Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioii20

Ocular Symptoms of SAR-CoV-2: Indication of Possible Ocular Transmission or Viral Shedding

Stephen Ocansey , Emmanuel Kwasi Abu , Carl Halladay Abraham , Andrew Owusu-Ansah , Samuel Bert Boadi-Kusi , Alex Azuka Ilechie & Desmond Omane Acheampong

To cite this article: Stephen Ocansey , Emmanuel Kwasi Abu , Carl Halladay Abraham , Andrew Owusu-Ansah , Samuel Bert Boadi-Kusi , Alex Azuka Ilechie & Desmond Omane Acheampong (2020): Ocular Symptoms of SAR-CoV-2: Indication of Possible Ocular Transmission or Viral Shedding, Ocular Immunology and Inflammation

To link to this article: https://doi.org/10.1080/09273948.2020.1799035

Published online: 01 Sep 2020.

OCULAR IMMUNOLOGY AND INFLAMMATION
https://doi.org/10.1080/09273948.2020.1799035

Taylor & Francis
Taylor & Francis Group

INVITED REVIEW

Ocular Symptoms of SAR-CoV-2: Indication of Possible Ocular Transmission or Viral Shedding

Stephen Ocansey, OD, MPhil, PhD, FAAO[a], Emmanuel Kwasi Abu, OD, PhD[a], Carl Halladay Abraham, OD, MSc, PhD[a], Andrew Owusu-Ansah, OD, MMed, PhD[a], Samuel Bert Boadi-Kusi, OD, MPhil, PhD[a], Alex Azuka Ilechie, OD, PhD[a], and Desmond Omane Acheampong, MSc, PhD[b]

[a]Department of Optometry and Vision Science, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana; [b]Department of Biomedical Science, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana

ABSTRACT

The recently identified novel coronavirus (CoV), the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causes the coronavirus disease 2019 (COVID-19). While published data about other highly infectious human COVs [that is, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV)] provide helpful information about the infectivity of SARS-CoV-2, there is limited understanding surrounding knowledge of ocular manifestation of the virus. This paper reviews published data which reveal the presence of SARS-CoV-2 RNA in tears and conjunctival scrappings of some COVID-19 patients by real-time-polymerase chain reaction assay, although the detection rate is low compared to samples from respiratory sites. Nevertheless, the ocular complications from SARS-CoV-2 infection are uncommon. The evidence partly supports the eye as a portal of entry for SARS-CoV-2 to infect respiratory cells or viral shedding from respiratory cells via the nasolacrimal duct unto the ocular surface. The possibility of ocular secretions as source for SARS-CoV-2 to spread externally has substantial public health implications

ARTICLE HISTORY
Received 25 May 2020
Revised 30 June 2020
Accepted 17 July 2020

KEYWORDS
Coronavirus; COVID-19; infection; ocular surface; shedding; transmission

Background

In December 2019, a new coronavirus (CoV) was found to be responsible for an outbreak of pneumonia cases of unknown etiology in clusters in Wuhan, Hubei Province, China.[1] The novel virus, referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an enveloped, positive-sense, single-stranded RNA virus belonging to the beta-coronaviruses genus of the Coronaviridae family that has been isolated from a broad range of vertebrates, including humans.[2] The last three recently determined human CoVs, that is, SARS-CoV, MERS-CoV, and SARS-CoV-2 have been recognized as highly infectious zoonotic viruses in humans.[3] Human coronaviruses (HCoV) are generally known to cause mild transient and resolving upper respiratory tract and enteric infections,[4] but SARS-CoV-2 causes a severe respiratory disease known as COVID-19. In extreme cases, death occurs due to gradual respiratory failure as a result of alveolar damage.[5,6]

Although the genome sequence of SARS-CoV-2 is not distinct from SARS-CoV-1 and MERS, its infection rate indicates it is highly transmissible and has a significant fatality rate (the case fatality rate for SARS-CoV-1 was 10% and 34% for MERS) especially in the elderly and individuals with comorbidities such as cardiovascular diseases, diabetes, and chronic respiratory disease.[5] SARS-CoV-2 infected patients develop respiratory illness, with the early symptoms of pyrexia (fever) (in 88% of cases) during their illness course, but only 45% are febrile on early presentation, dry cough (68%), fatigue (38%), and shortness of breath (19%). Other less specific extra-pulmonary symptoms include diarrhea, headache, nausea, vomiting, or even present with asymptomatic infection.[7] Complications in severe cases include pneumonia, renal failure, cardiomyopathy, and encephalopathy.[8]

Currently, several investigations have extensively discussed the transmission of SARS-CoV-2.[9,10] While it is widely accepted that the virus is transmitted primarily via person-to-person interaction through respiratory droplets produced when an infected person coughs or sneezes or direct contact with virus-contaminated surfaces (fomites),[11] alternative modes of transmission are still being investigated. The ocular mucosa surface (cornea and conjunctiva) is easily exposed to infectious droplets during close contact with infected patients or contaminated hands. Due to the anatomical linkage between the mucosa of the ocular surface and the upper respiratory tract via the nasolacrimal duct, which also shares the same entry receptors with some respiratory viruses, the eye is postulated to be an important portal of entry for SARS-CoV-2.

There have been many case reports in which frontline medical personnel were found to be infected through routine care of COVID-19 patients. Indeed, the early information about the outbreak of the virus was first reported by an Ophthalmologist, Li Wenliang, in an eye clinic, who later died of the disease.[12] Furthermore, Dr. Guang fa Wang, a member of the national expert panel on pneumonia, reported that he was infected by SARS-CoV-2 during the inspection in Wuhan, through

CONTACT Stephen Ocansey socansey2@ucc.edu.gh Department of Optometry, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana

unprotected eye exposure.[13] Since then, several reports suggest the virus can cause mild follicular conjunctivitis otherwise indistinguishable from other viral causes, and possibly be transmitted by aerosol contact with the conjunctiva.[1,5,14,15] CoVs are known to be capable of causing a wide spectrum of ocular complications from anterior segment pathologies like conjunctivitis and anterior uveitis to sight-threatening conditions including retinitis, optic neuritis, choroiditis with retinal detachment and retinal vasculitis,[4] justifying the current inquisition about the ocular involvement of SARS-CoV-2.

Previous studies show that the genetic make-up of SARS-CoV-2 is similar to that of SARS-CoV-1 which caused a pandemic in 2002.[16,17] Published data indicated that SARS-CoV-1 nucleic acid can be found in tears of SARS patients and reported that the disease can be transmitted through direct or indirect contact with the mucous membranes in the eyes, including the conjunctiva.[14,15] Considering that the SARS-CoV-2 is present in some body fluids of patients, the speculation about the risk of tear and conjunctival transmission is scientifically justified. Therefore, several current research have focused on investigating whether COVID-19 eye symptoms are produced as a result of ocular inoculation of the virus or is induced during viral shedding via the nasolacrimal duct.

Similar to SARS-CoV-1, SARS-CoV-2 gains entry into host cells through recognizing and binding to its potential host receptor, angiotensin-converting enzyme 2 (ACE2) which is distributed among various cell types and tissues, including the conjunctiva.[18–20] Although there is no direct evidence that SARS-CoV-1 replication resulted in conjunctivitis, SARS-CoV-2 transmission through the eye has been suspected because of the similarities in the genome and pathologic characteristics of COVs.

In response to the existing controversy concerning ophthalmologic involvement of SARS-CoV-2, substantial research has focused on understanding the ocular manifestation of the disease. This review presents published evidence which may indicate ocular involvement in the transmission of the virus or viral shedding in patients with COVID-19, ocular symptoms of SAR-CoV-2, mechanisms of human CoVs eye infection as well as the role of eye protection in the transmission of SAR-CoV-2.

Ocular Tropism and Viral Transmission

Viruses represent the most common cause of acute respiratory illness. Four of the identified human CoVs (that is, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV- HKU1) have low infectivity and primarily infect the upper respiratory tract with mild respiratory symptoms (common cold). On the other hand, the other three human CoVs (that is, SARS-CoV, MERS-CoV, and SARS-CoV 2) are zoonotic and highly infectious. They predominantly cause severe lower respiratory tract infection which could rapidly progress to pneumonia.[3,16] Common features of human CoVs illnesses include high transmissibility leading to global distribution, mucosal establishment of infection, and several overlying symptoms[21] (Figure 1). However, the number of SARS-CoV-2 infected patients is several hundred times that of SARS-CoV patients in total, implying 2019-nCoV is more transmissible than SARS-CoV-1 and MERS-CoV.[16]

At present, the transmission route of the novel coronavirus is still being studied. Like other SARS viruses, many researchers now believe that it is mainly spread by inhalation of virus-containing aerosols expelled by infected individuals through coughing, sneezing or by indirect contact with virus-contaminated surfaces. For patients with the disease, the virus RNA has been detected in samples taken from the respiratory tract 1–2 days before the onset of symptoms and it persisted for up to 8 days in mild cases, and for longer periods in more severe cases, peaking after the first week of infection.[22] The detection of the infectious virus particles in body specimen indicates shedding. Viral shedding occurs when a virus replicates inside a host cell and is released into extracellular environment, at which stage it may be contagious. Recently, prolonged shedding of SARS-CoV-2 have been detected in stool samples from infected persons by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, and have also been isolated from the mucous membranes of the gastrointestinal tract in a few cases, raising the possibility of transmission through the fecal-oral route[23,24] Detection of viral genome in a particular sample does not necessary mean infectivity, unless the infectious virus RNA have been isolated and cultured. Viral load, which measure of the number of viral particles in a sample can however be a potentially useful marker for assessing disease severity and prognosis. A recent investigation found that viral loads in severe cases were up to 60 times higher than in mild cases. In terms of viral load profile, SARS-CoV-2 is reported to peaks at around the time of symptom show up[25]. Older age has also been associated with higher viral loads, but viral loads in symptomatic children of all ages are comparable to adults. The high viral load close to symptom onset also suggests that SARS-CoV-2 can spread during the incubation period by asymptomatic transmission.[22,25-28] A recent study found that the mean incubation period for SARS-CoV-2 was 5 to 7 days (range 2–14 days).[8,29] The long period it takes for symptoms of COVID-19 to manifest along with the ability to transmit infection during this incubation period show how contagious SARS-CoV-2 can potentially be.

Additionally, local spread can be traced back to direct or indirect contact with infected patients' bodily fluids such as saliva, feces, urine, and tears.[27] With regards to the eye, RT-PCR assay found fragments of the SAR-CoV-2 RNA in tear and conjunctival specimen of COVID-19 infested patients.[30] Whereas antimicrobial factors and the epithelia of the human mucosa surface act as additional mucosal barriers to prevent the entry of viruses when exposed to infectious aerosols and contaminated hands, HCoV are capable of causing ocular complications in infected individuals and establishing a respiratory infection following ocular exposure.[31] Some respiratory viruses such as human adenovirus (species D) and avian influenza virus (H7) have been demonstrated to cause highly infectious conjunctivitis or keratoconjunctivitis.[21] Besides, the binding receptor for SARS-CoV-1, SARS-CoV-2 to gain entry into host cells, angiotensin-converting enzyme 2 (ACE2) is distributed among the conjunctiva, making the eye a preferred site of entry for the CoV.[18–20] Moreover, since COVID-19 is an unfolding pandemic, scholars are still trying to understand better the possible mode of ocular transmission. Figure 1 illustrates a possible replication, transmission routes, and systemic complications of SARS-CoV-2. Since the current available evidence indicates that COVID-19 is transmitted from person-to-person through

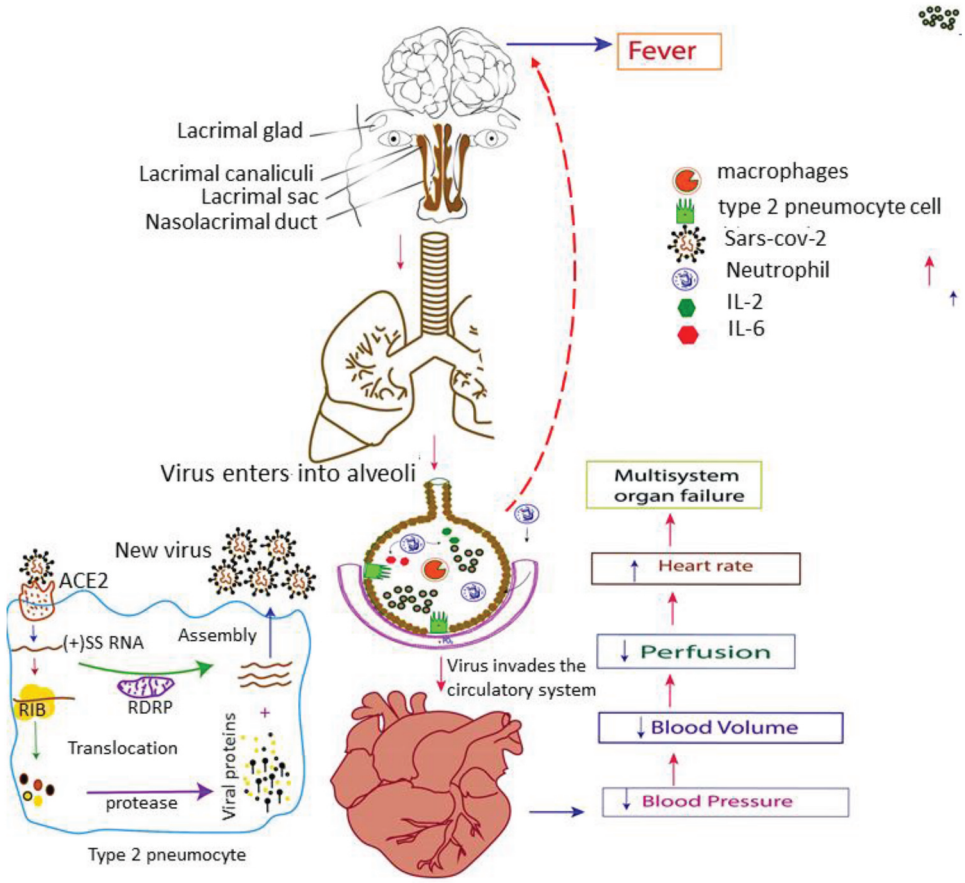

Figure 1. Replication, possible transmission routes, and systemic complications of Covid-19.

several different routes mainly via respiratory aerosols, it suffices to say that certain environments may provide transmission risks. COVID-19 transmission will be particularly effective in crowded, confined indoor spaces such as workplaces including factories, churches, restaurants, bars, markets, shopping centers, school dormitories, transport vehicles, or events occurring indoor such as, parties, and political rallies.[32]

Ocular Infection of SARS-CoV-2

Since the outbreak of COVID-19 in December 2019, several published studies and anecdotal evidence suggest that SARS-CoV-2 can cause conjunctivitis.[5,7,33-35] While some evidence confirms the presence of SARS-CoV-2 RNA fragments in the tears and conjunctival swabs of patients with the early form of the disease, shedding of the viral RNA has also been speculated in patients with severe COVID-19 disease[36,37] (Table 1). In spite of these, the ocular involvement of COVID-19 is uncertain, and concerted efforts are underway to understand the ocular manifestations of SARS-CoV-2.

Ocular involvement of HCoV had previously been reported to be associated with conjunctivitis in humans,[40] by successfully identifying SARS-CoV nucleic acid in tears of patients.[15] Additionally, retinal disorders, such as retinal vasculitis,[41] retinal degeneration,[42] and blood-retinal barrier breakdown,[43] had been demonstrated in experimental animal models of coronavirus infection. As we know now, the chromosome of SARS-CoV-2 was found to be 79.5–82% similar to that of SARS-CoV-1.[16,17,44] This suggests that SARS-CoV-2 may show similar ocular pathogenesis as other strains of SARS-CoV. The report of ocular involvement of COVID-19 is not surprising considering the tropism of CoV virus to the eye. However, legitimate questions remain about how the virus ends up in ocular secretions. Could it be a result of direct inoculation at the time of infection into permissive conjunctival epithelial cells, either by a fomite or aerosol, or could it be the result of shedding from a nasolacrimal gland infected hematogenous? Researchers have tried to answer these questions by examining the dynamics of the infectious SARS-CoV-2 genomic fragments in ocular secretions and its ocular manifestation permissibility. So far, ocular involvement of SARS-CoV-2 has been reported in many cases as an early sign of infection[33,34,38] or appearing as a complication for severe COVID-19 disease.[5,35] The implications of these studies point to two possibilities. First, SARS-CoV-2 may directly inoculate the conjunctiva by aerosol or contaminated fomites and second, an induction of ocular symptoms by viral shedding through infested lacrimal gland from upper respiratory cells. The shedding hypothesis is supported by previous reports that showed that people could contract the infectious SARS virus from individuals who had no fever and minor or no signs of infection.[45] During the outbreak of SARS in 2003, unprotected eyes were associated with an increased risk of transmission of the disease.[45] It is believed that during systemic shedding, the nasolacrimal

Table 1. Reported investigation of ocular surface tissues for the presence of COVID-19.

Title	Authors	Country	
Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva	Zhou et al[38]	China	• 67 participants • confirmed (63) and suspected (4) cases of NCP • Majority of participants were health-care workers or nurses • Nasopharyngeal and conjunctival sac swabs were taken • 1 patient has positive • 2 yielded probable positive PCR results • One patient with conjunctivitis yielded negative • None of the suspected cases was positive for conjunctival swab PCR test
The infection evidence of SARS-COV-2 in ocular surface: a single-center cross-sectional study	Zhang et al[34]	China	• 102 clinically diagnosed cases of SARS-CoV-2 • 72 cases were confirmed by laboratory diagnosis with SARS-CoV-2 PCR • Only 2 out of the 72 had conjunctivitis • Only one had virus in ocular discharges • Nasopharyngeal and conjunctival swabs were taken
Clinical Characteristics of Coronavirus Disease 2019 in China	Guan et al[5]	China	• 1099 patients • No conjunctival swabs were taken • Conjunctival congestion was found in 9 cases(5 in non-severe cases and 4 in severe cases)
Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection	Xia et al[39]	China	• Conjunctival swabs were taken from 21 patients with common-type NCP and 9 patients with severe type. • Only 1 common-type patient tested positive of virus in conjunctival secretion only one patient had conjunctivitis of the viral form
Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China	Wu et al[35]	China	• Conjunctival and nasopharyngeal swabs of 38 patients were taken • 28 positive nasopharyngeal swabs and only 2 patients yielded positive SAR-CoV-2 RNA findings in conjunctival tears • Both were in critical condition • 12 of the 38 cases had conjunctivitis, hyperemia, chemosis, epiphora, secretion • More significant changes in blood test values (including higher white blood cell and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase) appeared in patients with ocular abnormalities • Ocular abnormalities frequently occurred in patients with more severe COVID-19
Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients	Jun et al[37]	Singapore	• 17 COVID-19 cases • Schirmers strips tear collection method. • Multiple swabs were taken for each patient over the period of stay of the patient. • None presented with ocular symptoms • One had conjunctival chemosis during the stay in the hospital • None of the 64 samples showed a viral shedding in tears • Nasal and throat swabs were elevated for a period of 2 weeks from onset of symptoms

system can act as a channel for viruses to travel from the upper respiratory tract to the eye. Hence, ocular tissues and fluid such as the tears may represent a potential source of SARS-CoV-2 infection. However, in a recent prospective study to assess potential viral shedding and infectivity of tears in SARS-CoV -2 patients, it was revealed that neither viral isolation nor quantitative assay by RT-PCR detected the virus in tears, with only one patient out of 17 patients showing ocular symptoms.[37] The study followed the course of the disease by collecting 64 tear samples from the 17 COVID-19 patients, between Day 3 and Day 20 from initial symptoms.[37] A similar investigation[39] that assessed the presence of the novel SARS-CoV-2 in both the tears and conjunctival secretion of COVID-19 infected patients provided little evidence of viral shedding in these ocular tissues. In a sample of 30 severe COVID-19 patients in China, only 1 (3.3%) of the patients developed conjunctivitis during the illness. Unlike the previous study,[37] patients used in this study consisted of 21 (70%) mild-moderate and 9 (30%) severe novel coronavirus pneumonia (NCP) cases. RT-PCR analysis detected no viral RNA in the tear fluid and conjunctival secretions in the mild-moderate (common-type patients) or severe COVID-19 patients without conjunctivitis. Only the patient who had conjunctivitis had SARS-CoV-2 RNA in ocular secretions. It is important to note that, in this same study,[38] RT-PCR analysis of 55 out of 60 (91.7%) sputum samples yielded positive for viral RNA fragments compared to only one patient who had SARS-CoV-2 RNA in the ocular secretions. In another report by Zhang et al.[34] in a single-center cross-sectional investigation at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, among 102 patients with a clinical diagnosis of COVID-19, they did not isolate SARS-CoV-2 RNA in ocular surface secretions by RT-PCR assay. Among 72 (70.6%) SARS-CoV-2 patients confirmed by laboratory diagnosis with RT-PCR, only 2 patients (2.78%) developed conjunctivitis. Of that number, only one of the two with conjunctivitis had SARS-CoV-2 RNA detected in tears.[34]

While these studies indicate that the tears and conjunctiva are not a common means or sites for SARS-CoV-2 infection in humans, these studies had small sample sizes.

The challenge of prospective observations of larger sample sizes, hampered by late development of symptoms[45] which make sampling during early infection difficult was overcome by few prospective studies. In a recent study that utilized a much larger sample size, researchers documented "conjunctival congestion" in only 9 out of 1,099 (0.8%) patients hospitalized with laboratory-confirmed COVID-19 patients from 30 hospitals across China. None of the patients was documented to have seen ophthalmologists, even though the presence of the SARS-CoV-2 RNA in ocular tears were not checked.[5] More recently Zhou et al.[38] in a similar retrospective study investigated the possible transmission of SARS-CoV-2 RNA through aerosol contact with conjunctiva in a cohort of patients. The researchers enrolled 67 cases of confirmed or suspected cases of NCP. Nasopharyngeal and conjunctival swabs were collected for RT-PCR assay to detect viral RNA. Among all the cases, 63 (94%) were identified as laboratory-confirmed NCP and the remaining four were suspected NCP. Conjunctival swab samples from one NCP patient yielded positive for viral RNA and two NCP patients yielded probable positive PCR results. None of the three patients had ocular symptoms. The only one NCP patient who developed conjunctivitis as the first symptom was negative for conjunctival viral RNA. Conjunctival swab samples from the four suspected cases of NCP were negative.

On the other hand, there is some evidence that suggests a relatively high prevalence (5.2%) of SARS-CoV-2 RNA fragments in conjunctival swabs in severe COVID-19 patients. Wu et al.,[35] in a retrospective case series investigated the ocular manifestations and viral prevalence in the conjunctiva and revealed that about a third 12 (31.6%) of 38 clinically confirmed hospitalized cases of COVID-19 in Hubei Province, China, had ocular abnormalities, consistent with conjunctivitis. The authors characterized the most common clinical signs of presentation as hyperemia, epiphora, chemosis and/or secretions. Findings of blood tests, nasopharyngeal and conjunctival swabs from RT-PCR analysis for the same patients indicated that only two patients (5.2%) were positive for conjunctival as well as nasopharyngeal swabs for SARS-CoV-2 RNA. Among the two patients, one had signs of conjunctival hyperemia and the other with chemosis and epiphora. Concurrent nasopharyngeal swabs showed that 28 patients (73.7%) were positive for SARS-CoV-2.[35] It is suggested that, the relatively greater number of COVID-19 patients who developed ocular abnormalities in this study indicates that, ocular complications are prominent among patients with more severe systemic manifestations or abnormal findings on blood tests. However, accounting for conjunctivitis in patients with pneumonia could have been exaggerated as ''chemosis" which the authors characterized as conjunctivitis in critically ill patients. It could as well likely represent cellular infiltration or fluid overload, not conjunctivitis.[35]

All recent studies taken together, they demonstrate that the highly infectious human SAR-CoV-2 are rarely detected by RT-PCR, and difficult to be isolated by virus culture in tears and conjunctival secretions from COVID-19 patients. Against the backdrop of reports in 2003 that body fluids that might contain SARS-CoV (World Health Organization, 2004) it is hard to assess the infectivity of tears and conjunctival secretions and their roles in virus spread of the virus.

The evidence yields to a number of interpretations. First, it demonstrates that nasopharyngeal swabs contain significantly higher SARS-CoV-2 concentration than swabs from the ocular mucosal surface. Drosten et al. found that tracheal aspirates yielded significantly higher SARS-CoV concentration, compared with the nasopharyngeal swab and sputum specimens.[46] This suggests that the viral load and genome fraction differ in different sites. Secondly, the extremely low prevalence of SARS-CoV-2 RNA in tears and conjunctival secretions in confirmed COVID-19 patients does not support viral shedding from infested nasolacrimal system unto the mucosa of the ocular surface (conjunctiva and cornea) but rather suggests that for patients who developed conjunctivitis, the virus was involved in viral transmission to pulmonary sites. This perhaps explains why infectious particles are often detected in the early phase of COVID-19 patients with conjunctivitis.[33,34,38] In considering that the ocular mucosa surface is an openly lubricated microenvironment, and the virus may transport to the inferior meatus of the nose rapidly,

SARS-CoV-2 concentration in ocular secretions is likely to be very low. Hence, it is reasonable to think that viral RNA fragments may be present in tears only for a short incubation period or during the early phase of the disease.

Furthermore, the detection of the virus may also be limited by antimicrobial factors such as lactoferrin and secretory IgA, and force from tear rinsing which constantly eliminates pathogens on the ocular surface into the nasal cavity through the nasolacrimal duct. Lactoferrin is known to inhibit the binding of SARS-CoV to its entry receptor, angiotensin-converting enzyme 2, by preventing the attachment of SARS-CoV to heparan sulfate proteoglycans (HSPGs).[47] Secretory IgA helps to kill both bacteria and viruses.[47]

In addition to lower viral load, the lower positive rate of SARS-CoV-2 RNA findings in COVID-19 ocular tissues may be indicative of sampling time lag and inefficient diagnostic methods. In studies conducted, evidence indicates tear and conjunctival samples were collected in the early phase of illness or the later phase during hospitalization.[7,30-34,42-44,48] As the average incubation period for SARS-CoV-2 was found to be 5 to 7 days,[8] the sampling time and delay in testing may influence the viral load present in the sample. There are also reports that suspected patients often had repeated tests of nasopharyngeal swabs before the positive result confirmed SARS-CoV -2 infection.[34] The rather lower positive rate for the presence of SARS-CoV-2 RNA in ocular secretions makes using RT-PCR assay for diagnosis a challenge. Therefore, improvements in the sensitivity of other molecular diagnostic tests need to be taken into account in the future.[34]

Collectively, while these studies indicate that ocular complications of SARS-CoV-2 infection are not a frequent manifestation of coronavirus infections in humans, the ocular exposure to the virus may represent a meaningful route of entry into the body for this virus.

Clinical Ocular Presentation of SARS-CoV-2

According to published data, the clinical course of SARS-CoV -2 ocular infections shows no specific pattern of presentation and varies between patients (Table 2). It can affect one or both eyes.[7,33,34]The time that it takes for symptoms to develop in the eyes is also not clear, even though many cases reported it occurred in the early phase of infection[33] and nonspecific signs developed later in the clinical course.[35] In a confirmed COVID-19 patient in Shenzhen, China, who developed bilateral conjunctivitis after 13 days of onset of systemic symptoms, RT-PCR assay detected the presence of viral RNA in the conjunctival specimen on the same day (cycle threshold (Ct) value: 31 compared to nasopharyngeal (Ct value: 23.52) and sputum (Ct value: 25) specimens). The conjunctival swab specimens remained positive for SARS-CoV-2 on DAYS 14 and 17. SARS-CoV-2 viral loads decreased (Ct values increased) gradually with resolution. On day 19, the RT-PCR result was negative for SARS-CoV-2 for conjunctival swab specimens.[7] The result showed a trend toward decreasing levels of viral RNA (Ct values increases with the course of the disease), and suggested that viral loads in conjunctival specimens gradually decrease over time with less potential for transmissibility accompanied by improvement of the ocular symptoms.[7]

In the early stage of the disease, ophthalmic examination showed bilateral moderate conjunctival injection (redness), watery discharge (tearing), inferior palpebral conjunctival follicles, tender palpable preauricular lymph nodes, swollen lids and foreign body sensation without blurred vision.[7,33] Substantial ocular congestion/chemosis is reported to be associated with severe cases of COVID-19, perhaps aided by systemic infiltration of cellular cells associated with increased secretion of interstitial tissues during severe cases of the disease.[35] The clinical ocular diagnosis of COVID-19 is consistent with acute follicular conjunctivitis, with conjunctival hyperemia and minor discharges.[7,34] Like other SARS-CoV ocular infections, the secretions are watery and akin to thin mucus, with occasionally small spots (patches) of conjunctival hemorrhages in some cases. Ocular symptoms of COVID-19 are mild and tend to be self-healing, although patients may benefit from treatment with ribavirin eye-drops.[7] No posterior segment eye involvement in COVID-19 has been reported yet but previous corona virus infections have involved retinal disorders such as retinal vasculitis,[41] retinal degeneration[42] and blood-retinal barrier breakdown.[43]

Table 2. Ocular Manifestations of COVID −19 and management.

Country	Demographics	Time of ocular involvement	Ocular symptoms	Ocular signs	Management	Resolution	Presence of virus in conjunctival swabs
Canada[33]	• 29 year old woman		• Monocular Red eye • Photophobia • Sore and swollen eyelid • Mucous discharge in right eye • Ocular signs	• VA: 20/20 • 1–2+ injection • 3+ follicles • pseudodendrite at inferior temporal cornea • 8 small subepithelial infiltrates	• Treatment: Valacyclovir 500mp PO tid and moxifloxacin 1 drop qid		• positive
China[7]	• 30 year old adult male	• Ocular symptoms began on day 13 after symptoms	• Symptoms included tearing, redness and foreign body sensation, Signs included:	• Follicle, moderate redness and preauricular lymphadenopathy.	• Administered Umifenovir • Patient placed on topical antiviral ribavirim on day 14	• Symptoms resolved after 7 days under treatment	• Positive

Possible Mechanism of Ocular Transmission of COVID-19 Virus

There are several anatomical and immune properties which permit the eye to serve as both a potential site of virus replication as well as a gateway for the transfer of virus to respiratory sites to establish infection. The dichotomy between the possibility of ocular transmission or viral shedding, however, may be explained from the anatomic and pathogenesis standpoints. From the anatomic point, the linkage between the ocular and respiratory tract tissues, primarily through the nasolacrimal duct has been implicated[21] (See Figure 1). Once at the ocular surface mucosa, it can be transported through the lacrimal duct which collects tear fluid from the ocular surface and transferred to the inferior meatus of the nose. The lacrimal system drainage could then facilitate the drainage of the virus to respiratory tract tissues in a replication-independent manner.[6,40] Though the virus-containing fluid can be absorbed by the conjunctiva, sclera, or cornea, the majority of fluid exchange is between the nasopharyngeal space, through absorption by the epithelial lining of the lacrimal duct.[15,49]

The anatomical linkage of the ocular mucosal immune system (composed of the lacrimal glands and ocular surface; including the tear film, conjunctiva, and corneal epithelium) with nasopharyngeal space supports the immunological interdependence between ocular and respiratory tract tissues.[40,49] However, despite the ocular mucosal surface being protected from infectious organisms by an array of antimicrobial factors (lactoferrin, lysozyme, immunoglobulin A (IgA), and cationic peptides) present in the tear film and blink shear forces which together limit access to the corneal epithelium,[47] CoV genomic fractions have been detected in the tear fluid of symptomatic and asymptomatic patients.[21] Perhaps, entrapment of microorganisms in secreted mucins and ocular surface defects increase the likelihood of colonization by infectious agents, underscoring the potential for ocular involvement following an outbreak of SAR-CoV-2 infection. Viral conjunctivitis, as characterized by conjunctival congestion and aqueous secretion, is subsequent to the pathology mediated by the immune responses and toxic effectors produced by the infectious agent.

One possibility for the variation in the clinical presentation of SARS-CoV-2 could lie in the genetic makeup of patients and could differentiate people who get mild cases from those who die. Already, there are cases of COVID-19 that are asymptomatic and being elderly or having an underlying condition does not always determine the course of the disease[8,26] From the pathogenic viewpoint, the structure and distribution of host cellular epithelial cell glycoproteins in the human respiratory tract and ocular tissues which serve as terminal receptor sites for viruses may govern virus tropism to the ocular surface. The effectiveness of transmission of the virus into host tissues is modulated by the invasiveness of the virus, viral-host receptor membrane interaction, and immune mediators of the host.[28,49] MERS-CoV and most α-CoVs have been identified to utilize dipeptidyl peptidase 4 and aminopeptidase N as an entry receptor of their host cells, respectively.[49,50]

The cellular entry receptor utilized by HCoV-NL63, SARS-CoV and 2019-nCoV is Angiotensin-Converting Enzyme 2 (ACE-2)[51] (Figure 2).

ACE2 is a type I transmembrane metallocarboxypeptidase with homology to ACE, a cell surface protein enzyme that attaches to epithelial cells of the conjunctiva and cornea[14,21]ACE-2 is also expressed in the respiratory tract, heart, kidney, and gastrointestinal tract, but it is much less

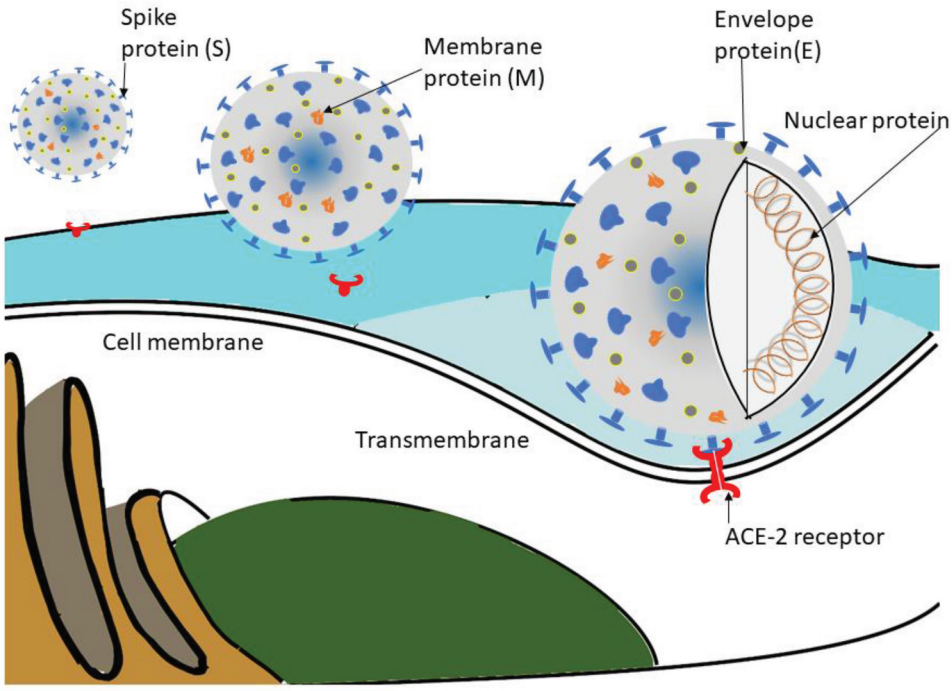

Figure 2. ACE-2 is the host cell receptor responsible for facilitating infection by SARS-CoV-2. The viruses first docked and bound to host cell membrane by its receptors to gain entry into host cells by the interaction between spike protein on the viral surface and on host cell membranes. It then bound spike protein to its entry receptor, ACE2, on the host cell surface for attachment before recruitment of antibody mediators follows.

expressed in the human conjunctival and corneal epithelial cells compared to lung alveolar epithelial cells, enterocytes of the small intestine and the proximal tubular cells of the kidney.[14] Tissues that harbor SARS-CoV are known to infect cells via ACE2 receptors.[47] Consequently, one possibility for the differences in systemic and ocular symptoms of SARS-CoV -2 is variation in the ACE2 gene. Variations in the ACE2 gene that alter the receptor could make it easier or harder for the virus to get into host functional receptor cells mediated by ACE2.[52] In addition to genetic variants of the ACE2 receptor, the location of ACE2, on cardiac and pulmonary tissue likely contributes to the severity of COVID-19. It is thought that the binding ability of ACE2 protein on conjunctival epithelial cells to HCoV spike protein is much lower than respiratory cells.[53]

On the other hand, the basic mechanism to think of is how the body's immune system responds to viruses in the first place. The innate response of the body's immunity cells is a very reactive inflammatory mediator to the invading viruses that can vary in response. Differences in the human leukocyte antigen genes, which influence the immune system's response to viruses, affect the disease presentation and severity. For instance, individuals with type A blood have been shown to have a higher risk of contracting the new SARS-CoV-2 than those with type O do.[48] Indeed, there is evidence to support immune mediators as treatment with steroids, an immune system suppressant, seems to offer benefit in some patients.[10,25,31] More studies on patients with ocular symptoms are required to definitively prove the role of ACE2 present on corneal and conjunctival cells in SARS-CoV-2 infection. The continued identification of the cellular receptors utilized by coronaviruses will allow for a greater understanding of the transmission of SARS-CoV-2 in ocular tissues. Collectively, it appears that the presence of the same permissive receptors on adjacent pulmonary and ocular tissues contribute to the tropism of a virus to ocular tissues, but does not restrict respiratory viruses from using the eye as a portal of entry to gain passage to extraocular tissues to establish a productive infection.[23]

Eye Protection

With the spread of COVID-19, many healthcare professionals have many concerns and fears regarding the possibility of contracting the disease through ocular secretions. Some are contemplating closing their clinics or limiting their practice urgent cases, the possibility of converting operating rooms into ICU if needed, and the possibility of participating to manage patients with acute respiratory distress with its grave responsibility. With regards to eye, current understanding of the ocular complications of COVID-19, including the full clinical course of manifestations is determined by the dynamic changes of SARS-CoV-2 detection in conjunctival and tear swab samples. RT-PCR identification of the virus RNA in ocular secretions of COVID-19 patients with symptoms has not been successful compared to respiratory specimens.[7] However, the low abundance of the virus in tear and conjunctival secretions does not eliminate the risk of transmission through ocular tissue but rather presents safety issues.

Asymptomatic SARS-CoV-2 patients have no obvious fever or respiratory manifestations, and even mild cases of the disease do not show obvious symptoms in the early stages of the disease.[13,15,16,26] During clinical diagnosis and treatment, particularly at the outpatient clinic, it is inherently difficult to quickly screen patients with early-stage disease or carriers of the virus. Li Wenliang, the whistleblower ophthalmologist who sounded the initial alarms on the coronavirus, believed he was infected by an asymptomatic glaucoma patient.[12] The sum of these reports points to asymptomatic transmission as a significant cause for concern. According to recent reports, a large number of ophthalmologists involved in the diagnosis and treatment of eye disease daily accidentally acquired COVID-19 suspected to be related to contact with tears or conjunctival secretions of patients.[12,13] As already indicated, reports suggest that viral loads in conjunctival specimens gradually decrease over time accompanied by improvement of the ocular symptoms, but the potential for transmissibility remains unclear.[7] Direct contact with the ocular surface and mucosal membrane during routine ophthalmic examination may have risk of infection. Most commonly used ophthalmic instruments require close contact with patients. The doctor–patient distance during examination is usually less than 1 m, where the possibility of droplet transmission is high if there is no proper protection. Since the primary route of infection for SAR-CoV -2 is by aerosol and fomites in the local environment, there is also the possibility of a temporary exposure of ophthalmic instruments in a virus contaminated environment. Van Doremalen and his colleagues[9] identified viable SARS-CoV-2 in aerosols up to 3 hours post-aerosolization. They also found that the infectious virus could survive up to 24 hours on cardboard, up to 4 hours on copper, and up to 2 to 3 days on plastic and stainless steel.[11] The CDC also detected SARS-CoV-2 RNA on various surfaces within cabins of passengers in a cruise ship who tested positive for COVID-19 up to 17 days after they disembarked the ship.[54] A more recent report using RT-PCR found SARS-CoV-2 in the hospital rooms of COVID-19 patients.[36] Though these reports do not implicate direct infection, general disinfection using alcohol wipes may be ineffective due to continues exposure. For eye care personnel such as ophthalmologists and optometrists who come into contact with patients at a close-range during clinical examination, there is a need to balance the risk of infection with continuing care for patients in this unique time of COVID-19. Aerosol and saliva of infected patients may still cause infection through conjunctival tissue. There is a report of an anesthesiologist who developed ocular symptoms after performing intubation anesthesia for a patient, followed by fever and cough.[43] The patient was diagnosed with NCP, however during the anesthesia, the anesthesiologist wore only an ordinary surgical mask, hats, and gloves, and did not wear goggles, protective clothing, or other protective devices. Five surgeons who operated on the NCP patient were also infected with SARS-COV-2, but none of them developed any ocular complications.[38]

Several eye infection prevention and control measures have been suggested to avert the spread of COVID-19 through ocular transmission. Personal eye protection, thus, wearing face shields or goggles is necessary protective measures to prevent temporary

aerosol contact with the conjunctiva.[29] A triage system must be set up at outpatients units to identify patients with fever, respiratory symptoms, and ocular manifestations such as epiphora and acute conjunctivitis in order to minimize SAR-CoV-2 cross-infections. Micro-aerosol generating procedures, such as noncontact tonometry and where applicable, operations under general anesthesia has to be done under aseptic conditions. Nasal endoscopy which may provoke sneezing and cause generation of droplets must be evaluated. Additionally, infection control training must be provided to all clinical staff. These include the need for environmental control to reduce droplet transmission of COVID-19 such as the installation of protective shields on slit lamps, frequent disinfection of equipment, and provision of eye protection to staff. Lastly, universal hygiene such as the washing of hands under running water and use of hand sanitizers are to be promoted.[55]The findings of clinical observations serve notice that all eye care personnel just like other medical personnel should take stringent precautions to protect their eyes when coming into contact with COVID-19 patients. As conjunctivitis is a common eye condition, an ophthalmologists or optometrist may be the first professionals to evaluate a patient with COVID-19. Adherence to ocular protective measures can serve to cut off transmission channels and prevent cross-infection in support of public health and safety.

Future Studies

At present, findings from studies suggest the ocular infectivity of SARS-CoV-2 is low. Further definitive investigations into the mechanism of SARS-CoV-2 –host receptor cell interactions are required to evaluate the role of this novel coronaviruses in the eyes.[39] SARS-CoV-2 has been known to infect cells via ACE2 receptors. However, future mechanistic studies are required to definitively prove the presence of ACE2 on ocular surface mucosa. Furthermore, studies to gain more understanding of the ocular complications of COVID-19, especially regarding ocular transmissibility or viral shedding and the pathogenesis of ocular disease has to be conducted. The COVID-19 pandemic is ongoing, making a balance between patient care and research difficult. Most prospectively controlled studies have used a small cohort of patients. Negative viral RNA results from samples taken from the ocular surface could be influenced by the sampling amount and time, as viral conjunctivitis is self-healing. Therefore, further large-sample and more comprehensive studies involving patients with early ocular symptoms should be considered to understand the progression of the disease. Conjunctival, cornea, and tear samples should be collected as early as possible when ocular symptoms develop in suspected cases. Also, detailed ocular examinations should be performed to examine SARS-CoV-2 infectivity of intraocular tissues in patients who develop ocular complications to allow for a better understanding of the permissiveness of non-respiratory tissues. Finally, future studies should consider investigating factors underlying the relationship between sputum and serum viral loads and viral shedding into ocular secretions, as well as the effect of the presence of antimicrobial agents on the eye and pharmacological agents such as antiviral treatment on detection of the virus on the ocular surface.

CONCLUSION

Findings from published investigations about the ocular complications of SAR-CoV-2 have been inconclusive. While previous reports show potential shedding of an infectious virus such as SARS-CoV-1 in tears, the detection rate was low.[15] Studies reviewed show a low prevalence of SARS-CoV-2 nucleotide fragments in conjunctival and tear specimens of patients with COVID-19, consistent with previous studies on SARS-CoV-1[56] The results suggest SARS-CoV-2 may be detected in ocular secretions in COVID-19 patients with conjunctivitis, but not in patients without conjunctivitis. Common characteristics of COVID-19 cases with ocular complications were occupational exposure and the occurrence of conjunctivitis in the early stage. The existing evidence demonstrates that the eye may not be a common route for transmission of the virus and there is relatively low likelihood of the infectious virus shedding in the eyes of COVID-19 patients. The possibility of viral shedding may only be likely in patients with more severe COVID-19 as pronounced complications frequently occurred in these patients.

There is an inevitable possibility of many false positive and false negative results, which are often caused by sampling time lag, contamination, and damage to genetic material. However, the RT-PCR employed in SARS-CoV-2 identification is an effective technique for detecting viral RNA, due to its high sensitivity and specificity. Like other highly contagious respiratory viruses, respiratory droplets are considered as the main route of SARS-CoV-2 transmission. Nevertheless, considering that the eye is directly exposed to infectious droplets and fomites during close contact with infected individuals and contaminated hands, and the mucosa of the ocular surface and upper respiratory tract being connected by the nasolacrimal duct and share certain entry receptors for some respiratory viruses, the eye as a possible transmission route should be taken into account owing to the rapid transmission of the virus. The risk of ocular nosocomial infection of SARS-CoV-2 and as a potential route of transmission should further be examined and scientific protection should not completely be eliminated.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ORCID

Stephen Ocansey http://orcid.org/0000-0002-3992-0969
Emmanuel Kwasi Abu http://orcid.org/0000-0003-2354-9170
Carl Halladay Abraham http://orcid.org/0000-0003-1733-3509
Andrew Owusu-Ansah http://orcid.org/0000-0002-4278-2237
Samuel Bert Boadi-Kusi http://orcid.org/0000-0002-4866-4960
Desmond Omane Acheampong http://orcid.org/0000-0001-8197-2618

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia

in Wuhan, China: a descriptive study. *Lancet*. 2020;395 (10223):507–513. doi:10.1016/S0140-6736(20)30211-7.
2. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol*. 2020;92(4):401, 402.
3. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of 2019 novel coronavirus diseases (COVID-19) in Jingmen, China. *SSRN Electron J*. 2020;2(8): 113–122.
4. 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 coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm*. 2020;1–5. Internet. doi:10.1080/09273948.2020.1738501.
5. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
6. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579 (7798):265–269. doi:10.1038/s41586-020-2008-3.
7. Chen L, Liu M, Zhang Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. 2020; figure 2. 1–4.
8. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172(9):577–582. doi:10.7326/M20-0504.
9. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564–1567. doi:10.1056/NEJMc2004973.
10. Tang A, Tong ZD, Wang HL, et al. Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China. *Emerg Infect Dis*. 2020;26:6. doi:10.3201/eid2606.200301.
11. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382(10):970–971. doi:10.1056/NEJMc2001468.
12. Green A. Li Wenliang. *Lancet*. 2020;395(10225):682. doi:10.1016/S0140-6736(20)30382-2.
13. Lu C, Liu X, Jia Z. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet*. 2020;395(10224):e39. doi:10.1016/S0140-6736(20)30313-5.
14. Liu L, Sun Y, Pan X, Shen W, Liu ZY, Liu YP. Expression of SARS coronavirus S proteinfunctional receptor-angiotensin-converting enzyme 2 in human cornea and conjunctiva. *Chin Ophthal Res*. 2004;22:561–564.
15. Loon SC, Teoh SCB, Oon LLE, et al. The severe acute respiratory syndrome coronavirus in tears. *Br J Ophthalmol*. 2004;88 (7):861–863. doi:10.1136/bjo.2003.035931.
16. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol*. 2020;92(4):418–423. doi:10.1002/jmv.25681.
17. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565–574. doi:10.1016/S0140-6736(20)30251-8.
18. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol*. 2020;94:7. doi:10.1128/JVI.00127-20.
19. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol A J Pathol Soc Gt Britain Irel*. 2004;203:631–637.
20. Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system - focus on eye. *Open Ophthalmol J*. 2017;11(1):122–142. doi:10.2174/1874364101711010122.
21. Belser JA, Rota PA, Tumpey TM. Ocular tropism of respiratory viruses. *Microbiol Mol Biol Rev*. 2013;77(1):144–156. doi:10.1128/MMBR.00058-12.
22. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* [Internet]. 2020 May 28;581(7809):465–469. doi:10.1038/s41586-020-2196-x.
23. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020;382 (10):929–936. doi:10.1056/NEJMoa2001191.
24. General Office of National Health Commission. General office of national administration of traditional Chinese medicine. *Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia* Trial version 7, revised form. 2020.
25. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19 [Internet]. Vol. 20, The Lancet infectious diseases. *Lancet* Publishing Group; 2020. doi:10.1016/S1473-3099(20)30232-2.
26. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *Jama*. 2020;323(14):1406. doi:10.1001/jama.2020.2565.
27. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and pre-symptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility—King County, Washington, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(13):377.
28. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *N Engl J Med*. 2020;382(13):1199–1207. doi:10.1056/NEJMoa2001316.
29. Mission, WHO-China Joint. *Report of the Who-china Joint Mission on Coronavirus Disease 2019 (Covid-19)*. Geneva; 2020.
30. Ong SWX, Tan YK, Chia PY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *Jama*. 2020;323(16):1610. doi:10.1001/jama.2020.3227.
31. Paulsen F. Functional anatomy and immunological interactions of ocular surface and adnexa. In: Geerling G, Brewitt H, eds. *Surgery for the Dry Eye*. Dev Ophthalmol. Vol. 41. Basel: Karger Publishers; 2008:21–35.
32. Leclerc QJ, Fuller NM, Knight LE, Funk S, Knight GM, What settings have been linked to SARS-CoV-2 transmission clusters? *Wellcome Open Res* Internet]. 2020 Jun 5;5:83. doi: 10.12688/wellcomeopenres.15889.2.
33. Cheema M, Aghazadeh H, Nazarali S, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19): X A case report. *Can J Ophthalmol Can D'ophtalmologie* [Internet]. 2020;1–6. doi:10.1016/j.jcjo.2020.03.003.
34. Zhang X, Chen X, Chen L, et al. The infection evidence of SARS-COV-2 in ocular surface: a single-center cross-sectional study. 2020. 8197033356.
35. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol*. 2020;2019:4–7.
36. Santarpia JL, Rivera DN, Herrera V, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the university of nebraska medical center. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.23.20039446. Accessed April 4, 2020.
37. Yu SI, Jun ADE, Eng A, et al. Assessing viral shedding and infectivity of tears in coronavirus disease 2019 (COVID-19) patients. *Ophthalmology* [Internet]. 2020;2019. doi:https://doi.org/10.1016/j.ophtha.2020.03.026
38. Zhou Y, Zeng Y, Tong Y, Chen C 2020 Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. 2.
39. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol*. 2020;92(6):589–594. doi:10.1002/jmv.25725.
40. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med*. 2004;10(4):368–373. doi:10.1038/nm1024.
41. Chin MS, Hooper LC, Hooks JJ, Detrick B. Identification of α-fodrin as an autoantigen in experimental coronavirus retinopathy (ECOR). *J Neuroimmunol*. 2014;272(1–2):42–50. doi:10.1016/j.jneuroim.2014.05.002.
42. Wang Y, Detrick B, Yu Z-X, Zhang J, Chesky L, Hooks JJ. The role of apoptosis within the retina of coronavirus-infected mice. *Invest Ophthalmol Vis Sci*. 2000;41:3011–3018.

43. Vinores SA, Wang Y, Vinores MA, et al. Blood–retinal barrier breakdown in experimental coronavirus retinopathy: association with viral antigen, inflammation, and VEGF in sensitive and resistant strains. *J Neuroimmunol*. 2001;119(2):175–182. doi:10.1016/S0165-5728(01)00374-5.
44. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273. doi:10.1038/s41586-020-2012-7.
45. Raboud J, Shigayeva A, McGeer A, et al. Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada. *PLoS One*. 2010;5:5. doi:10.1371/journal.pone.0010717.
46. Drosten C, Chiu -L-L, Panning M, et al. Evaluation of advanced reverse transcription-PCR assays and an alternative PCR target region for detection of severe acute respiratory syndrome-associated coronavirus. *J Clin Microbiol*. 2004;42(5):2043–2047. doi:10.1128/JCM.42.5.2043-2047.2004.
47. Lang J, Yang N, Deng J, et al. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. *PLoS One*. 2011;6:8. doi:10.1371/journal.pone.0023710.
48. Zhao J, Yang Y, Huang H, et al. Relationship between the ABO Blood Group and the COVID-19 susceptibility. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.11.20031096.
49. Sun C, Wang Y, Liu G, Liu Z. Role of the eye in transmitting human coronavirus: what we know and what we do not know. 2020.
50. Stalin Raj VS, Mou H, Smits S, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nat Int Wkly J Sci*. 2013;495(7440):251–254.
51. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450–454. doi:10.1038/nature02145.
52. Kaiser J. How sick will the coronavirus make you? The answer may be in your genes. *Science*. 2020;368. https://www.sciencemag.org/news/2020/03/how-sick-will-coronavirus-make-you-answer-may-be-your-genes. Accessed March 20, 2020.
53. Sun Y, Liu L, Pan X, Jing M. Mechanism of the action between the SARS-CoV S240 protein and the ACE2 receptor in eyes. *Int J Ophthalmol Chi*. 2006;6:783.
54. Bialek S, Boundy E, Bowen V, COVID CDC, Team R. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(12):343–346. doi:10.15585/mmwr.mm6912e2.
55. Lai THT, Tang EWH, Chau SKY, Fung KSC, Li KKW. Stepping up infection control measures in ophthalmology during the novelcoronavirus outbreak: an experience from Hong Kong. *Graefes Arch Clin Exp Ophthalmol*. 2020;258:1049–1055. https://doi.org/10.1007/s00417-020-04641-8.
56. Peiris JSM, Yuen KY, Osterhaus ADME, Stöhr K. The severe acute respiratory syndrome. *N Engl J Med*. 2003;349(25):2431–2441. doi:10.1056/NEJMra032498.