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.

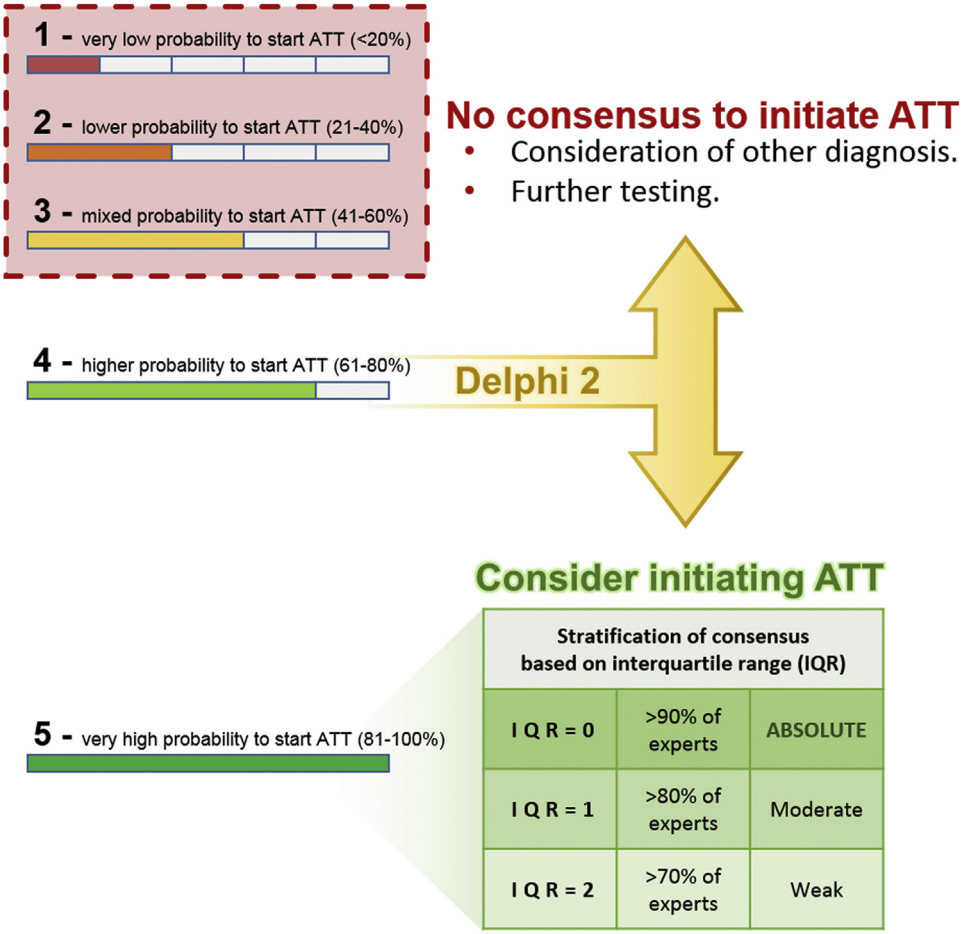

Figure 1. The figure explains the probability scale of starting anti-tubercular therapy that was utilized in the study. The stratification of the consensus based on the interquartile range has also been explained.

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Re: Seah et al.: Assessing viral shedding and infectivity of tears in Coronavirus disease 2019 (COVID-19) patients

(*Ophthalmology*. 2020;127:977-979)

TO THE EDITOR: We would like to congratulate Seah et al[1] for the well-written article that evaluated 64 tear samples from 17 patients with coronavirus disease-2019 (COVID-19) and found that all tear samples tested negative for severe acute respiratory

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