



COVID, the end of pandemic and vaccine-induced Uveitis: is this the showdown?

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Severe Acute Respiratory Syndrome (SARS)-COV-2 was first known in the Hubei district of the Republic of China in December 2019 as COVID-19 [1]. COVID affected 8000 people when the first outbreak occurred, and around 3000 died due to fatal pulmonary complications [1]. Three years ago, on March 11, 2020, the World Health Organization (WHO) proclaimed the SARS-COV-2 pandemic, given its dramatic spread worldwide. [1]

Despite the global astonishment, SARS-COV-2 was just the last of a well-known Coronavirus family: HKU1 (betacoronavirus), NL63 (alphacoronavirus), SARS-CoV (betacoronavirus), OC43 (betacoronavirus), 229E (alphacoronavirus), MERS-CoV (betacoronavirus), and SARS-CoV-2 were the protagonists of numerous scientific papers in the past years [2].

In addition, although CoV is new to most, it is familiar to the ophthalmology community: CoV has a high level of multi-organ tropisms, such as the gastrointestinal and respiratory tracts and the eye, among others. Over two decades ago, HCoV-NL63 infection was described as bronchiolitis and conjunctivitis [2]. A year later, another publication reported

HCoV-NL63 infection leading to conjunctivitis in a French cohort of patients reported in 2005 [6]. Those two reports represented the first description of CoV ocular tropism.

Although after the SARS-COV-2 outbreak, many reports speculated on a possible entrance door through the ocular surface, other authors challenged this assumption, proving no significant virus expression in the collected conjunctival samples [3]. In its first outbreak, SARS-Cov-2 showed a dangerous inclination to involve the lungs severely [9], skin, central nervous system, gastrointestinal tract, and the eye [3]. This last tropism was not new to the ophthalmology community, given the use of CoV for the experimental coronavirus retinopathy (ECOR) described by Robbins et al. in 1990 [4]. During the pandemic, the ECOR model was later used to hypothesize the pathophysiology of lung poly thrombosis in the late stages of SARS-Cov-2. Both in ECOR and pneumonia, the inflammation of the interstitial space degenerated into hyaline thrombi, given secondary perivasculitis. In addition, the ECOR model drove researchers to hypothesize a tri-phasic behavior of CoV: the primary infection (first phase) triggered an autoinflammatory phase (second phase), leading to a third phase that was a *tout court* autoimmune reaction [5] that was overlapping the hemophagocytic lymphohistiocytosis (sHLH) observed in T-cell therapy. At this point, the interplay between SARS-COV-2 and the eye was more than a hypothesis.

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The dramatic situation generated by the SARS-COV-2 outbreak forced researchers to accelerate their vaccine research. Since their first employment, vaccines have become one of the hot topics in the scientific community. Unfortunately, after vaccines were broadly employed in an urgent, broad campaign, ocular adverse events started being observed. The side effect variability depended on the vaccine type and patients' immunophenotype. However, although most countries have applied a massive vaccination campaign, global vaccination is still an unaccomplished task [6].

Six vaccines out of 151 currently under investigation are available in the market. Viral vector, inactivated virus vaccines, and mRNA are the three categories presently available and approved by the leading medical authorities [2]: Astra-Zeneca ChAdOx1-S (recombinant) viral adenovirus from Oxford (UK), Janssen (two recombinant vector viral adenoviruses) belonging to Johnson & Johnson (USA), Moderna mRNA 1273 (USA), and Pfizer-BioNTech mRNA BNT162b2 (Comirnaty) (USA) are the primary vaccines available in the market, although whole inactivated vaccines (Sinopharm Group and Sinovac Biotech) were early on use in several countries that had early vaccination campaigns' kick-off; Turkey, United Arab Emirates, Brazil, Indonesia, and India were among the first ones with an early vaccination campaign begin. Albeit abandoned in most of the vaccination campaigns, inactivated vaccine by Sinopharm trialed in significant multi-country Phase 3 trials has shown that a 21-day interval of two doses showed an efficacy of 79% against symptomatic SARS-CoV-2 infection 14 or more days after the second dose. In contrast, efficacy against hospitalization was 79% [2].

The mRNA BNT162b2 (Pfizer) and mRNA 1273 (Moderna) vaccines effectively prevented severe illness or disease at 87.5–95% and 94.5–100%, respectively. Astra-Zeneca and Janssen's efficacy levels accounted for approximately 70% and 65% protection, respectively. However, depending on the geographical area, Janssen/Johnson & Johnson ranges from 72 to 57%.

Albeit at the pandemic's beginning, the number of doses needed was questioned [19]. As a result, the vaccination strategy and a series of models were proposed. Age-based vaccination strategy (AVS) remains the simplest, most transparent, and fairest criterion worldwide. AVS's plan also aims to accelerate

vaccine administration, protect as many subjects as possible, and quickly reach "herd immunity," which represents the only goal of the vaccination campaign. In addition, a booster six months after the first two doses has been adopted worldwide and represents the gold standard of the vaccination strategy up to date [2].

On May 5, 2023, the World Health Organization (WHO) announced on Friday that COVID-19 is no longer a public health emergency of international concern (PHEIC) [7]. At this stage, a (SARS)-COV-2 direct eye involvement appears to be unlikely, while we will continue experiencing potential vaccine side effects as reported in recent publications [2]. However, this is another potentially debatable matter [8]. Anyways, considering this possible warning, it might be recommended to have regular eye checkups, particularly in patients affected by either systemic or ocular immunological diseases.

However, since the pandemic has been declared over, and it is unclear whether a further vaccination jab will be necessary, the showdown might be started already, or maybe the show is finally over.

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References

1. Neri P, Pichi F (2020) COVID-19 and the eye immunity: lesson learned from the past and possible new therapeutic insights. *Int Ophthalmol* 40(5):1057–1060. <https://doi.org/10.1007/s10792-020-01389-2>. PMID:32314322;PMCID: PMC7167536
2. Habet-Wilner Z, Neri P, Okada AA, Agrawal R, Le Xin N, Cohen S, Fischer N, Kilmartin F, Coman A, Kilmartin D (2023) COVID vaccine-associated uveitis. *Ocul Immunol Inflamm*. <https://doi.org/10.1080/09273948.2023.2200858>
3. Neri P, Pichi F (2021) SARS-CoV-2 and the eye: the Pandora's box of ocular immunology. *J Ocul Pharmacol Ther* 37(9):502–509. <https://doi.org/10.1089/jop.2021.0058>. (Epub 2021 Sep 9) PMID: 34515538
4. Robbins SG, Detrick B, Hooks JJ (1990) Retinopathy following intravitreal injection of mice with MHV strain JHM. *Adv Exp Med Biol* 276:519–524. https://doi.org/10.1007/978-1-4684-5823-7_72

5. Neri P, Lamperti M, Pichi F (2020) SARS-COV-2 and eye immunity: the lesson was learned but we are not done yet. Brainstorming on possible pathophysiology inspired by ocular models. *Int Ophthalmol* 40(8):1879–1883. <https://doi.org/10.1007/s10792-020-01495-1>. (PMID: 32621017; PMCID: PMC7332849)
6. WHO Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/table>.
7. Lenharo M (2023) WHO declares end to COVID-19's emergency phase. *Nature*. <https://doi.org/10.1038/d41586-023-01559-z>. Epub ahead of print. PMID: 37147368.
8. Jampol LM, Tauscher R, Schwarz HP (2021) COVID-19, COVID-19 vaccinations, and subsequent abnormalities in

the retina: causation or coincidence? *JAMA Ophthalmol* 139(10):1135–1136. <https://doi.org/10.1001/jamaophthamol.2021.3483>

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