Perspective

Implications of COVID-19 for Ophthalmologists

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• PURPOSE: To describe and explain the implications of coronavirus disease 2019 (COVID-19) for ophthalmologists considering the rapid developments in our understanding of the virology, transmission, and ocular involvement.
• DESIGN: Evidence-based perspective.
• METHODS: Review and synthesis of pertinent literature.
• RESULTS: Retrospective studies highlight that < 1% of patients display COVID-19–related conjunctivitis. However, prospective studies suggest the rate is higher (~6%). Viral RNA has been identified in tears and conjunctival secretions in patients with active conjunctivitis as well as asymptomatic cases. Overall, conjunctival swabs are positive in 2.5%. Samples taken earlier in the disease course are more likely to demonstrate positive virus. Viral transmission through ocular tissues has not been substantiated. Ophthalmologists are in the high-risk category for COVID-19 infection for several reasons: high-volume clinics, close proximity with patients, equipment-intense clinics, and direct contact with patients' conjunctival mucosal surfaces. COVID-19 is predominantly contracted through direct or airborne transmission by inhalation of respiratory droplets. Evidence that aerosol transmission occurs is increasing in particularly prolonged exposure to high concentrations in a relatively closed environment. Based on the current evidence, ophthalmologists should consider measures that include social distancing, wearing masks, sterilization techniques, and managing clinic volumes.
• CONCLUSIONS: A major challenge to containing COVID-19 is that many infected people are asymptomatic. Droplet spread, contaminated environmental surfaces, and shared medical devices are areas that require management by ophthalmologists. More studies are required to explore the role of the conjunctiva and ocular tissues in the transmission of disease. (Am J Ophthalmol 2021;223:108–118. © 2020 Published by Elsevier Inc.)

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THE PRACTICE OF MEDICINE HAS MORE RAPIDLY changed in the last several months than it has over the past few decades. This has been due to the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 has reached at least 124 countries and territories and has emerged as a global health threat. Our understanding of the virus, its epidemiology, transmission, and implications for ophthalmology is continually evolving. The goals of this perspective are to address several key questions that are particularly critical for ophthalmologists. First, what is the evidence regarding the proposed modes of transmission of the virus and how transmissible is it? Second, how common are ocular symptoms and signs as part of our present understanding of the spectrum of disease? Third, what is the science that supports ocular transmission? Of particular interest is whether there is convincing evidence that tears and the ocular surface of asymptomatic, as well as symptomatic, patients with COVID-19 harbor active virus. Finally, what are the key issues for ophthalmologists in routine clinical practice?

VIROLOGY

THE CAUSE OF COVID-19 IS A NEWLY DISCOVERED VIRUS termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Coronaviruses rose to public prominence after the outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003 and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) in 2012.[2] Coronaviruses belong to the subfamily Coronavirinae, in the family Coronaviridae of the order Nidovirales with 4 known genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The coronavirus name is a derivative from the Latin *corona*, describing its characteristic structure of surface projections on the viral envelope giving it an appearance similar to a crown.[3]

SARS-CoV-2 is a single positive sense single-stranded RNA virus with a genome of around 30 kb in length, making it the largest known RNA virus.[4] As in all

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coronaviruses, a positive sense signifies that the viral RNA sequence may be directly translated into viral proteins and the RNA strand acts as a mRNA and therefore does not require a RNA polymerase to be packaged into the virion in order for the virus' genome to replicate. All coronaviruses share a similar structure made of 4 main structural proteins and some also encode special structural and accessory proteins.[5] The structural proteins aid the viral infection of host cells and subsequent replication with each structural protein having a specific role in this process, such as attachment to the host cell and binding to the nucleocapsid, as well as to a replication–transcription complex that facilitates replication of genomic material.

Presently, 7 human coronaviruses have been identified: HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV-1, MERS-CoV, and more recently SARS-CoV-2.[6] The sequence of SARS-CoV-2 has been shown to be 75% to 80% identical to SARS-CoV-1 and 40% identical to MERS-CoV. SARS-CoV-2and SARS-CoV-1 share the same host receptor, human angiotensin-converting enzyme 2 (ACE2), which is the primary target of the virus.[7] The virus binds to the lung epithelial cells with ACE2 receptors and fusion with the cell membrane is the first step of viral infection.

RNA viruses (eg, coronavirus, HIV, hepatitis C, Ebola, measles, and poxvirus) have greater mutation rates compared with DNA viruses (eg, herpesviruses, cytomegalovirus, and human papillomavirus), providing the virus a more efficient adaptation process for survival. COVID-19 is highly contagious in humans although the transmissibility is not precisely known. A meta-analysis suggests that its basic reproduction number (RO) ranges between 1.4 and 6.49 (mean 3.23; median 2.79).[8] The RO represents the average number of people who will catch the disease from 1 infected person. The seasonal flu is considered to have an RO of 1.2 to 1.4 while measles has a RO of 12 to 18.

Coronaviruses are recognized to affect birds and mammals, including household animals, such as the domestic cat (feline) and dog (canine). However, there is no evidence that pets can spread the virus. Larger mammals such as beluga whales and tigers are also affected by coronaviruses. The genesis of the COVID-19 is, as yet, unclear, although several theories regarding its origin have been proposed. Natural selection in an animal host before zoonotic transfer has been suggested (bats to intermediate hosts and from animal hosts to humans). However, to date no coronavirus has been found in animals that is sufficiently similar to SARS-CoV-2. Another possibility is selection during passage in cell culture, although no laboratory escape episodes have been reported. The third hypothesis suggested is natural selection in humans after zoonotic transfer where there was an unrecognized human-to-human transmission. Presently, there are not enough data available to accept or reject any of these hypotheses.[9] Coronaviruses in general can produce heterogeneous ocular conditions in animals, such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis. However, this occurs through mechanisms that are different than the manner in which human coronaviruses presently behave.

SEASONALITY

COVID-19 IS SUSPECTED OF EXHIBITING A STRONG SEAsonal cycle, peaking in winter in temperate regions and during the rainy season in tropical regions similar to influenza epidemics. Coronavirus are thought to last longer in environments at lower temperatures and relative humidity, which would suggest that there may be some seasonality of virus spread. However, the seasonality of Covid-19 remains to be established.[10,11] Lower temperatures also result in more indoor activities, less social distancing, and a greater risk of viral transmission.

TRANSMISSION PERIOD

PATIENTS WITH COVID-19 HAVE BEEN SHOWN TO HAVE high viral loads soon after symptom onset, which then gradually decrease to low levels at day 21.[12,13] Infectiousness is estimated to decline quickly within 7 days.[14,15] However, infectiousness commences from 2.3 days before symptom onset and peaks just before symptoms or at the start of symptoms.[14] This pattern is distinct from that of SARS-Cov-1 that shows an increased infectiousness around 7 to 10 days after symptom onset.[16] In contrast to SARS-Cov-1 but similar to SARS-CoV-2/COVID-19, influenza virus is characterized by increased infectiousness just before and shortly after symptom onset.[17,18] The incubation period for COVID-19 is approximately 5.2 days. Furthermore, several studies have estimated the proportion of presymptomatic transmission to range between 44% and 62%.[19] Interestingly, a point-prevalence study of nursing residents demonstrated that more than half of the positive tests were in an asymptomatic nursing faculty.[20]

ROUTES OF TRANSMISSIONS

PRIMARY VIRAL REPLICATION IS PRESUMED TO OCCUR IN the mucosal epithelium of the upper respiratory tract (nasal cavity and pharynx), with further multiplication in the lower respiratory tract and possibly the gastrointestinal mucosa.[21] COVID-19 is considered to have a similar mode of transmission to SARS-CoV and MERS-CoV, spreading predominantly through direct or airborne transmission by inhalation of respiratory secretions, droplets, or aerosols. According to the World Health Organization, airborne transmission can occur in 2 ways: either through relatively large particles of respiratory fluid (droplets >5 μm) or through smaller such particles that can remain aerosolized, such as droplet nuclei (<5 μm).[22] Some researchers suggest that particles of <20 μm should be considered aerosols because of their potential to remain in the air for prolonged period or because they can reach the respirable fraction of the lung (ie, the alveoli).[22] As larger droplets are quickly pulled to the ground by gravity, droplet transmission requires close physical proximity between infected and susceptible individuals, whereas aerosolized transmission can occur over larger distances and does not necessarily require that infected and susceptible individuals be at the same location at the same time.[23]

• **DROPLETS:** There is extensive research investigating the behavior of the virus in droplets and aerosols.[24–26] Droplet transmission occurs when particles are emitted from the respiratory tract of an infectious person, travel directly to reach people who are nearby, and can then be inhaled into the lungs.[27] Talking, breathing, sneezing, and coughing all discharge droplets. Droplets are considered to be >5 μm and therefore they remain airborne only briefly before settling because of gravity spreading in a space of about 1 to 2 m (3–6 ft) from the source.[28]

• **AEROSOLS:** Breathing and talking also produce smaller and much more numerous particles, known as aerosol particles, that may distribute and disperse by diffusion and air turbulence. Researchers have established that aerosols are involved in the spread of SARS-CoV and MERS-CoV.[29] The evidence regarding aerosol transmission of COVID-19 remains mixed. The World Health Organization has stated that there is insufficient evidence to suggest that COVID-19 is spread by aerosol transmission.[30] However, several studies have reported viral RNA particles in air samples in crowded environments or those with poor ventilation.[31,32] Air outlet fans and other room sites, such as toilets, also tested positive for SARS-CoV-2.[33] Whether such identified particles are infectious still remains to be substantiated. However, viral particles have been shown to survive in aerosol for ≥3 h.[26] One study that identified a significant virus-laden aerosol concentration in hospital hallways in Wuhan suggested that aerosol concentration may be the resuspension of virus particles from the surface of protective apparel worn by medical staff while they are being removed or the resuspension of floor dust aerosol containing the virus.[32] Another variable that is still under investigation is the infectious dose in aerosol that could lead to transmission. Therefore, while aerosol transmission is currently not considered the primary mode of transmission for COVID-19, evidence suggests that it is possible with prolonged exposure to high concentrations in a relatively closed environment.[34]

• **DIRECT TRANSMISSION:** An analysis of 22 studies found that human coronaviruses, including SARS-CoV-1, MERS-CoV, and endemic human coronaviruses, can persist on metal, glass, plastic, and other inanimate surfaces for ≤9 days.[35] Studies that specifically have considered SARS-CoV-2 viability also show it lasts on various surfaces for a significant period of time. A study that assessed the stability as well as estimated the decay rate of SARS-CoV-2 showed that the virus is more stable on plastic and stainless steel than on copper or cardboard. Viable virus was detected up to 24 h on cardboard and 72 h on plastic (a half-life of 6.8 h) and stainless steel (a half-life of 5.6 h), although the viral titer shows an exponential decay. On copper, no viable virus was measured after 4 h. In general, the virus persists for shorter periods of time on surfaces with low porosity (eg, copper or latex).[26] A study in Singapore that evaluated environmental samples from hospital rooms of 3 patients with COVID-19 found that with 1 patient, where the samples were taken before cleaning, positive viral polymerase chain reaction (PCR) was demonstrated in 87% of room sites, including air outlet fans, and in 60% of 5 toilet sites. In contrast, samples from rooms that had undergone cleaning were all negative.[36] Importantly, personal protective equipment of health care workers who are tending to positive COVID-19 patients have predominantly been negative.[33]

• **FECAL-TO-ORAL ROUTE:** Fecal-to-oral transmission has been suggested, but little evidence supports it.[37] SARS-CoV-2 RNA has been detected in stool, whole blood, and urine of patients, but whether transmission via such media is possible is still unknown. Some patients have been shown to experience diarrhea before respiratory symptoms. SARS-CoV-1 also was identified in stools of infected patients and thought to survive through sewage that has not undergone adequate disinfection.[38]

• **CLINICAL SPECTRUM:** Most patients with COVID-19 experience fever, dry cough, and dyspnea with other common symptoms, including myalgia, headache, and diarrhea. Other symptoms include anorexia, nausea, sore throat, anosmia, and ageusia. Shortness of breath develops a median of 5 to 8 days after the initial symptom onset. Laboratory investigations show lymphopenia and elevated C-reactive protein and erythrocyte sedimentation rate in most patients. In patients who are more likely to require intensive care unit admission, there have been higher levels of prothrombin time, D-dimer levels, and plasma levels of interleukins-2, -7, and -10, granulocyte colony-stimulating factor, interferon γ-induced protein 10 kDa, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α, and tumor necrosis factor α.[39] Computed tomography (CT) scans of the chest show bilateral pneumonia with ground-glass opacity and bilateral patchy shadows. Death most commonly results from acute respiratory distress secondary to a "cytokine storm." When death was the outcome, the period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days, with shorter time among patients ≥70 years of age.[40]

Risk factors for complications include age ≥65 years, cardiovascular disease, chronic lung disease, hypertension, diabetes mellitus, and obesity. It is unclear whether other conditions, such as kidney disease, immunosuppression, or cancer, confer an increased risk of complications. Laboratory findings associated with worst outcome include increasing white cell count with lymphopenia, prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, interleukin C, C-reactive protein, and procalcitonin.[41]

• **OCULAR INVOLVEMENT IN COVID-19:** *Conjunctivitis*. Conjunctivitis has been reported to be a presenting symptom of COVID-19, although Chinese ophthalmologists believe that the extent of ocular involvement has largely been ignored.[42] There are several well-documented case reports.[43–45] The most extensively documented case report is that of a 29-year-old, otherwise healthy woman with a 1-day history of unilateral conjunctivitis, photophobia, and clear watery discharge. There was a background of mild respiratory symptoms with no fever. Examination features included pseudodendrites in the inferior cornea, small subepithelial infiltrates, and epithelial defects. The diagnosis was made through both nasopharyngeal and conjunctival swab using reverse transcription PCR (RT-PCR).[45]

A case series of 38 patients with COVID-19 from a hospital in Hubai province reported only 1 patient presenting with conjunctivitis, but 31.6% of the cohort had symptoms of conjunctival hyperemia, chemosis, epiphora, or increased secretions during their illness.[46] Ocular symptoms were most severe in patients with severe pneumonia. The virus was detectable in 18% of patients who had conjunctival swabs (2/11). A larger retrospective study extracted data from 1099 cases from the first 2 months of the COVID-19 outbreak in Wuhan revealing that "conjunctival congestion" was recorded in 0.8% of the patients.[47] However, there was incomplete documentation of many patients, and it is difficult to determine the consistency of the history and examination given the acute and extensive nature of the outbreak. It is also unclear how the symptoms for eye involvement were elicited and clinical information recorded. In a prospective study of 72 patients with COVID-19, 2.78% were identified with conjunctivitis.[48] In addition, based on the Report of the WHO-China Joint Mission on Coronavirus Disease 2019"[49] summarized from 55,924 laboratory-confirmed cases, the typical signs and symptoms reported only 0.8% conjunctival congestion.

A recent case report suggests retinal changes associated with COVID-19 infection. A case series of 11 patients who underwent optical coherence tomography found that all patients showed hyper-reflective lesions at the level of ganglion cell and inner plexiform layers more prominently at the papillomacular bundle in both eyes. This was not associated with any visual dysfunction or changes in optical coherence tomography angiography or ganglion cells complex analysis. Four of the patients showed subtle cotton wool spots and microhemorrhages along the retinal arcade.[50]

Presence in ocular tissues. Several coronaviruses have been identified in ocular tissues.[51] The coronavirus HCoV-NL63 in 2000–2003 was first isolated from a 7-month-old child who presented with bronchiolitis and conjunctivitis.[52] A retrospective study that analyzed the nasal swabs of children with that virus identified that 17% (n = 3) of patients (n = 18) developed conjunctivitis.[53] Studies have also investigated the presence of SARS-CoV-1 in tears or conjunctival sac with variable results. Conjunctival secretions analyzed by RT-PCR assay from 36 highly suspected cases of SARS-CoV-1 were positive in 3 patients (8.6%). Tear samples were used to confirm SARS-CoV-1 in 1 of the 3 patients, who was virus-positive only in tears.[51] The cases that were positive were sampled early in the phase of their disease compared with negative cases. Other investigators report only negative results with RT-PCR in tears and conjunctival scrapings.[54,55] Overall, while several investigators have detected SARS-CoV-1 in the tears or conjunctiva of patients, the detection rate has been low. In a study that evaluated MERS-CoV,[56] investigators demonstrated that in the rhesus macaque model, MERS-CoV RNA could be detected in the conjunctiva, but the viral loads could no longer be detected in the conjunctiva 6 days postinfection. Therefore, it has been suggested that the negative results could be partly attributed to timing, viral load, and the sensitivity of the testing method.

Studies investigating COVID-19 have similarly revealed mixed results. A prospective study in Singapore followed 17 patients with COVID-19 who had serial nasopharyngeal swabs for RT-PCR and serial tear sampling using Schirmer strips. All tear samples were negative on viral isolation and RT-PCR throughout the course of the disease.[57] Another group tested tears and conjunctival secretions with conjunctival test paper and standard RT-PCR in 30 confirmed COVID-19 with 2 samples from each patient. None of the samples collected from 29 patients with COVID-19 without conjunctivitis were positive. One patient who had active viral conjunctivitis but no fever or respiratory symptoms for an additional 3 days was shown to have COVID-19 RNA in the 2 samples.[58]

However, some investigators have identified viral RNA in the conjunctival sac of patients without ocular symptoms. Three of 67 patients with COVID-19 pneumonia had positive RT-PCR in the conjunctival sac of 3 patients with COVID-19 without ocular symptoms.[59] Similarly, a group evaluating 72 patients with confirmed COVID-19 found that virus RNA was identified by conjunctival swabs in 1 patient. The largest study of 121 patients with confirmed COVID-19 in Wuhan had conjunctival and nasopharyngeal swabs collected on the same day. The mean duration of disease in the study population was 15 days with nearly half being severe and mild or moderate cases. While 6.6% had ocular symptoms, only 1 conjunctival swab tested positive. Two patients with no ocular symptoms had positive conjunctival swabs, with 1 being critical and the other mild to moderate. Overall, conjunctival swabbing was positive in 2.5% (3/121) cases.[60] The aforementioned studies confirm that SARS-CoV-2 can exist in tears or the conjunctival sac, but that infection of SARS-CoV-2 via the eyes remains uncertain. However, the testing methods and conditions may contribute partly to the low positive rate.[61]

There are several possibilities to account for the low yield of virus RNA in tear or conjunctival samples. Viral concentration, sampling time, and diagnostic method may influence the sensitivity. With SARS-CoV-1, samples from tracheal aspirates had a significantly higher yield compared with sputum specimens suggesting viral concentration varies with different sites.[62] The time of exposure is critical because of the higher viral load at the early stage of infection. In most studies, the sampling from tears and conjunctiva occurred later in the disease cycle, while virus load is recognized to be highest early in the course of the illness. Furthermore, the collection technique is variable, including the type of swabs, the presence of calcium alginate swabs (which may inactivate virus and inhibit PCR tests), and the use of topical anesthesia for sample collection influencing the viability of viruses.[63] The volume of tears collected may further influence the result. Finally, improvements in the sensitivity of molecular diagnostic methods may result in higher yields. Notably, patients often require repeat nasopharyngeal swabs to confirm a positive result. Future studies should consider the association between serum viral load and viral shedding in tears.

Role of ocular tissue in the transmission of COVID-19. The mechanism of how the virus appears in tears remains unclear, and whether there can be transmission through infected ocular tissue or fluid is controversial.[46] One hypothesis is that the nasolacrimal system behaves as a channel for viruses to travel from upper respiratory tract to the eye. Alternatively, because patients with COVID-19 have viremia during the acute phase, the presence of viral RNA is likely to be the result of exudation of the virus into the conjunctiva. However, several anatomic and physiologic properties of the ocular surface may also facilitate its role both in serving as a gateway for respiratory infections as well as a potential site for viral replication.[64]

The conjunctival epithelium is exposed directly to the external environment that may include droplets containing virus particles and contaminated fomites. Direct inoculation of the conjunctiva from infected droplets results in some absorption by the cornea, conjunctiva, and ultimately sclera, but most drain into the nasolacrimal system with the lacrimal duct transporting tears to the inferior meatus of the nose or into the nasopharyngeal space. Hence, ocular tissue and fluid may represent a potential source of, and route for, COVID-19 infection, although the role of the conjunctiva in transmission of the virus currently remains unclear.

Another theoretical avenue that SARS-CoV-2 may access entry through ocular tissues is through ACE2 receptors. SARS-CoV-2 requires access to host cells through the ACE2 receptor. The ACE2 receptor has been identified on the ocular surface as part of a local autocrine function of the renin-angiotensin system.[65] ACE2 has been found in aqueous humor and the retina.[66] However, the expression of ACE2 in more anterior tissues, such as the conjunctiva or cornea, is not completely understood. The renin-angiotensin system has been investigated for the potential development of antiglaucoma drugs.[67] Therefore, although the ACE2 receptors are present in ocular tissue, whether this provides a pathway for viral replication has not been established. Presently, there are insufficient data to determine whether systemic ACE inhibitors alter risks for patients.

Risks to ophthalmologists. Health care workers are at high risk for infection through human-to-human infection, droplet, and direct contact with fomites.[47] It has been estimated that tens of thousands of health care workers have developed infection internationally.[68] Furthermore, the risk is compounded given that patients with COVID-19 have been shown to be infectious when mildly symptomatic or even asymptomatic plus viral shedding appears to be highest in the earliest stage.

Ophthalmologists, anesthetists, dentists, and ear, nose and throat specialists have been identified to be at high risk for infection while carrying out their routine patient care.[58] Ophthalmologists are in the high-risk category for multiple reasons. Ophthalmologists have high-volume clinics and are in particularly close proximity with patients. The US Centers for Disease Control and Prevention defined close contact as being approximately 2 m from a patient for a prolonged duration, where any contact longer than 1 to 2 min of exposure is considered prolonged.[69] There is also the use of equipment by ophthalmologists that requires close patient proximity, such as slit lamp, tonometer, fundus camera, ocular ultrasound, perimetry, and laser treatments.[59] In addition, ophthalmologists have direct contact with patients' conjunctival mucosal surfaces during procedures, such as using 3-mirrored lens and gonioscopes, which potentially may serve as a route for COVID-19 transmission.

Warning regarding noncontact tonometry as a source of microaerosols has also been raised. Disruption to the tear film with a pulse of pressurized air and formation of microaesols with noncontact tonometry has been documented using a camera and flash electrically coupled to a noncontact machine.[70] Ophthalmologist who perform endoscopic dacryo-cystorhinosotomy are in contact with the nasal mucosa, which as previously noted is a high-risk area.

Several case reports have highlighted the potential risks to ophthalmologists. An ophthalmologist, the late Dr Li Wenliang at Wuhan Central Hospital, believed he contracted COVID-19 from an asymptomatic patient with glaucoma and reportedly died 1 month later.[71] Since these early reports there have been many cases of ophthalmologists infected through routine diagnosis and treatment.[46] The mechanism of transmission remains unclear as to whether it was through droplets or direct contact with secretion followed by subsequent inoculation into mucous membranes.[72] Hypothetically, the risk of COVID-19 infection to staff may be compounded in crowded hospitals that serve both eye, and ear, nose, and throat conditions.

• INFECTION CONTROL IN AN OPHTHALMOLOGIC SETTING: The risk of COVID-19 will fluctuate with the prevalence in each population. The specifics of appropriate personal protection equipment and policies and the failure to provide adequate supplies to health care workers is beyond the scope of this perspective and has been recently addressed.[73] Each country and institution is dealing with the unique challenges of balancing appropriate protection with rationing diminishing supplies.[69,74,75] However, there are certain overarching principles of infection control that must be adhered to in order for ophthalmologist to practice safely.

A recent systematic reviewed analyzed data from studies that considered the role of physical distance, face masks, and eye protection in decreasing infection rates from coronaviruses. The investigators confirmed that there is a large reduction in infection rates with physical distancing of 1 m (3.28 ft).[76] Protection was increased as distance was lengthened so that transmission rates were further reduced at 2 m. As overcrowding of clinics has been associated with high concentration of airborne particles, measures are recommended to modify clinic sizes and maintain social distancing. Several strategies have been suggested, including reducing clinic volumes and making alterations to waiting spaces and patient flow with the underlying intention to reduce the volume and increase the space between patients. Other possible ways of maintaining social distancing in small clinic spaces is to have patients wait in their vehicles while they undergo pupil dilation or until actual review time, and for patients advised to come alone or be limited to 1 support person.

Evidence suggests that wearing face masks protects both health care workers and the general public against infection by coronaviruses. Face masks can be considered in 2 major categories, each with different uses: N95 respirators and surgical masks.[77] The N95 designation means that in testing conditions, the respirator blocks ≥95% of very small particles (0.3 μm). When assessing patients with known COVID-19 (or those who are at high risk) or during aerosol-generating procedures, N95 respirators are unanimously recommended by national and international guidelines.[78] Systematic analysis for coronaviruses suggest that N95 masks are strongly associated with protection from viral transmission compared with surgical masks and should be considered in a health care setting.[76]

Surgical masks, on the other hand, are effective in blocking large-particle droplets. They do not necessarily filter small particles in the air but can minimize respiratory transmission and hand-to-face contact, but they do decrease the release of the viral load into the environment. A systematic review suggested that N95 or similar respirators offer a greater degree of protection than disposable medical masks or reusable multilayer cotton masks in particular in a health care setting. Studies have shown that surgical face masks reduced the detection of both influenza virus RNA and coronavirus RNA in droplets and aerosols.[79] There is some evidence from studies of the influenza virus that in diverse ambulatory practice, medical masks applied to both patient and caregiver provides effectively similar protection as N95 masks.[80]

In addition to face masks, there is some evidence to support the use of eye protection, such as goggles and face shields, in a health care environment. Eye protection was associated with less infection with an adjusted odds ratio of 0.22 and a relative decrease in risk of infection by 10.6%.[76] This is a further strategy that should be considered to provide protection to health care workers.

Another strategy recommended to minimize infection is forward triaging, or the identification of high-risk patients before the appointment. Questionnaires regarding symptoms, health of contacts, and travel history are required. Some public health authorities recommend taking of temperatures before arriving at work given that emerging evidence suggests that fever is the most common symptom.[39]

There is extensive evidence that thorough disinfection protocols are required to minimize the risk of direct transmission. Frequent hand washing is critical, preferably with the use of chlorhexidine alcoholic hand rub (0.5–1.0% chlorhexidine in 80% ethyl alcohol), or a similar commercial product. Some institutions recommend gloves, but these should be changed in between each contact with different patients. Disinfection of surfaces is particularly relevant for ophthalmology given the equipment intense consultation rooms. All potentially contaminated equipment, such as slit-lamp biomicroscopes, contact surfaces, indirect ophthalmoscope, diagnostic lenses, etc, need to be disinfected between each patient.

There has been some particular interest in the role of ultraviolet (UV) light exposure for inactivation of SARS-CoV-2. UV light exposure has been shown to be effective against various strains of airborne viruses.[81] The most commonly used type of UV light for germicidal application is a low pressure mercury-vapor arc lamp, emitting around 254 nm. However, used directly, this can cause damage to the skin and eyes. Investigations have shown that 222-

nm far-UVC light at low doses of between 1.7 and 1.2 mJ/cm^2 inactivates 99.9% of aerosolized coronavirus (although the SARS-Cov-2 strain was not specifically tested). Use in public locations at the current regulatory exposure limit (~3 $mJ/cm^2/h$) would result in approximately 90% viral inactivation in 8 min and 99.9% inactivation in ~25 min.[82] Therefore, UV light can be used to disinfect surfaces and equipment after the manual chemical disinfection process is completed to shield against errors in the manual disinfection process.

If aerosol transmission is confirmed to have a significant role in the spread of COVID-19, then alterations to room ventilation systems may also be helpful. Based on some evidence of collection of virus-laden particles in areas of poor ventilation, it has been suggested that particular attention should be given to areas of poor ventilation, such as toilets. Evidence suggests that the virus is efficiently inactivated with 62%-71% ethanol, 0.5% hydrogen peroxide, and 0.1% sodium hypochlorite within 1 min.[83] Researchers have used mathematical modeling with the influenza virus and computationally evaluated the potential effectiveness of improved ventilation as a mitigation strategy. They concluded that simply upgrading ventilation in high-density spaces to recommended levels had an equally mitigating effect on transmission comparable to vaccination coverage of 50%-60%.[84]

Special measures should be considered for the unique circumstances of ophthalmologists. Ophthalmic instruments especially those in direct contact with patients' mucosal membranes like the Goldmann applanation prism tip and diagnostic lenses require specific disinfection measure using 10% diluted sodium hypochlorite.[35,85]

Breath shields on slit lamps may act as a barrier to respiratory droplet transmission given that the range of droplet transmission from a sneeze has been shown to be as far as 6 m. However, such barriers could also become a potential source for contamination and care must also be taken to properly sterilize such barrier shields between each patient.[86]

Guidelines are also available for cleaning and sterilizing perimeters with specific instructions provided by companies for machines. General recommendations include using masks during visual field testing and wiping down interface surfaces with isopropyl alcohol in between each patient including eye patch, chin rest, head rest, patient response button, trial lens holder, and trial lenses. To clean the bowl of visual field machines, it is important to follow the guidelines provided by the manufacters.[87,88]

OTHER IMPLICATIONS FOR OPHTHALMOLOGISTS

• **TELEHEALTH:** The role of telehealth has been evolving over the past decades. However, the COVID-19 pandemic has hurled telemedicine into the forefront.[89] The argument is that much of medical decision-making is cognitive and telemedicine allows access to patients who are more appropriately managed from home. Using telehealth where possible reduces the number of health care workers who interact with potentially infected patients. Insurance companies and funding providers are increasingly aware that telemedicine has an important place in providing health care.

The suitability of telehealth varies significantly from specialty to specialty. Ophthalmology might be one of the most challenging applications of telemedicine given the requirements to measure intraocular pressure, examine the anterior segment, gonioscopy, and obtain high-definition images of the posterior pole and retina. However, technological advances are expanding the potential of teleophthalmology. Although teleophthalmology is not a replacement for traditional eye care and still faces challenges for adequate implementation, it represents an option to provide effective care for a subgroup of patients which allows the appropriate and timely distribution of service. Regulatory structures, credentialing, and implementation are all challenges that will need to be overcome.

• **IMPACT ON PATIENTS WHO DO NOT HAVE COVID-19:** The focus of health care has understandably been on tackling the management of COVID-19 patients and protecting others from infection. As a consequence, people with chronic conditions may have been forced to postpone much of their eye care. Therefore, a potential second wave of this crisis may be addressing the chronic ocular conditions that have had delayed care or patients who have been afraid to present with acute conditions. Studies during the SARS-CoV-1 outbreak showed that while hospitalizations for diabetes plummeted during the crisis, these skyrocketed afterward.[90] During the present crisis, there has already been fewer admissions for stroke and heart attack. The concern is that the incidence is the same but that cautious or frightened patients are not presenting for care.[91,92] Over the coming 12 months, ophthalmology will have to assess the fallout from delayed care and develop triaging strategies to manage health demands.

In conclusion, the COVID-19 pandemic has had far-reaching and permanent implications for health care globally with ophthalmology being no exception. While we are still learning about the behavior of the virus, it is well-established that SARS-CoV-2/COVID-19 is highly infectious and spread predominantly by direct transmission and droplets. Conjunctivitis should be recognized as a possible symptom of COVID-19, although it is presently documented to occur in only approximately 1% of patients.

There are, however, several areas of uncertainty. While it is also clear that patients who are asymptomatic have a significant viral load, the spread from asymptomatic or pre-symptomatic patients has not been quantified. There is increasing evidence emerging on the possibility of aerosol transmission although the extent of this requires further investigation. Although SARS-CoV-2 has been detected in a minority of patients in tears and conjunctival secretions, there are unresolved issues with the timing and testing of these samples. Most conjunctival tests have been conducted later in the disease course and therefore the role of greater viral load in the early stages of the disease still requires further elucidation. In particular, ongoing research is required to understand the permissiveness of ocular tissue to SARS-CoV-2 and the role it may play as an alternative physiologic pathway for COVID-19 infection.

Ophthalmologists need to maintain vigilance given the increased risk of infection they face because of close and prolonged proximity to patients in equipment intense examination rooms that provides additional surfaces to be contaminated—thus increasing the risk of exposure. Maintaining social distancing measures, appropriate personal protective equipment, and sterilization are all key steps. Teleophthalmology will emerge as a prominent part of clinical practice, in particular as technology advances allowing opportunities for examination techniques through the digital medium. The COVID-19 crisis has also had far-reaching impact on patients with non–COVID-19 conditions, and in the midst of the pandemic we will need to continue to provide high-level quality care to all our patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

HELEN V. DANESH-MEYER: CONCEPTUALIZATION, METHodology, Writing - original draft, Writing - review & editing, Visualization. **Charles N.J. McGhee:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Visualization.

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