Corneal transplantation in the aftermath of the COVID-19 pandemic: an international perspective

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Corneal blindness is the third leading cause of blindness worldwide.¹ Corneal transplantation remains the only method of restoring vision in eyes with end-stage corneal decompensation and is the most frequently performed type of transplant worldwide.² Due to the immunological and lymphogenic privilege of the avascular cornea, keratoplasty is the most successful tissue transplantation procedure currently performed in humans.³ However, as with most solid-organ transplants, the risk of transmitting infectious diseases and viruses is an important aspect of corneal transplantation that can affect recipients or those handling donor tissue.⁴ Thus, the rapid emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since December 2019 has led to a devastating impact on corneal transplantation worldwide.

To date, the SARS-CoV-2 has infected close to 13 million people and led to more than 560000 deaths worldwide in

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Correspondence to Jodhbir Mehta, Singapore National Eye Centre, Singapore, Singapore; jodmehta@gmail.com a short space of 6 months (WHO COVID-2019 situation report as of July 13, 2020). Since its emergence in Wuhan China, the SARS-CoV-2 has been reported to cause conjunctivitis and detected in tears or conjunctival secretions.⁵ The potential for SARS-CoV-2 to affect the ocular surface had immediate implications for eye banking around the world. Furthermore, travel restrictions and curtailed elective procedures have led to the reduction in the supply, retrieval and demand for corneal transplantation.⁶ Thus, the future of corneal transplantation faces an unprecedented threat, as access to this sightrestoring surgery is affected on a global scale.⁷ Beyond the pandemic, COVID-19 may have lasting effects on corneal transplantation, as healthcare services resume to face long waiting lists and a potential shortage of donors. Therefore, there is an urgent need for a consensus on recommendations for restoring corneal transplantation services, even as the outbreak evolves and we learn more about the SARS-CoV-2.

OCULAR TRANSMISSION OF SARS-COV-2

In order to do this, there are several issues that need to be considered. The first is whether the SARS-CoV-2 is shed in the tears, which may allow transmission of this virus through the ocular surface, either from asymptomatic carriers or infected individuals to close contacts. Conjunctival signs such as injection and chemosis have been reported, ranging from 0.8% in the largest retrospective study from China,⁵ to 5.9%⁸ and 66%⁹ in other smaller studies. In a study of 38 confirmed cases, 12 (31.6%) patients were noted to have conjunctival signs.¹⁰ However, two-thirds of these 12 patients were in critical condition, where thirdspacing and ventilation may also have contributed to these ocular signs. Overall, surveillance studies from confirmed COVID-19 positive patients suggest that few patients have conjunctival involvement.⁹ Still fewer have positive RT-PCR results from conjunctival swabs, even in the presence of conjunctival inflammation.9 This may be due to a lower diagnostic sensitivity of tear and conjunctival swabs, which have low sample volumes-or it may reflect an inflammatory response, a low viral load or non-infective RNA fragments.8 The timing of tear sample acquisition during the course of disease may also play a role, as one case study reported the presence of SARS-CoV-2 RNA in tears up to 27 days after onset of symptoms, although viral culture replication was only performed on the early ocular sample (3 days).¹¹ On the other hand, the tear film has a dynamic turnover with antimicrobial proteins such as lactoferrin, which have been shown to have a protective function by inhibiting the binding of SARS-CoV to the angiotensin-converting enzyme 2 receptor.¹² ¹³ Hence, current studies suggest that even if SARS-CoV-2 is present in tears, the risk of direct transmission through the ocular surface is not vet established.

The next issue is whether the SARS-CoV-2 virus infects ocular tissue, which may affect the potential for transmission from corneal donor to recipient.¹⁴ SARS-CoV-2 gains cellular entry through the ACE2 receptor after cellular protease priming via transmembrane serine protease 2 (TMPRSS2) and other comediators.¹⁵ While the ACE2 receptor and TMPRSS2 were found to be significantly expressed in conjunctival tissue using immunohistochemistry based on mouse and human studies,16 17 high throughput sequencing of mRNA and protein levels suggested no significant expression in healthy and diseased human conjunctiva biopsies for melanoma and squamous cell carcinoma.¹⁸ Nonetheless, emerging studies have now shown both ACE2 and TMPRSS2 expression in cornea and conjunctival epithelium,¹⁹ with expression of other proteins such as cysteine proteases cathepsin B and L that may enable viral entry.²⁰ Hence, the potential ocular infectivity of SARS-CoV-2 transmission through the ocular surface remains a concern based on these molecular and animal studies.²¹ Given the prevalence of asymptomatic carriers, high transmission rates and a possible conjunctival infectivity, current recommendations to exclude potential donors who are PCR positive for SARS-CoV-2 and the duration needed from symptom resolution, requires further discussion. This exclusion criteria would also depend on the availability of SARS-CoV-2 PCR testing, given the limited availability of these assays in various healthcare settings around the world.

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A GLOBAL PERSPECTIVE OF CURRENT EYE-BANKING GUIDELINES DURING THE COVID-19 PANDEMIC

In light of these uncertainties, guidelines (frequently updated) from major eve banks such as the Eye Bank Association of America (EBAA) and the Global Alliance of Eye Bank Associations (GAEBA) have recommended excluding donors recently infected with COVID-19, or those at high-risk such as a significant contact history-table 1.6 Though this is in line with US Food and Drug Administration (FDA) guidance on human cell, tissue and cellular or tissue-based products, the FDA guidelines further indicate that there is currently no evidence for transmission of respiratory viruses through tissue transplantation in general.²² Moreover, corneal donors are usually double disinfected with povidone iodine before removal and preparation; and/or polyvinylpyrrolidone solution just before storage. Polyvinylpyrrolidone solution (0.23-7.5%) has been shown to be capable of up to 99.99% inactivation of viruses such as SARS-CoV, within 15-60 s at room temperature on inanimate surfaces, but this requires further study specifically for SARS-CoV-2.23 These studies also need to be replicated on tissue samples and storage media. A review of current eye bank recommendations across the world demonstrates a wide variation in donor exclusion criteria, such as the duration of recovery from COVID-19 or days from positive contact-table 1. These restrictions could greatly impact the availability of corneal donors, as current criteria for exclusion can be rather broad.

RE-OPENING CORNEAL TRANSPLANT SERVICES AROUND THE WORLD

As we emerge from the pandemic and healthcare services are restored, restarting corneal transplant programmes will require cautious planning and execution. The sustainability of corneal donation and eye-banking programmes will also have to be examined carefully. For example, the United Kingdom National Health Service (NHS) has already set out issues for consideration when re-opening transplant programmes (NHS Blood and Transplant: Article POL296/1 dated April 28, 2020). This includes nose, throat and endotracheal swabs for SARS-CoV-2 PCR testing and blood serological testing for all potential deceased organ donors, which should be negative before the donor is deemed suitable. It has been recommended that recipients should also be tested via PCR and serological testing before undergoing surgery, and SARS-CoV-2 positive patients should be taken off the donor waiting-list until two consecutive nose and throat PCR swab tests are negative. The situation is undoubtedly more complicated in solid organ or tissue transplant recipients requiring systemic immune suppression. Some centres in China have also recommended performing CT scans of the lungs in selected potential donors. On the other hand, the Eye Bank Association of Australia & New Zealand (EBAANZ) and European Centre of Disease Control advises against routine testing for donors due to limited test kits, which are also not validated for use in deceased patients. Further studies on the validity of SARS-CoV-2 PCR tests on deceased donors are needed to inform policy decisions on donor testing requirements.

It is also recognised that re-opening corneal transplant programmes require a multi-disciplinary coordination from eve bank technicians to nurses and surgeons, where new infection control protocols require training and familiarisation.²⁴ Patient education with regards to the implications of SARS-CoV-2 PCR results and risks of transmission should be discussed thoroughly, with anticipation of potential delays to the preoperative process and unexpected cancellations. Restrictions to global and regional travel in the longer term may affect transport of corneal donors, leading to delays and shortages in countries which rely heavily on foreign tissue. Protections to eye bank technicians with full personal protective equipment (PPE) and eye protection have been recommended by most eye bank associations. Surgeons performing corneal transplantation under general anaesthesia may consider using full PPE with N95 masks due to the increased risk of aerosolisation during intubation and extubation. Routine PCR recipient testing has been recommended by EBAA and other organisations if available. Antibody testing has gained attention as a potential tool in managing SARS-CoV-2, including patient contact tracing, serosurveillance and vaccine evaluation.²⁵

However, its utility in screening potential donors and evaluating recipients is currently unclear, as seropositivity may not reflect immunity. Finally, the economic impact of COVID-19 and subsequent measures on eye banking and corneal transplantation, including increased costs from donor transport, testing, and PPE utility, must be considered in the long-term planning and sustainability of resuming corneal transplant services.

In summary, the impact of the COVID-19 pandemic on corneal transplantation may have long-lasting effects. Moving forward, more research is needed to examine the risk of ocular transmission of SARS-CoV-2, both from an eve banking and healthcare provider perspective. In order to resume corneal transplant services, we have summarised some recommendations for future research and consensus required, adapted from two of the largest volume eye bank/organisations that is, the EBAA and European Eye Bank, recommendations-table 2. However, considerations should be made within the context of each healthcare system for these recommendations to be applicable. Donor eligibility criteria and recipient testing should also be individually reviewed by the medical director, as the situation constantly changes during the COVID-19 pandemic. Consensus on guidelines for potential donor exclusion is important for coordination of donor export/import to ensure the cornea donor supply chain remains intact, while mitigating the risk of SARS-CoV-2 transmission to all persons handling the donor tissue, and recipients. Subsequently, the cost of corneal donor processing may increase with testing and infection control measures, affecting the less wellresourced healthcare services. The impact of global travel restrictions and reduced corneal donation may lead to a severe shortage of corneal donor supply, which may necessitate increased utility of available donors of poorer quality through techniques such as anterior lamellar keratoplasty, or accelerate innovation in treatments that reduce reliance on cadaveric corneal donors such as artificial cornea or corneal cell therapies. As we learn more about the SARS-CoV-2 virus and the effect of this global outbreak evolves, it is clear that this pandemic may have a significant long-term impact on corneal transplantation worldwide.

Table 1 Current eye-banking recommendations (at time of publication) with regard to selection of donors with COVID-19

Organisation	*Current recommendations on potential donors who may have COVID-19
Eye Bank Association of America (EBAA)†	Exclusion: Tested positive for or diagnosed with COVID-19 within past 28 days –Acute respiratory distress syndrome, pneumonia or pulmonary CT scanning showing 'ground glass opacities' (regardless of whether another organism is present) within the last 28 days –Acute symptoms consistent with COVID-19 infection within the 28 days prior to death such as cough and shortness of breath/ difficulty breathing or two of the following: Two of the following: Fever, Chills, Repeated shaking with chills, Muscle, Pain, Headache, Sore throat, New loss of taste or smell
	Discretionary inclusion after review if: —Plausible aetiology of signs or symptoms as above —Close contact as defined by the CDC but PCR negative or asymptomatic within last 28 days prior to death
	'Close contact' as being within approximately 6 feet (2 m) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for, living with, visiting, or sharing a healthcare waiting area or room with a COVID-19 case; or having direct contact with infectious secretions of a COVID-19 case (eg, being coughed on) if such contact occurs while not wearing recommended personal protective equipment (PPE).
European Eye Bank Association (in line with European Centre of Disease Control)‡	Exclusion: —Any with active COVID-19 at the time of death are not eligible for organ donation.
	*Inclusion: —Tissues should not be collected from deceased donors who are without symptoms or diagnosis of COVID-19, and who have lived in or visited areas of sustained community transmission of the virus unless: procured tissues are disinfected, sterilised or microbially inactivated using a procedure validated for enveloped viruses, or donors tested negative for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in upper or lower respiratory tract specimens collected within 72 hours before procurement.
	-Any who have recovered from COVID-19 may donate tissues if they tested negative for the presence of SARS-CoV-2 RNA in upper respiratory tract specimens at least 14 days before death or if they became asymptomatic at least 28 days before death.
United Kingdom National Health Service Blood and Transplant§	Exclusion: —Any donor with confirmed COVID-19 infection
	*Inclusion: Donors with proven or suspected COVID-19 with recovery and no symptoms for more than 28 days may be eligible for assessment if no significant end organ damage and subject to negative: Nose and throat swab PCR, endotracheal aspirate PCR and blood in EDTA for retrospective PCR and serological testing
Eye Bank Association of Australia & New Zealand (EBAANZ)¶	Exclusion: -Any who have a history of international travel in the past 4 weeks will be excluded for 4 weeks. -Any who have had close contact with a known or suspected COVID-19 case will be excluded for 4 weeks from the time of contact -Any who have been infected with COVID-19 will be excluded from donation for three months after recovery from the virus.
Global Alliance of Eye Bank Associations (GAEBA)**	Exclusion: –Any potential donors with less than 14 days since resolution of symptoms from confirmed COVID-19 infection –Any awaiting test results for suspected COVID-19 infection –Any contact with confirmed or suspected COVID-19 infection less than 14 days
	*Discretionary inclusion: -Any more than 14 days have passed since resolution of symptoms in confirmed COVID-19 infections -Any more than 14 days since the first day of contact with an individual with a confirmed or suspected COVID-19 infection, and the donor remained well, with no symptoms of coronavirus infection -If less than 14 days and the donor remained well, with no symptoms of COVID-19 infection—subject to individual risk assessment -Donors without respiratory symptoms who are suspected COVID-19 infection but untested, and those who were in intensive care units with patients who had been tested for COVID-19 infection and subsequently moved to isolation facilities following confirmation of infection—subject to individual risk assessment
Pan American Association of Eye Banks††	Exclusion: -Any who have had contact with a known or suspected COVID-19 case will be excluded for 30 days from the time of contact -Any who have been infected with COVID-19 will be excluded from donation for 90 days after recovery from the virus. -Any who have symptoms compatible with COVID-19 infection but had no lab confirmation will be excluded from donation for 90 days.
	Individual countries may follow specific local guidelines, or closely following guidance from Eye Bank Association of America (EBAA).† for example, Brazil following EBAA
Asia	No published consensus and guidelines across Asia at time of publication (July 2020).
	Individual countries follow specific local guidelines, many closely following guidance from Eye Bank Association of America (EBAA).†
	Eye Bank Association of India (EBAI) have specific guidelines: URL: https://www.ebai.org/pdf/EyeBankingGuidelines1105202V.1.pdf

+Adapted from Eye Bank Association of America (EBAA) (URL: https://restoresight.org/covid-19-updates/, accessed May 2020).

 [†]Adapted from Eye Bank Association of America (EBAA) (URL: https://restoresight.org/covid-19-updates/, accessed May 2020).
 ‡Adapted from European Eye Bank Association in line with European Centre of Disease Control (updated April 2020).
 §Adapted from NHS Blood and Transplant POL296/1—Re-opening of Transplant Programmes: Issues for Consideration (URL: https://www.odt.nhs.uk/deceased-donation/covid-19-advice-for-clinicians/and https://hsbtdbe.blob.core.windows.net/umbraco-assets-corp/18436/pol296.pdf, accessed May 2020).
 ¶Adapted from Eye Bank Association of Australia and New Zealand (URL:http://www.ebaanz.org/medical-standards-and-quality/ebaanz-covid-19-20-march-2020/).
 **Adapted from URL: http://www.gaeba.org/2020/alert-coronavirus-2019-ncov-and-ocular-tissue-donation/updated, March 25, 2020.
 †Pan American Association of Eye Banks (URL: http://www.apaboeyebanks.org).

Table 2 Recommendations for fut	ure research and consensus required for corneal transplantation during and beyond the COVID-19 pandemic
	Recommendations, considerations and consensus required
Donor exclusion due to confirmed COVID- 19 infection or contact with confirmed cases	Exclusion: –Potential donor with confirmed COVID-19 infection –Positive contact history with person with confirmed COVID-19 infection.
	Consensus required: Duration from resolution of symptoms or first day of contact (currently varies from 14 days to 3 months).
	Recommendation: Discretionary inclusion of potential donors with duration of 28 days from resolution of symptoms or first day of contact or pending negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests from respiratory sample.
Donor exclusion from suspected COVID-19 cases	Exclusion: -Acute respiratory illness (fever of 100.4 °F/38°C) and at least one severe common symptom of respiratory disease with no other aetiology that fully explains the clinical presentation within the last 28 days -Acute respiratory distress syndrome, pneumonia or pulmonary CT scanning showing 'ground glass opacities' (regardless of whether another organism is present) within the last 28 days
	Consensus required: —Significant travel history to 'high-risk' countries as defined by CDC, WHO or local governments —Those who have lived in areas of sustained community COVID-19 transmission (ECDC) —Contacts of suspected COVID-19 cases
	Recommendation: Discretionary inclusion of suspected cases with duration of 28 days with or without symptoms but with negative SARS-CoV-2 PCR tests from respiratory sample.
Routine testing of all potential donors	In conditions where testing is readily available for all hospitalised patients and/or community testing is performed, a record of a recent nose and throat SARS-CoV-2 PCR may be already performed or available within days.
	Serological testing for the presence of antibodies to SARS-CoV-2 may indicate previous or recent infection, but viral RNA has been detected in individuals despite the development of antibodies. Therefore, serology is currently not recommended as screening test for donors.
	Medical director review for final determination of donor eligibility in certain cases
	Recommendation: Considering current evidence and limited test kits, PCR testing may not be mandatory for donor selection. However, once performed a positive test should be exclusion criteria. While a negative test should be taken into consideration, a potential donor might still be excluded depending on signs/symptoms/history of contact.
	Research needed: Validation studies of SARS-CoV-2 PCR on cadaveric donor samples and donor storage medium
Precautions during cornea donor acquisition	 –Full personal protective equipment for technicians including eye protection or goggles –Corneal donor disinfection with povidone iodine before removal and preparation –Corneal donor preparation with polyvinylpyrrolidone solution just before storage
	Research needed: -Evaluation of presence and viability of viral RNA on cornea and conjunctival donor tissue from SARS-CoV-2 infected individuals -Evaluation of presence and viability of viral RNA on cornea and conjunctival tissue after standard tissue acquisition and processing (with povidone iodine). -Development of methods of viral inactivation on corneal tissue
Precautions during corneal transplant procedure	Elective corneal transplants: -Recipients should be tested via PCR testing before undergoing surgery -Recipients should be confirmed SARS-CoV-2 PCR negative and in self isolation from testing until time of surgery -SARS-CoV-2 positive recipients would not be eligible for elective corneal transplants at this time and should be taken off the donor waiting list until two consecutive nose and throat PCR swab tests are negative and symptom-free.
	Emergency corneal transplants: –Recipients should be tested via PCR testing before undergoing surgery –For SARS-CoV-2 positive recipients undergoing emergency corneal transplants, all staff should be protected with full personal protective equipment with N95
	 -Full personal protective equipment with N95 for cases undergoing general anaesthesia as per guidelines, not for local anaesthesia cases -Standard personal protective equipment for cases under local anaesthesia, low risk of blood contamination or aerosolisation such as lamellar keratoplasty -Recipient eye disinfection with povidone iodine
	Consensus needed: Personal protection needed for suspected cases or possible asymptomatic carriers, role of serological testing or CT chest for recipients, requirements for eye protection as part of personal protective equipment for surgery on SARS-CoV-2 positive cases.
Other considerations	Consensus needed for recipient priority: –Patients with risk factors for severe COVID-19 complications (>60 years-old, systemic comorbidities) might consider having elective corneal transplants postponed –Patients with correctable visual acuity with minimal functional impact may consider having elective corneal transplants postponed
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Correction notice This paper has been updated since it was published online. The authors have added an Author note in the end statements.

Author note As mentioned in our article, as the guidances and recommendations are dynamic and likely to change, our colleagues from the UK would like to add in an active link for for the most up-to-date information, as the guidance described in the article is currently not fully applicable to UK eye donor selection criteria: https://www.transfusionguidelines.org/dsg/ctd/guide lines/coronavirus-infection-1

https://nhsbtdbe.blob.core.windows.net/umbracoassets corp/19370/pol301.pdf

https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/ 19175/tes-covid-19-position-statement-july-2020.pdf.

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