Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

syndrome coronavirus 2 (SARS-CoV-2), even for the 1 patient with ocular symptoms. They obtained a meaningful conclusion that the risk of ocular transmission of COVID-19 is low.

We applaud the authors for a major endeavor. However, we have different views on the role the ocular surface plays in COVID-19 transmission. Several potential limitations are worth discussing. First, the authors used a Schirmer strip to collect tears, which may not be reliable enough to test SARS-CoV-2. Although the Schirmer strip was previously validated in testing herpes simplex virus-1 from tears,[2] no evidence shows it also works for SARS-CoV-2. In recent studies in China,[3,4] a conjunctival swab technique was used, and it obtained positive results. The authors only collected tears and may have missed the virus attached to the epithelium of the ocular surface or in conjunctival secretion, which may have led to incomplete results. Second, reverse transcriptase polymerase chain reaction may not be sensitive enough to detect small quantities of SARS-CoV-2 RNA. Therefore, negative test results may be false negatives and cannot exclude the presence of the virus. Multiple specimens are needed to increase sensitivity. Finally, even if the Schirmer strip and reverse transcriptase polymerase chain reaction tests were highly accurate, it still cannot be concluded that transmission through tears is likely to be low.

We think that 2 possible explanations can account for this. One is that the COVID-19 infection above the ocular surface may not express SARS-CoV-2 in the tears, or the concentration of SARS-CoV-2 may be low. The other is that the authors may have missed the window, because viral shedding in ocular tissue may only last for a short period. The authors did not mention the exact time of testing. Xia et al[3] detected positive conjunctival swab samples at 3 days after the course of the disease, when the patient had no severe fever or respiratory symptoms. Owing to these limitations, the negative results must be interpreted with caution.

In all, we believe negative results do not conclusively show that the risk of ocular transmission for COVID-19 is low and even positive results cannot be understood as the risk is high. Until now, the issue has been controversial, but we suggest that the conjunctiva is another transmission route for COVID-19. In Deng's study (Deng et al, 2020 Preprint, available from https://doi.org/10.1101/2020.03.13.990036), 2 rhesus macaques received 1×10^6 50% tissue-culture infectious doses of SARS-CoV-2 conjunctival inoculation, and the results showed the viral load was distributed in the whole body at 7 days after inoculation. However, this is a preprint article, and direct evidence for this conjecture is lacking. Nevertheless, we suggest that appropriate precautions are needed to prevent transmission through ocular tissues and secretions, especially for clinical staff. We hope convincing evidence from related animal experiments will be put forward soon.

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REPLY: We thank Min et al for their comments regarding our study. To reiterate our conclusion, our study suggested that the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission through tears is low, not impossible. This was a conclusion made based on the analysis of 17 patients with coronavirus disease-2019 (COVID-19) and the available literature at the time of article submission on March 19, 2020. Majority of the limitations raised by Min et al have been acknowledged in our article.

First, Min et al probed the validity of the Schirmer strip collection method and the likely presence of viral material in tear samples. These limitations have already been acknowledged in the article. However, we point out that, apart from herpes simplex virus-1, the Schirmer strip has also been used to detect other herpes-family viruses including Epstein-Barr virus (types 1 and 2) and non-herpes viruses (e.g., adenovirus).[1,2] They have also been used routinely for the study of proteins in tear films. To date, there is no known scientific rationale to indicate that these strips are not able to collect coronaviruses. Regarding the presence of viral material in tear samples, we have mentioned that, if the ocular surface tissue was infected, lysis of these cells (a part of the viral replication cycle), would have led to the release of viral particles or genetic material.

Second, in our article, we had already acknowledged the concerns of Min et al regarding the sensitivity of reverse transcriptase polymerase chain reaction to detect small quantities of SARS-CoV-2 RNA. To further improve the sensitivity, collected samples were also used to inoculate Vero-E6 cells to observe for cytopathic effect over a 4-day duration. The observation of cytopathic effect (which indicates infection) along with reverse transcriptase polymerase chain reaction would likely detect the presence of any SARS-CoV-2.

Finally, Figure 1 (in the original article) shows the full testing schedule for both nasopharyngeal and tear samples. As Min et al stated, it was difficult recruiting patients in early disease of <3 days. Only 2 tear samples were collected during this time period. We have previously acknowledged this in our article and explained that most patients presented to the hospital a couple of days after developing symptoms.

There have been multiple published case studies with conjunctival samples testing positive for SARS-CoV-2. Furthermore, ex vivo studies have also shown the ability of SARS-CoV-2 to infect conjunctival cells.[3] However, to our knowledge, in the largest case series as of May 18, 2020, by Zhou et al, only 3 of 121 recruited COVID-19 patients (2.5%) had conjunctival samples that tested positive for SARS-CoV-2 RNA.[4] Findings from

other small case series were also similar.[5] The nature of research in pandemic settings is that conclusions can change as more data are gathered. Early data can provide a suggestion of the possible implications of a novel pathogen like SARS-CoV-2. Unless there is a large study showing a large proportion of COVID-19 patients with positive ocular samples, respiratory droplet transmission should still be the primary concern of ophthalmologists owing to the close proximity to the patient during physical examination.

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Re: Francis et al.: Immune checkpoint inhibitor associated optic neuritis

(*Ophthalmology*. 2020;127:1585-1589)

TO THE EDITOR: We read the article by Francis et al[1] describing 18 eyes of 11 patients with immune checkpoint inhibitor (ICI)-associated optic neuritis (ON). Having diagnosed and treated patients with ICI-associated ON, we understand the need for a larger series to clarify the presenting features and approach to treatment, as the available literature is very limited at this point. However, after reading this article, we would like to argue that many of the patients described likely did not have a diagnosis of ON.

In case 2, the patient had bilateral trace optic nerve head swelling and symmetric cecocentral scotomas, no abnormalities on magnetic resonance imaging (MRI), and no improvement of visual deficits after corticosteroids, plasmapheresis, intravenous immunoglobulin, and rituximab. This presentation is more consistent with toxic, nutritional, or hereditary optic neuropathies, all of which should have been ruled out and reported to the readers. In case 3, the patient had a unilateral full optic nerve with hemorrhage, normal MRI, no improvement of visual deficit with treatment and residual segmental optic nerve head pallor. This finding is most consistent with nonarteritic anterior ischemic optic neuropathy (NAION) and patients with malignancies have a hypercoagulable state, which increases their risk for NAION. In case 5, a 54-year-old woman with bilateral decreased vision without pain had large areas of fundus hyperautofluorescence in the peripapillary and macular areas and no MRI optic nerve enhancement. We believe a widespread retinopathy/choroidopathy rather than optic neuropathy is the most likely diagnosis in this case. B-scan ultrasound examination performed for optic nerve thickening is not an accepted imaging modality to assess for ON and its utility in this context is unclear. In case 6, the patient had unilateral segmental optic nerve head edema with bilateral visual field defects with normal brain MRI and some improvement in the visual field defect after treatment. We argue that this presentation is more consistent with NAION rather than ICI-associated ON. In case 7, a 73-year-old woman had bilateral "2+ optic nerve edema" with preserved visual function and bilateral anterior uveitis with vitreous cells. We believe that the cause of optic disc edema here was likely secondary to uveitis. If the authors were convinced that this was not the case owing to only trace vitreous cells, further investigations to rule out increased intracranial pressure as a cause of bilateral disc edema should have been carried out, such as MRI/magnetic resonance venogram and lumbar puncture with opening pressure measurement and cerebrospinal fluid analysis. In case 8, again the description is that of NAION: optic nerve head edema with no enhancement of the optic nerve on MRI and no improvement after treatment. With unilateral optic nerve head edema, a normal orbital MRI, no improvement with treatment and lesser (but not resolved) optic disc edema, case 9 is also consistent with NAION. One also wonders about an infiltrative optic neuropathy given the persistent optic disc edema. In case 10, the patient developed sequential optic nerve head edema with a normal MRI. The disc edema resolved leaving bilateral optic nerve pallor with no improvement of visual function, consistent with sequential NAION.

Although we recognize that orbital MRI is imperfect and variable rates of optic nerve enhancement have been reported in inflammatory optic neuropathies, using high-quality fat-suppressed orbital imaging, one should be able to detect at least some degree of optic nerve enhancement after gadolinium administration in most cases of inflammatory optic neuropathies.[2,3] The fact that only 3 of 11 patients in this article had enhancement of the optic nerves on MRI is far out of proportion to what one would expect, especially given the presumed etiology of ON in this cohort of patients, which is an immune-mediated attack on myelin.