. 8 and 13 cases occurred after the first and second BNT162b2 doses respectively. There were 19 patients with anterior uveitis whereas two patients were diagnosed to have multiple evanescent white dot syndrome (MEWDS) (after receiving the initial diagnosis of anterior uveitis). MEWDS is a rare self-limiting condition of the retinal pigment epithelium (RPE) or outer retina,[65] following the second vaccination. MEWDS cases were not treated. Mean time between vaccination to uveitis onset was 7.5 ± 7.3 days (1–30 days). At final follow-up, complete resolution was achieved in all but two eyes, which showed significant improvement. One case of severe anterior uveitis developed vitritis and macular edema following second vaccination, which needed and completely resolved following intravitreal dexamethasone.[35]

VKH Reactivation

One article by Papasavvas *et al.* was identified.[33] The reported subject was a woman with a pre-existing diagnosis of VKH well controlled for the past six years. The initial onset of VKH was severe, necessitating infliximab infusions which were continued as regular maintenance therapy. She manifested a severe reactivation of VKH 6 weeks after receiving the second dose of the BNT162b2 vaccine. She had received infliximab infusions 3.5 weeks before the first vaccine dose and 7.5 weeks before the second vaccine dose.[33] Slit-lamp examination showed anterior chamber inflammation with mutton-fat keratic precipitates, and OCT was performed, revealing retinal folds, subretinal fluid and increased choroidal thickness. Oral corticosteroids were initiated, alongside infliximab therapy, with the disease reactivation brought under control. However, as the VKH reactivation was reported six weeks after receiving the second dose of vaccination, it is difficult to establish a temporal association between COVID-19 vaccination and VKH reactivation based on this single case report.

Graves' Disease

Onset of Graves' disease (GD) in two subjects was reported a few days after the first dose of BNT162b2.[42] One patient had suffered a prior COVID-19 infection and a history pulmonary arterial hypertension. Both were newly diagnosed with GD on the manifestation of symptoms. Both received a dose of the BNT162b2 vaccine and reported symptoms 2–3 days after. No description of ocular symptoms or ophthalmic investigations were included in the study. The study found the subjects' presentation to fit the diagnostic criteria for autoimmune/inflammatory syndrome induced by adjuvants (ASIA),[66] also known as Shoenfeld's Syndrome. As Graves' disease is known to involve orbits and/or ocular surface, we have included this two cases in this comprehensive review even though the reported cases did not had any ocular manifestations at time of presentation.

Discussion

At present, given the nascent nature of COVID-19 vaccines and evolving data on their adverse effects, it is imperative to emphasize that no causality can be established from this review. Furthermore, of the published cases with clear ocular pathology demonstrated on examination and investigation, most recovered well with swift initiation of treatment. It is important to remember the remarkably low incidence of adverse events related to the vaccine considering the massive rollout campaign across the world. To date, there is no evidence to suggest that individuals should avoid getting vaccinated for ophthalmic-related reasons.

Most of the reviewed literature includes case reports and series, and there are limits to the detail provided regarding ophthalmic assessment, treatment initiated, visual outcome and of underreporting of cases. Furthermore, there is heterogeneity in terms of investigations performed, affecting analysis of the cases. Given that vaccine induced ocular phenomena have been established with a multitude of other vaccines, that COVID-19 vaccinations are not exempt is unsurprising. There remains a larger question of elucidating the mechanisms involved in a maladaptive immune response and identifying the susceptible individuals for closer follow up.

Vaccinations in the autoimmune population decreases the burden of infection. To boost vaccine efficacy, adjuvants are often added to potentiate their effect on the innate and adaptive immune systems. While generally safe and effective, in a fraction of subjects (perhaps genetically or otherwise predisposed), the administration of adjuvants can lead to an autoimmune or inflammatory syndrome.[52] The adjuvants included in COVID-19 mRNA vaccines stimulate innate immunity through endosolic or cytoplasmic nucleic acid receptors.[67] Several autoimmune diseases, particularly connective tissues diseases are associated with an altered nucleic acid metabolism and processing which may trigger an immune response following immunization.[68,69]

The consequences of maladaptive immune response in those with autoimmune disease resulting in reactivation of disease should be considered. It is also essential to establish the response of autoimmune disease patients to vaccines and if the response is suboptimal in this population. This would have far-reaching consequences on future development of vaccines and risk-stratification of at-risk groups. Leibowitz *et al.*[70] reviewed evidence that suggests uveitis and autoimmune diseases have a systemic overlap, and the development of uveitis may represent an undiagnosed autoimmune condition. There may thus be a role for further workup for more widespread inflammatory disease in individuals who develop ocular inflammatory events following COVID vaccination.

Comparative models for reactivation of autoimmune diseases post-vaccination have not demonstrated an increased risk in reactivation following vaccination for other diseases.[71] Regarding the COVID-19 vaccine, Achiron *et al.*[85] found no increase in relapse activity in multiple sclerosis (MS) patients in an observational study. In fact, the recommendations provided were to vaccinate MS patients to alleviate the disease burden of COVID-19.

Conclusions

The current literature shows substantial overlap between the ocular adverse effects of COVID-19 infection and COVID-19 vaccination. Reports on such adverse effects are rare, and

further longitudinal, multicenter studies are required to prove such associations, if any. It may be useful to identify the high risk characteristics for the patients developing ocular adverse events in response to COVID-19 infection or vaccination. As COVID-19 gradually becomes an endemic disease, a dedicated international registry for compiling of rare ocular adverse effects post COVID-19 vaccination could facilitate our understanding of the subject. Such cases can be retrospectively reviewed or prospectively followed-up.

Author contributions

All authors contributed to the intellectual development of this paper. NXL and RA conceived and planned the review. NXL, BKB, MDS, and RA wrote the manuscript. NXL and BKB performed the literature review. NXL, BKB, IT, SLH, MT, MZ, SPC, VG, CP, MDS, and RA contributed to interpreting the results and provided critical feedback to the manuscript. The final version of the paper has been seen and approved by all authors.

Declaration of interest

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References

1. Marinho PM, Nascimento H, Romano A, Muccioli C, Belfort R Jr. Diffuse uveitis and chorioretinal changes after yellow fever vaccination: a re-emerging epidemic. *Int J Retina Vitreous*. 2019;5:30. doi:10.1186/s40942-019-0180-0.
2. Ng CC, Jumper JM, Cunningham ET Jr. Multiple evanescent white dot syndrome following influenza immunization - A multimodal imaging study. *Am J Ophthalmol Case Rep*. Sep, 2020;19:100845. doi:10.1016/j.ajoc.2020.100845.
3. Jorge LF, Queiroz RP, Gasparin F, Vasconcelos-Santos DV. Presumed unilateral acute idiopathic maculopathy following H1N1 vaccination. *Ocul Immunol Inflamm*. Mar 11, 2020;1-3. doi:10.1080/09273948.2020.1734213.
4. Shah P, Zaveri JS, Haddock LJ. Acute macular neuroretinopathy following the administration of an influenza vaccination. *Ophthalmic Surg Lasers Imaging Retina*. Oct 1, 2018;49(10):e165–e168. doi:10.3928/23258160-20181002-23.
5. Sood AB, O'Keefe G, Bui D, Jain N. Vogt-Koyanagi-Harada disease associated with hepatitis B vaccination. *Ocul Immunol Inflamm*. 2019;27(4):524–527. doi:10.1080/09273948.2018.1483520.
6. Abou-Samra A, Tarabishy AB. Multiple evanescent white dot syndrome following intradermal influenza vaccination. *Ocul Immunol Inflamm*. 2019;27(4):528–530. doi:10.1080/09273948.2017.1423334.
7. Biancardi AL, Moraes HV Jr. Anterior and intermediate uveitis following yellow fever vaccination with fractional dose: case reports. *Ocul Immunol Inflamm*. 2019;27(4):521–523. doi:10.1080/09273948.2018.1510529.
8. Aggarwal K, Agarwal A, Jaiswal N, et al. Ocular surface manifestations of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *PLoS One*. Nov 5, 2020;15(11):e0241661. doi:10.1371/journal.pone.0241661.
9. Lim LW, Tan GS, Yong V, et al. Acute onset of bilateral follicular conjunctivitis in two patients with confirmed SARS-CoV-2 infections. *Ocul Immunol Inflamm*. Nov 16, 2020;28(8):1280–1284. Epub 2020 Oct 6. PMID: 33021847. doi:10.1080/09273948.2020.1821901.
10. Seah I, Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm*. Apr 2, 2020;28(3):391–395. Epub 2020 Mar 16. doi:10.1080/09273948.2020.1738501.
11. Elenga N, Martin E, Gerard M, Osei L, Rasouly N. Unilateral diplopia and ptosis in a child with COVID-19 revealing third cranial nerve palsy. *J Infect Public Health*. Aug 10, 2021;14(9):1198–1200. Epub ahead of print. doi:10.1016/j.jiph.2021.08.007.
12. Umapathi T, Li KZ, Chin CF, et al. Acute isolated near vision difficulty in patients with COVID-19 infection. *J Neuroophthalmol*. Sep 1, 2021;41(3):e279–e282. doi:10.1097/WNO.0000000000001120.
13. Sen S, Kannan NB, Kumar J, et al. Retinal manifestations in patients with SARS-CoV-2 infection and pathogenetic implications: a systematic review. *Int Ophthalmol*. Aug 11, 2021;1–14. (Epub ahead of print. PMID: 34379290; PMCID: PMC8356207). doi:10.1007/s10792-021-01996-7.
14. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. Dec 31, 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577.
15. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. Feb 4, 2021;384(5):403–416. doi:10.1056/NEJMoa2035389.
16. Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med*. Jun 30, 2021. doi:10.1056/NEJMoa2107659.
17. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med*. Jun 10, 2021;384(23):2187–2201. doi:10.1056/NEJMoa2101544.
18. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. Jan 9, 2021;397(10269):99–111. doi:10.1016/s0140-6736(20)32661-1.
19. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. Jul 3, 2020;369(6499):77–81. doi:10.1126/science.abc1932.
20. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. Jan, 2021;21(1):39–51. doi:10.1016/s1473-3099(20)30831-8.
21. Bayas A, Menacher M, Christ M, Behrens L, Rank A, Naumann M. Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *Lancet*. May 1, 2021;397(10285):e11. doi:10.1016/s0140-6736(21)00872-2.
22. Bøhler AD, Strøm ME, Sandvig KU, Moe MC, Jørstad ØK. Acute macular neuroretinopathy following COVID-19 vaccination. *Eye (Lond)*. Jun 22, 2021;1-2. doi:10.1038/s41433-021-01610-1.
23. Book BAJ, Schmidt B, Foerster AMH. Bilateral acute macular neuroretinopathy after vaccination against SARS-CoV-2. *JAMA Ophthalmol*. Jul 1, 2021;139(7):e212471. doi:10.1001/jamaophthalmol.2021.2471.
24. Colella G, Orlandi M, Cirillo N. Bell's palsy following COVID-19 vaccination. *J Neurol*. Feb 21, 2021;1-3. doi:10.1007/s00415-021-10462-4.
25. Crnej A, Khoueir Z, Cherfan G, Saad A. Acute corneal endothelial graft rejection following COVID-19 vaccination. *J Fr Ophtalmol*. Jul 8, 2021. doi:10.1016/j.jfo.2021.06.001.
26. ElSheikh RH, Haseeb A, Eleiwa TK, Elhusseiny AM. Acute uveitis following COVID-19 vaccination. *Ocul Immunol Inflamm*. Aug 11, 2021;1-3. doi:10.1080/09273948.2021.1962917.
27. Fowler N, Mendez Martinez NR, Pallares BV, Maldonado RS. Acute-onset central serous retinopathy after immunization with COVID-19 mRNA vaccine. *Am J Ophthalmol Case Rep*. Sep, 2021;23:101136. doi:10.1016/j.ajoc.2021.101136.

28. Goyal M, Murthy SI, Annum S. Bilateral multifocal choroiditis following COVID-19 vaccination. *Ocul Immunol Inflamm*. Aug 3, 2021;1-5. doi:10.1080/09273948.2021.1957123.
29. Mambretti M, Huemer J, Torregrossa G, Ullrich M, Findl O, Casalino G. Acute macular neuroretinopathy following coronavirus disease 2019 vaccination. *Ocul Immunol Inflamm*. Jun 30, 2021;1-4. doi:10.1080/09273948.2021.1946567.
30. Michel T, Stolowy N, Gascon P, et al. *Acute Macular Neuroretinopathy After COVID-19 Vaccine. J Ophthalmic Inflamm Infect*.2021.
31. Mudie LI, Zick JD, Dacey MS, Palestine AG. Panuveitis following vaccination for COVID-19. *Ocul Immunol Inflamm*. Jul 2, 2021;1-2. doi:10.1080/09273948.2021.1949478.
32. Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. *Lancet Infect Dis*. Apr, 2021;21(4):450–452. doi:10.1016/s1473-3099(21)00076-1.
33. Papasavvas I, Herbort CP Jr. Reactivation of Vogt-Koyanagi-Harada disease under control for more than 6 years, following anti-SARS-CoV-2 vaccination. *J Ophthalmic Inflamm Infect*. Jul 5, 2021;11(1):21. doi:10.1186/s12348-021-00251-5.
34. Phylactou M, Li JO, Larkin DFP. Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine. *Br J Ophthalmol*. Jul, 2021;105(7):893–896. doi:10.1136/bjophthalmol-2021-319338.
35. Rabinovitch T, Ben-Arie-Weintrob Y, Hareuveni-Blum T, et al. Uveitis following the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: a possible association. *Retina*. Aug 2, 2021. doi:10.1097/iae.0000000000003277.
36. Ravichandran S, Natarajan R. Corneal graft rejection after COVID-19 vaccination. *Indian J Ophthalmol*. Jul, 2021;69(7):1953–1954. doi:10.4103/ijo.IJO_1028_21.
37. Renisi G, Lombardi A, Stanzione M, Invernizzi A, Bandera A, Gori A. Anterior uveitis onset after bnt162b2 vaccination: is this just a coincidence? *Int J Infect Dis*. Jul 18, 2021;110:95–97. doi:10.1016/j.ijid.2021.07.035.
38. Repajic M, Lai XL, Xu P, Bell's LA. Palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell's palsy. *Brain Behav Immun Health*. May, 2021;13:100217. doi:10.1016/j.bbih.2021.100217.
39. Reyes-Capo DP, Stevens SM, Cavuoto KM. Acute abducens nerve palsy following COVID-19 vaccination. *J Aapos*. May 24, 2021. doi:10.1016/j.jaapos.2021.05.003.
40. Santovito LS, Pinna G. Acute reduction of visual acuity and visual field after Pfizer-BioNTech COVID-19 vaccine 2nd dose: a case report. *Inflamm Res*. Jun 4, 2021;1-3. doi:10.1007/s00011-021-01476-9.
41. Shemer A, Pras E, Einan-Lifshitz A, Dubinsky-Pertzov B, Hecht I. Association of COVID-19 vaccination and facial nerve palsy: a case-control study. *JAMA Otolaryngol Head Neck Surg*. Aug 1, 2021;147(8):739–743. doi:10.1001/jamaoto.2021.1259.
42. Vera-Lastra O, Ordinola Navarro A, Cruz Domiguez MP, Medina G, Sánchez Valadez TI, Jara LJ. Two cases of graves' disease following SARS-CoV-2 vaccination: an autoimmune/inflammatory syndrome induced by adjuvants. *Thyroid*. May 3, 2021. doi:10.1089/thy.2021.0142.
43. Wasser LM, Roditi E, Zadok D, Berkowitz L, Weill Y. Keratoplasty rejection after the BNT162b2 messenger RNA vaccine. *Cornea*. Aug 1, 2021;40(8):1070–1072. doi:10.1097/ico.0000000000002761.
44. US Food and Drug Administration. Pfizer-BioNTech COVID-19 vaccine/ BNT162b2 emergency use authorization review memorandum. Accessed 1 August, 2021. https://www.fda.gov/media/144416/download
45. US Food and Drug Administration. Moderna COVID-19 vaccine/ mRNA-1273 emergency use authorization review memorandum. Accessed 1 August, 2021. https://www.fda.gov/media/144673/download
46. Cirillo N, Doan R. Bell's palsy and SARS-CoV-2 vaccines-an unfolding story. *Lancet Infect Dis*. Jun 7, 2021;21:1210–1211. doi:10.1016/s1473-3099(21)00273-5.
47. Erdur H, Ernst S, Ahmadi M, et al. Evidence for seasonal variation of Bell's Palsy in Germany. *Neuroepidemiology*. 2018;51(3–4):128–130.doi:10.1159/000492097.
48. Bhavsar KV, Lin S, Rahimy E, et al. Acute macular neuroretinopathy: a comprehensive review of the literature. *Surv Ophthalmol*. Sep-Oct, 2016;61(5):538–565. doi:10.1016/j.survophthal.2016.03.003.
49. Hwang CK, Sen HN. Concurrent vascular flow defects at the deep capillary plexus and choriocapillaris layers in acute macular neuroretinopathy on multimodal imaging: a case series. *Am J Ophthalmol Case Rep*. Dec, 2020;20:100866. doi:10.1016/j.ajoc.2020.100866.
50. Madendag Y, Acmaz G, Atas M, et al. The effect of oral contraceptive pills on the macula, the retinal nerve fiber layer, and choroidal thickness. *Med Sci Monit*. Nov 27, 2017;23:5657–5661. doi:10.12659/msm.905183.
51. Fuchsjäger-Mayrl G, Nepp J, Schneeberger C, et al. Identification of estrogen and progesterone receptor mRNA expression in the conjunctiva of premenopausal women. *Invest Ophthalmol Vis Sci*. Sep, 2002;43(9):2841–2844.
52. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. *J Neurol Sci*. Aug 3, 2021;428:117607. doi:10.1016/j.jns.2021.117607.
53. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. Jun 3, 2021;384(22):2092–2101. doi:10.1056/NEJMoa2104840.
54. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. Jun 3, 2021;384(22):2124–2130. doi:10.1056/NEJMoa2104882.
55. Perry RJ, Tamborska A, Singh B, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. *Lancet*. Aug 6, 2021. doi:10.1016/s0140-6736(21)01608-1.
56. See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *Jama*. Jun 22, 2021;325(24):2448–2456. doi:10.1001/jama.2021.7517.
57. Schulz JB, Berlit P, Diener HC, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. *Ann Neurol*. Jul 19, 2021. doi:10.1002/ana.26172.
58. Panovska-Stavridis I, Pivkova-Veljanovska A, Trajkova S, et al. Case of superior ophthalmic vein thrombosis and thrombocytopenia following ChAdOx1 nCoV-19 vaccine against SARS-CoV-2. *Mediterr J Hematol Infect Dis*. 2021;13(1):e2021048. doi:10.4084/mjhid.2021.048.
59. Tan DT, Dart JK, Holland EJ, Kinoshita S. Corneal transplantation. *Lancet*. May 5, 2012;379(9827):1749–1761. doi:10.1016/s0140-6736(12)60437-1.
60. Jin SX, Juthani VV. Acute corneal endothelial graft rejection with coinciding COVID-19 infection. *Cornea*. Jan, 2021;40(1):123–124. doi:10.1097/ico.0000000000002556.
61. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. Aug 7, 2020;369(6504):718–724. doi:10.1126/science.abc6027.
62. Hamilton A, Massera R, Maloof A. Stromal rejection in a deep anterior lamellar keratoplasty following influenza vaccination. *Clin Exp Ophthalmol*. Dec, 2015;43(9):838–839. doi:10.1111/ceo.12560.
63. Matoba A. Corneal allograft rejection associated with herpes zoster recombinant adjuvanted vaccine. *Cornea*. Jun 9, 2021. doi:10.1097/ico.0000000000002787.
64. Vignapiano R, Vicchio L, Favuzza E, Cennamo M, Mencucci R. Corneal graft rejection after yellow fever vaccine: a case report. *Ocul Immunol Inflamm*. Jan 28, 2021;1-4. doi:10.1080/09273948.2020.1870146.
65. Ramakrishnan MS, Patel AP, Melles R, Vora RA. Multiple evanescent white dot syndrome: findings from a large Northern California Cohort. *Ophthalmol Retina*. Nov 30, 2020. doi:10.1016/j.oret.2020.11.016.

66. Bragazzi NL, Hejly A, Watad A, Adawi M, Amital H, Shoenfeld Y. ASIA syndrome and endocrine autoimmune disorders. *Best Pract Res Clin Endocrinol Metab*. Jan, 2020;34(1):101412. doi:10.1016/j.beem.2020.101412.
67. Watad A, De Marco G, Mahajna H, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination. *Vaccines (Basel)*. Apr 29, 2021;9(5). doi:10.3390/vaccines9050435.
68. Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. *Nat Rev Immunol*. Apr, 2021;21 (4):195–197. doi:10.1038/s41577-021-00526-x.
69. Rodero MP, Crow YJ. Type I interferon-mediated monogenic autoinflammation: the type I interferonopathies, a conceptual overview. *J Exp Med*. Nov 14, 2016;213(12):2527–2538. doi:10.1084/jem.20161596.
70. Leibowitz JA, Woods AT, Kesselman MM, Mayi BS. Uveitis as a predictor of predisposition to autoimmunity. *Cureus*. Mar 28, 2020;12(3):e7451. doi:10.7759/cureus.7451.
71. Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. *J Neurol*. Jun, 2017;264(6):1035–1050. doi:10.1007/s00415-016-8263-4.