

Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA - second update

10 December 2020

Scope of the document

This second update of the original document integrates the experience of maintaining safe and sufficient supply of substances of human origin (SoHO) gained in the course of the COVID-19 pandemic and through recent scientific developments in understanding the evolution of the disease. The document reassesses the risk posed by COVID-19 and revises management options for the safe and sustainable supply of SoHO. It also includes information relating to the safety of staff in SoHO establishments and recipients of SoHO products. The aim is to assist the European Union and European Economic Area (EU/EEA) Member States in responding to the threat posed by the pandemic.

Since the very beginning of the COVID-19 outbreak, the European Centre for Disease Prevention and Control (ECDC) has been continuously publishing rapid risk assessments and relevant technical documents. These also include risk assessments and recommendations for keeping the SoHO supply safe while maintaining the supply level required by the healthcare community [1-3]. In this respect, the EU/EEA Member States have been encouraged to activate national SoHO contingency/pandemic plans to prepare for large outbreaks and community transmission.

ECDC will update the document as and when new relevant information becomes available, or as required by the epidemiological situation.

What is new in this document?

- Classification of areas for regulating the movement of population.
- New information on SoHO-related topics.
- Reassessment of the risk of COVID-19 transmission via SoHO based on the new evidence.
- New data on the impact of COVID-19 on SoHO supply.
- Revised recommendation for mitigation measures in relation to all types of SoHO.
- Common mitigation measures.
- Advice for conducting intra-action analysis.

Suggested citation: European Centre for Disease Prevention and Control. Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA – second update. 10 December 2020. Stockholm: ECDC; 2020.

Erratum 9 February 2021: in order to clarify the statement on the selection and deferral of donors who have received a COVID-19 vaccine, the first two sentences of the paragraph related to SoHO donation and SARS-CoV-2 vaccination (page 10) have been changed to:

“According to EU Directives, after vaccination with attenuated viruses (e.g. replication competent virus vector-based vaccines, live-attenuated virus vaccines) SoHO donors must be deferred for four weeks. Individuals vaccinated with inactivated/killed viruses or vaccines that do not contain live agents (i.e. mRNA vaccines, non-replicating/replication deficient virus vector-based vaccines and protein subunit vaccines) may be accepted as SoHO donors if they feel well [4-6].”

Target institutions

National competent authorities for SoHO, blood and tissue establishments, organ, tissue and cell procurement organisations and transplant centres in the EU/EEA.

Definitions

The definition of the substances of human origin (SoHO) and the priority classification of SoHO remain the same as in the first update of this document [3].

In this document, the term 'SoHO establishment' refers to blood, blood component, and tissue establishments, organ procurement organisations and transplant centres, as defined in the EU/EEA directives [4-6].

Classification of areas for regulating the movement of population

In October, the European Council adopted a recommendation on a coordinated approach to the restrictions of free movement in response to the COVID-19 pandemic [7]. Based on the number of newly-notified cases per 100 000 population in the previous 14 days, testing rate and test positivity rate, the Council recommends that areas be classified as green, orange, red and grey.

ECDC publishes a weekly map of EU Member States on its website, broken down by region and indicating the epidemiological situation with the relevant colour [8]. Given the differences in the epidemiological situation, Member States may require persons travelling from non-green areas to go into quarantine or take a test upon arrival (or before arrival) if they will be entering a Member State at lower risk. Member States may also require those entering their territory to submit passenger locator forms. Member States should not refuse entry to people travelling from the other Member States.

Background

Detailed information on the virus, disease epidemiology, COVID-19 case definition for EU surveillance, clinical manifestations and risk and prevention in the population is available on ECDC's website and in ECDC's regularly-updated rapid risk assessments [9,10].

Laboratory testing

There are three main types of detection assay relevant for COVID-19 diagnostic testing and screening, based on the detection target.

- Nucleic acid tests to detect the presence of viral ribonucleic acid (RNA). Typically, these use an amplification step based on reverse transcription-polymerase chain reaction (RT-PCR) or transcription-mediated amplification (TMA).
- Antigen tests to detect the presence of a viral antigen, typically part of a surface protein.
- Antibody tests to detect the presence of antibodies generated against SARS-CoV-2. The three most commonly-used assays are enzyme-linked immunosorbent assays (ELISA), chemiluminescence enzyme immunoassays (CLIA) and lateral flow assays (LFA). Virus neutralisation tests and pseudovirus neutralisation tests, which are used mainly for assay validation and research, can specifically detect the presence of neutralising antibodies. Preliminary reports on some ELISA assays have shown a good correlation of antibody titration results with virus-neutralising antibodies.

The RT-PCR performed on respiratory tract specimens remains the gold standard for detecting SARS-CoV-2 and is characterised by both high sensitivity and specificity in detecting viral RNA. The types of specimens to be collected from symptomatic patients and contacts are listed in the World Health Organization (WHO)'s laboratory guidance [11]. Data comparing the accuracy of RT-PCR testing suggest that test sensitivity may vary by specimen type [12].

Rapid antigen tests are becoming more readily available and are being increasingly used by the Member States as a possible tool for rapid SARS-CoV-2 diagnosis. While these tests are less sensitive than RT-PCR [13], they offer the possibility of rapid, inexpensive and early detection of the most infectious COVID-19 cases (i.e. those with a high viral load). Rapid antigen tests with acceptable sensitivity and specificity [14] are now available in the EU. Rapid antigen tests are likely to perform best in the immediate pre-symptomatic (1–3 days before symptom onset) and early symptomatic phases of the illness (within the first 5–7 days of illness) [13].

Laboratory tests used for clinical and public health purposes need to be CE marked and authorised at national level in accordance with WHO [13] or national minimum performance criteria. Individual rapid antigen test results should be evaluated, taking into consideration the performance characteristics of the test used and the patient's clinical status. Proper interpretation of test results, in the context of the epidemiological situation and virus prevalence at the time of testing, is important for accurate case management.

Due to the high demand for testing, shortages are expected in the availability of tests, laboratory capacity, material and personnel for sampling and carrying out the tests. The Member States should plan for surge capacity and ensure the supply of materials, as well as the additional training of staff in sampling and laboratory testing. If the number of suspected cases exceeds the available testing capacity in a country or an area, specific groups (e.g. recent contacts of infected persons, healthcare workers, elderly people and those with underlying chronic medical conditions) could be prioritised for testing [15].

Antibody tests currently have limited diagnostic use. They can be used as a complement to the virus-detection tests for patients presenting symptoms late after onset in healthcare facilities and where virus detection tests are negative despite strong indications of infection. In addition, they can potentially be used to inform decisions on the discharge of patients who have recovered from SARS-CoV-2 infection but remain RNA-positive by RT-PCR for a long time after symptoms have subsided. The degree of protective immunity conferred by or correlated with the antibodies detected in subjects previously infected with SARS-CoV-2 is still under investigation. Once this has been clarified, these antibody tests, together with direct virus detection, could be essential tools in de-escalation strategies. Antibody tests are currently being used for sero-epidemiological surveys and studies.

On 3 June 2020, the Commission adopted Directive (EU) 2020/739 [16], updating the Biological Agents Directive 2000/54/EC with the classification of SARS-CoV-2 as risk group 3 in Annex III - list of biological agents. In line with Article 16(1) (c), and in accordance with WHO's interim recommendations on laboratory biosafety for COVID-19 laboratory procedures, non-propagative diagnostic laboratory work involving SARS-CoV-2 should be conducted at a facility using procedures equivalent to at least containment level 2. Propagative work (virus culture, neutralisation assays) involving infectious SARS-CoV-2 should be conducted at a containment level 3 laboratory with air pressure negative to the atmosphere.

ABO blood groups and COVID-19

The influence of ABO blood group polymorphism in humans on the susceptibility to infection with SARS-CoV has previously been described [17]. During the COVID-19 pandemic, several authors have reported a significantly higher proportion of patients with blood group A than in healthy individuals, while the proportion of patients with blood group O was significantly lower [18-22]. In addition, the secretion of A/B antigens may promote disease progression [23]. A few genetic analyses support these findings [24,25] and some studies reject the ABO influence on COVID-19 infection [26,27]. Potential biological mechanisms underlying the epidemiological association relate to the neutralising activity of natural anti-A on the SARS-CoV spike protein [28], and/or the known fact that group O individuals have 25% lower serum levels of the von Willebrand factor (vWF) and factor VIII (FVIII) which are essential for platelet adhesion, aggregation and fibrin clot formation. A recent study shows that critically-ill COVID-19 patients with blood group A or AB are at increased risk of requiring mechanical ventilation, continuous renal replacement therapy, and a prolonged stay in an intensive care unit (ICU) than patients with blood groups O or B [29]. However, further research is required to delineate the biological mechanisms underpinning these findings.

Positive direct antiglobulin test

Results of a recent study show that a high percentage of patients with COVID-19 have a positive IgG-specific direct antiglobulin test (DAT). These patients do not have any evidence of haemolytic anaemia and they do not require more blood transfusion than patients who are not infected with SARS-CoV-2. No underlying antibody specificity for blood-group antigens was identified in the eluate, and there was no association with antibiotic usage. No patient had a positive antibody screen, and the majority had not received a recent transfusion. These data indicate that DAT-positive results are probably due to SARS-CoV-2 infection. The pathogenesis of this possible association is unknown. Laboratories should be aware of this finding, meaning that for patients who are SARS-CoV-2 positive and DAT-positive but have a negative antibody screen and no clinical features of haemolysis, further serological testing is not required [30].

COVID-19 convalescent plasma

COVID-19, as a public health emergency of international concern, has prompted enormous amounts of global research into preventive and therapeutic options since its first appearance. Given the encouraging historical experiences of using convalescent plasma (CP) in other outbreaks, including SARS and MERS, and the absence of proven COVID-19 antiviral therapies or vaccines, CP therapy has been proposed as an option for the treatment of COVID-19. The immediate availability of CP and a growing pool of convalescent patients has supported the start of clinical trials, not only using CP directly but also fractionated into anti-SARS-CoV-2 hyperimmune globulin. It has also enabled the compassionate use of CP in critical cases. A few initial uncontrolled case series [31-33] and animal studies [34-36] have suggested a possible benefit of CP use in patients with COVID-19. Results from various types of clinical trials and the expanded emergency use of COVID-19 convalescent plasma (CCP) show the expected frequency of adverse transfusion reactions. These studies also suggest that the transfusion of CCP containing a higher titre of neutralising antibodies applied early during the clinical course is potentially effective in reducing the mortality of hospitalised non-intubated patients having a moderate or severe illness [37]. CCP may also accelerate viral clearance, decrease progression into the critical phase of diseases and shorten the hospital stay of COVID-19 patients. More evidence from randomised controlled trials is required to demonstrate the efficacy of CCP, and to determine the

indication, dosing and optimal CCP product characteristics. However, based on the evidence currently available, a Cochrane rapid review concluded that the beneficial effect of CCP for people admitted to hospital with COVID-19 remains uncertain. These results will probably change when further data become available [38].

Antibody-dependent enhancement (ADE) of viral infection could theoretically be an adverse effect of CCP therapy. ADE in viral infections has been documented to occur via two different mechanisms: by enhanced antibody-mediated virus uptake into immune cells expressing Fc gamma receptor IIa (FcγRIIa), leading to increased viral infection and replication, or by excessive antibody Fc-mediated effector functions or immune complex formation, causing enhanced inflammation and immunopathology [39]. This phenomenon has been described in the clinical course of dengue [40], Zika virus infection [41] and in the animal models of SARS-CoV [42], MERS-CoV [43] and feline coronavirus [44] infection. ADE of SARS-CoV-2 infection via antibody-mediated augmentation of viral entry into immune cells has been recently demonstrated in a laboratory setting [45]. In the in-vitro model, the authors used pseudo-typed SARS-CoV-2, human immune cell lines and plasma from recovered COVID-19 patients. The study shows that the antibodies causing ADE bind to trimeric spike proteins at a shift-angled pattern with one 'up' and two 'down' receptor-binding domains (RBDs) and only partially overlap with the receptor-binding motif (RBM). Meanwhile a neutralising monoclonal antibody lacking ADE activity binds to spike proteins with three 'up' RBDs, resulting in a complete overlap with RBM. The authors suggest that, in addition to the induction of neutralising antibodies, developers should evaluate COVID-19 vaccine candidates for induction of ADE. ADE after convalescent plasma treatment has not been observed in the current clinical use of CCP. Another theoretical adverse effect of CCP therapy is the possible presence of autoantibodies to interferons (IFN) in the donated CCP, which may affect the clinical course of COVID-19 by hindering the ability of IFN to block the infection of human cells with SARS-CoV-2 [46]. As this effect has not been reported during CCP treatments, further studies and data are needed to assess the possible role and risk of autoantibodies to IFN for the safety of CCP treatment.

Following consultation with the national competent authorities for blood and blood components, the European Centre for Disease Prevention and Control and the European Blood Alliance (EBA), the European Commission published guidance for a European programme of COVID-19 convalescent plasma collection and transfusion. The document provides blood establishments and clinicians with guidance on the collection, testing, processing, storage, distribution and monitored use of CCP [47]. It aims to support the possible treatment of seriously-ill patients within observational studies or randomised and case-control clinical trials, and the development of immune globulin concentrates by industry in the longer term. Furthermore, in collaboration with EBA, the European Commission (DG SANTE, DG DIGIT, and DG CNECT) has developed and is managing a database of donations and use of CCP. This open-access database gathers and makes available data on convalescent plasma donations and patient outcomes following transfusions (<https://www.euccp.dataplatform.tech.ec.europa.eu/>).

Impact of COVID-19 pandemic on SoHO supply

Maintaining a safe, sufficient and accessible supply of critical and essential SoHO during a pandemic is of vital interest to public health. It is therefore a prerequisite that SoHO establishments recognise the potential impact of the virus on the supply of SoHO and adequately respond to ensure the maintenance of core services. In assessing this potential, we have considered the likelihood of the virus entering and persisting in SoHO supply, being transmitted via SoHO, causing significant harm in recipients, reducing donations and having an adverse impact on activities and staff in SoHO establishments [48]. Given that the modes of transmission of COVID-19 are community-acquired or nosocomial and potentially derived from donors, the risks identified include the following:

- risk to the viral safety of SoHO;
- risk to SoHO recipients;
- risk to staff in SoHO establishments;
- risk to the sufficiency of SoHO supply.

The risk assessment should also take into account at country level:

- the extent of COVID-19 spread in the country or geographical area;
- the level of community circulation;
- the local epidemiology;
- the risk of COVID-19 transmission via SoHO in the context of the overall burden of disease;
- the quality of healthcare system;
- the public health response and the status of SoHO supply;
- operational impacts;
- The cost-effectiveness of SoHO safety interventions in reducing disease morbidity in relation to the overall situation in the country [49].

Risk to the viral safety of SoHO

At the time of this update, no cases of COVID-19 transmission via SoHO and plasma-derived medicinal products have been reported.

Published data have shown low levels of the SARS-CoV-2 RNA detected in a small proportion of the plasma or serum samples from COVID-19 symptomatic patients. A systematic review of the literature of 28 relevant studies reported a pooled estimate of RNA presence in blood in 10% (95%CI 5-18%) of patients with acute infection [50]. There is no evidence of the plasma and serum viral RNA load during the incubation period. The viral RNA load gradually increases from the first week after symptom onset and declines in the third week of the disease [51]. Low levels of RNA-in blood were only detectable in hospitalised, seriously-ill patients [50,52,53]. One study showed a significantly lower median viral load of 2.4 log₁₀ RNA copies/mL (range 1.8–3.8 log₁₀ RNA copies/mL), when compared with the viral load in the sputum of symptomatic patients [54]. RNA positivity in the blood of asymptomatic persons has not been thoroughly investigated. Case reports and lookback studies have shown that transfusion of blood products obtained from infected individuals who had not yet developed symptoms of COVID-19 did not result in disease transmission [55-58]. Moreover, the presence of viral RNA in the blood does not necessarily represent infectious viral particles. A recent study showed that none of the 20 RT-PCR positive serum samples investigated produced a viral culture [50]. There are no published data on the survival of SARS-CoV-2 or other coronaviruses in stored anticoagulated blood and blood components. SARS-CoV-1 persisted for four days in human serum and decayed completely after five days [59]. MERS-CoV and SARS-CoV-1 survived briefly in the control units from spiking studies to validate the effect of pathogen reduction systems on individual pathogens [60-62].

Generally, all respiratory viruses, except adenoviruses [63], attach to receptors in the airways. The cell-entry molecules for SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE 2) receptors, are not present in red blood cells, and are very limited or absent in immunocytes and lymphatic cells [64]. Routine donor screening procedures are sufficiently robust to identify donors having clinical signs of acute respiratory infection, including COVID-19, and defer them from donation. Several coronaviruses are susceptible to inactivation with amotosalen/riboflavin and ultraviolet light, methylene blue and light, and ultraviolet C light alone when applied to platelets and fresh frozen plasma [60-62,65,66]. Moreover, large-size lipid-enveloped RNA viruses such as SARS-CoV-2 [67] should be removed and/or inactivated during the manufacturing of plasma derivatives [68-70], as has been demonstrated for other lipid-enveloped model viruses [71].

Based on the current evidence, blood-borne transmission of COVID-19 seems unlikely. However, given the relatively short time that has elapsed since the outbreak of the virus, the possibility of COVID-19 transmission by transfusion in the future cannot be completely excluded. Therefore with the current status of knowledge, the risk of transfusion-transmitted COVID-19 remains theoretical.

Peripheral blood immune cells, including T cells, B cells, NK cells, NKT cells and monocytes, express low levels of ACE2 (<5%). A higher proportion of ACE2-expressing cells was found in haematopoietic peripheral cells (HPCs) and the highest in haematopoietic stem cells (HSCs). The presence of ACE2 means that the SARS-CoV-2 virus can enter these cells. The effects of viral infection on the function of immune and haematopoietic cells is under investigation. Ex vivo studies show that, exposure to the SARS-CoV-2 S protein alters the functional proliferation/expansion of HSCs and HPCs [72,73]. A recent study demonstrated that SARS-CoV-2 can infect CD4+ T cells but does not actively replicate within the host T cells [74]. Case reports showed that haematopoietic cell transplantation (HCT) from pre-symptomatic donors with a viral RNA-positive nasopharyngeal sample did not cause COVID-19 in the recipient [75,76]. The absence of SARS-CoV-2 transmission via HCT or blood transfusion, and the uncertainty surrounding the possibility of virus replication in HSC, suggest that the risk of COVID-19 transmission by HCT and chimeric antigen receptor T cells (CAR T-cells) therapy is theoretical.

SARS-CoV-2 RNA has been detected and the virus isolated in tears and conjunctival secretions of patients with COVID-19 [77-79]. However, studies suggest that conjunctival signs are not a common manifestation in COVID-19 symptomatic patients, ranging from 0.8% in a large study [80] to 3.0%, 5.9%, 6.6 % and 11.6% in smaller studies [77,81-83]. Only one study from China reported a higher proportion (31.6%) of COVID-19 patients experiencing conjunctivitis [78]. The reported low frequency (up to 2.5%) of RNA-positive conjunctival swabs in patients manifesting signs of conjunctivitis [78,82] could result from a lower diagnostic sensitivity of tear and conjunctival specimens or low viral loads. One case study reported the presence of SARS-CoV-2 RNA in tears up to 27 days after onset of symptoms, although prolonged shedding is also possible. The virus has been isolated from tears on the third day after disease onset. Further data on the dynamics of infectious SARS-CoV-2 in the tears and conjunctival secretions are needed. There are no data available on viral RNA in the tears of asymptomatic individuals diagnosed with COVID-19. The antimicrobial protein lactoferrin, which is present in tears, may inhibit the binding of SARS-CoV to the ACE2 receptor [84]. SARS-CoV-2 has not been detected directly in ocular cells and tissues. The presence of ACE2 and transmembrane protease serine 2 (TMPRSS2) and cathepsin in cornea and conjunctival epithelium [85] suggests that the virus may theoretically infect ocular tissues and be further transmitted through transplanted ocular tissues. Corneal transplants are usually disinfected during procurement with povidone-iodine and polyvinylpyrrolidone (PVP) solution before storage. PVP solution (0.23–7.5%) inactivates up to 99.99% of viruses such as SARS-CoV within 15–60 seconds at room temperature on inanimate surfaces. Further research is required to demonstrate PVP efficacy on SARS-CoV-2. These data and the absence of known

cases of ocular transmission indicate that the risk of SARS-CoV-2 entering the eye donor pool and being subsequently transmitted remains theoretical.

Most studies have not reported the presence of the SARS-CoV-2 RNA in the semen of adult patients with a recent infection or having recovered from COVID-19 [86-91]. In one study, authors found viral RNA in the semen of six of 38 patients (15.8%)[92]. In addition to testicular Leydig and Sertoli cells [93,94], ACE2 receptors and relevant activating membrane proteases are expressed in spermatozooids, indicating their potential susceptibility for infection with SARS-CoV-2. Although ACE2 receptors are present in the ovarian tissue cells [95], oocytes appear to lack TMPRSS2 [96], which makes their infection with the virus highly unlikely. The repeated washing steps required for the culture and freezing of gametes and embryos will result in the strong dilution of any possible secondary contaminations in the IVF laboratory [97]. As of the time of writing, there were no reports of sexual transmission of COVID-19 or transmission via donated sperm or oocytes. Given the theoretical possibility of SARS-CoV-2 infection through sperm, the risk of transmitting COVID-19 with donated sperm needs to be monitored.

At the beginning of the outbreak, most cases of COVID-19 in neonates were characterised as perinatal transmission [98-100]. In some new-borns where IgM and IgG antibodies against the virus were detected [101,102], infection was attributed to vertical transmission, because IgG, but not IgM, are normally transferred across the placenta. A recent study showed that ACE2 and TMPRSS2 have high levels of expression in maternal-foetal interface cells, including stromal cells and perivascular cells of decidua, and cytotrophoblast and syncytiotrophoblast in the placenta [103]. The SARS-CoV-2 genome was detected in umbilical cord blood and in at-term placentas, in the vaginal mucosa of pregnant women and in milk specimens [104]. During certain assisted reproduction technologies (ART) procedures, the continuity of the zona pellucida could be accidentally or intentionally breached (intracytoplasmic sperm injection, embryo biopsy, assisted hatching), representing an additional concern, given that human preimplantation embryos express high levels of ACE2. A systematic review of the studies describing 936 neonates from mothers with COVID-19 found 3.2% (22/936) cases of SARS-CoV-2 vertical transmission when the infection occurred in the third trimester of pregnancy. All infected neonates had viral RNA-positive nasopharyngeal swabs, and viral RNA was present in umbilical cord blood, placenta, rectal, or anal swabs in various proportions. These data confirm that in utero SARS-CoV-2 vertical transmission is possible. However, donor-derived COVID-19 through cord blood and amniotic membranes has not been reported.

Organs that express higher proportions of ACE2 receptors are lungs, heart and kidneys [105-108]. In particular, high ACE2 expression was identified in type II alveolar cells (AT2) of the lung [109,110], oesophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon [110], cholangiocytes [111], myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [105]. These findings indicate that organs with a high proportion of ACE2-expressing cells should be considered as a potentially high risk for COVID-19 infection [105]. Donor-derived SARS-CoV-2 infection in solid organ transplant recipients has not been reported.

Based on the current knowledge of ACE2 and TMPSS2 distribution, the absence of evidence for infectivity of viral RNA detectable in blood, cells, tissues and organs and any reports of transfusion and transplantation-transmitted cases, the risk of COVID-19 transmission through SoHO remains theoretical.

Risk to SoHO recipients

Donor-derived COVID-19 in transplanted or transfused patients has not been reported to date. However, the SARS-CoV-2 infection of solid organ transplant (SOT) and HCT recipients may occur in the community or in hospitals. Immunosuppression after transplantation renders transplant recipients susceptible to viral infections, including SARS-CoV-2. Post-transplant COVID-19 with severe clinical symptoms and occasional fatalities has been described in kidney [112-118], liver [119-121], lung [122] and haematopoietic stem cell (HSC) [112,123] transplant recipients. Preliminary data collected by the European Society of Blood and Marrow Transplantation (EBMT) show that early mortality (at about two weeks after diagnosis) was approximately 20% in allogeneic HCT recipients and 10% in autologous HCT recipients (Webinar EBMT-ASTCT 15 April 2020). These studies demonstrate that HCT recipients are at increased risk of mortality when compared to the general population. Being in an older age group, being on steroids when diagnosed with COVID-19, or becoming infected within one year of HCT were associated with poor outcomes, although the use of immunosuppressive drugs was not [123]. Due to immunosuppression, transplant recipients may have increased and prolonged shedding of the virus, thus potentially increasing the risk of transmission to contacts, including healthcare workers [124]. Solid-organ transplant recipients may present atypical COVID-19 symptoms, starting with gastrointestinal signs and fever, which then progress to respiratory symptoms [125]. A study in Spain investigating 778 (SOT, HCT and multi-visceral) transplant recipients found a two-fold higher incidence of COVID-19 in SOT recipients compared with the general population. Infection was hospital-acquired in 13% of cases [126]. Risk factors for death were lung transplantation, age >60 years and hospital-acquired COVID-19. Current data show that SOT and HCT recipients are a high-risk population for infection with SARS-CoV-2. COVID-19 may affect the morbidity and mortality of SOT and HCT recipients. The management of COVID-19 in the post-transplant setting presents complex challenges, emphasising the importance of strict prevention strategies. From 10 July 2020 and as of 27 November 2020, ScandiTransplant recorded a total of 245 COVID-19 infections in SOT recipients, including 32 deaths. At the time of this report, 27 transplant candidates had been infected before transplantation [127].

Increased COVID-19 morbidity and mortality in transfusion recipients has not been reported. Several published studies support observations that many patients with COVID-19 do not require transfusion [128-130]. One tertiary hospital in Madrid reported that a total of 6.2% of all COVID-19 hospitalised patients required transfusion support [131]. Among transfused patients, the main indication was anaemia (non-bleeding), with very few patients requiring platelets or plasma [130]. Some patients with COVID-19 had a positive direct antiglobulin test - but there were no signs of haemolytic anaemia [30,130].

Risk to staff in SoHO establishments

In SoHO establishments, organ procurement organisations and transplant centres, employees may be exposed to SARS-CoV-2 through close contact with other staff members, touching contaminated surfaces, or during the donation/clinical application process through contacts with living donors, deceased donors and potential recipients (and their relatives) and their bodily fluids. Transmission in the working environment is a well-recognised route and the risk of infection depends on the nature of the work and the proximity of contacts [91]. Occasionally, an infectious donor who is asymptomatic, pre-symptomatic, or has very mild symptoms may be accepted for donation. During the donation process, such a donor can infect attending staff or other donors in the waiting rooms of blood donation facilities. The respiratory route of transmission from a donor to a member of staff is more likely than through parenteral routes (including phlebotomy during blood donation). At the time of writing, SoHO establishments have not reported any such cases. Although it seems that this transmission route is not very probable, responsible management and employees should not neglect these risks. Therefore, once a vaccine is available, staff working in SoHO establishments should be considered, alongside other healthcare professionals, for the vaccination priority group to ensure continuity of SoHO supply.

Risk to sufficiency and sustainability of SoHO supply

COVID-19 poses a risk to the sufficiency and sustainability of SoHO supply by reducing donor availability, lowering the capacity of the collection establishment to accommodate donors due to distancing measures, affecting the staff at SoHO facilities, changing demand for SoHO products, and limiting the provision or distribution of critical materials, equipment, and SoHO products.

Blood supply is particularly vulnerable as it requires frequent, daily blood donations and labile blood components have limited storage time. In the first wave of the pandemic, a reduction in blood donor numbers was broadly matched by reductions in demand for transfusion, which prevented disruptions in blood supply [132]. Most countries across Europe have experienced a drop in the number of blood donations. Blood donors could not donate because they had been ill, were isolating after contact with a confirmed case or were practising recommended physical distancing. Other factors that play a role in the decrease of donors are restrictions in public transportation, work commitments, the need to care for family members, closure of schools or a reluctance to donate due to fear of being infected [133]. An analysis showed that self-efficacy and approval from others, underpinned by coping appraisals and organisational trust, play a critical role in intention to donate [134]. EU/EEA blood establishments have put in place specific preventive measures, reinforced the line of communication with donors, hospitals, other stakeholders and adapted their activities to the public health response. In parallel with blood donations, demand for blood and blood components has dropped, mainly due to the postponement of non-urgent interventions but also because of patients being reluctant to visit healthcare facilities and low transfusion requirements for the treatment of COVID-19 patients. Preliminary Italian data show that there was already a 25% reduction in the number of organs procured during the first four weeks of the COVID-19 outbreak [135]. According to data provided by the European Blood Alliance (EBA), 15 European national and regional blood services reported a 9% (median, range 1–27%) decrease in blood and blood components collected in March and April 2020 compared to the same period in 2019, while the decline in blood components distributed to hospitals was 12% (median, range 1–18%) (Table 1). During the first wave of the pandemic, the European Medicines Agency (EMA) reported no shortages in the supply of plasma-derived medicinal products (PDMPs) although the donations of plasma for fractionation had dropped. Plasma collectors experienced significant declines in collections due, in part, to the impact of physical distancing measures and other mobility restrictions caused by the COVID-19 pandemic. Given that the complex manufacturing of plasma-derived therapies can take 7–12 months, any decline in plasma donations could impact patients' ability to access their lifesaving therapies. PDMP availability in the EU is highly dependent on non-EU plasma supply, mainly from the US, and the current status may therefore reflect the status of plasma collection in the US.

Retrospective analysis of the data from the eye bank in Venice during the Italian lockdown period has shown a significant decline in the number of tissues procured (–41%) and distributed for transplantation (–62%). However, during the first week after the lockdown, the donation rate did not improve significantly (–30%) while requests for tissues for transplantation also increased (+14%) [136]. Germany reported a mean reduction in the number of harvested corneoscleral donor tissues of 17% compared to the period 1 March to 30 April 2019 (n = 1453) and 2020 (n = 1758) [137]. In ophthalmology departments across nine European countries during lockdowns, the European COVID-19 Cataract Group (EUROCOVCAT) registered an average decrease of 97% in keratoplasty procedures compared to the same period in 2019. As of July 2020, the average number of corneal transplantation procedures was still 15% lower [138]. Sixty-four eye banks, covering 95% of the European corneal donation

activity, reported a mean decrease in the number of corneas procured of 38%, 68% and 41%, respectively, in March, April and May 2020 against the mean for the previous two years. Meanwhile grafts decreased by 28%, 68% and 56% respectively, corresponding to 3 866 untreated patients in three months. The decrease in corneal donation and distribution varied significantly among countries, although this was also related to stringency in donor selection measures, irrespective of the severity of the pandemic [139].

Due to the inherent complexity and individualised donor/recipient approach to the transplantation of solid organs and HSC, the pandemic has had an impact on the organisation, coordination and control of all crucial activities and services at local, regional, national and international level. A further effect has been the fear and uncertainty experienced by transplant recipients, those waiting for transplantation, and their carers, resulting from information about the clinical severity of COVID-19 and the temporary suspension of transplantation [140].

In the UK, the number of deceased donors decreased by 66% and the number of deceased donor transplants decreased by 68% during the COVID-19 lockdown period from 23 March to 10 May 2020, compared to the same period in 2019. The number of potential donor referrals decreased by 39% [141]. Spain reported an even higher decrease in organ donation and transplantation (85%) [142]. However, the activity has been progressively recovering and has reached reasonable levels again, despite the ongoing pandemic situation [143]. From February to April 2020, the overall reduction in deceased donor transplantations since the COVID-19 outbreak was 90.6% in France and 51.1% in the USA, respectively [144]. In both France and the USA, this reduction was mostly driven by kidney transplantation, but a substantial effect was also seen for heart, lung, and liver transplants. There was a significant reduction in transplantation rates, even in regions where COVID-19 cases were low, suggesting a global and nationwide effect beyond the local COVID-19 infection prevalence [144]. By September 2020, Australia had reported a drop in kidney transplantation activity of 27% compared with 2019, with smaller reductions in liver (8%) and lung (12%) transplantations [145].

Table 1. Collected and distributed blood and blood components in 15 EU/EEA Member States/regions, March and April 2019–2020

Country/region	Collected blood and blood components (number of units)			Distributed blood and blood components (number of units)		
	March-April 2019	March-April 2020	Difference	March-April 2019	March-April 2020	Difference
Denmark	32 539	31 031	-5%	39 023	36 670	-6%
Croatia	34 358	26 995	-27%	46 331	39 321	-18%
Northern Ireland	8 037	6 820	-18%	7 875	6 747	-17%
Belgium FL*	52 235	51 503	-1%	51 104	45 530	-12%
Belgium W+B	66 322	65 962	-1%	62 952	57 624	-9%
Germany BWH	104 581	104 709	0%	95 270	93 996	-1%
Germany B	85 098	78 090	-9%	90 341	83 089	-9%
Republic of Ireland	20 021	19 959	0%	18 711	16 694	-12%
Lithuania	8 248	7 144	-15%	7 266	6 327	-15%
Luxemburg*	3 686	3 588	-3%	4 323	4 132	-5%
Latvia	9 077	8 365	-9%	14 698	13 842	-6%
Italy**	43 3277	402 896	-8%	422 544	367 433	-15%
Slovenia	1 4051	11 396	-23%	15 693	13 979	-12%
Portugal	31 535.00	27 689	-14%	32 718	31 109	-5%
Finland	33 394	29 273	-14%	-	-	-15%

Data provided by the European Blood Alliance

*Plasma for fractionation excluded.

** Only whole blood and red blood cells.

COVID-19 poses a risk to cells, tissues and organs supply and transplantations, not only by decreasing the donations and modifying demand, but also by extending waiting lists and prolonging waiting times for transplantation. Since the risk of COVID-19 transmission cannot be excluded because of the uncertain effects of SARS-CoV-2 infection in assisted reproduction technologies (ART) and pregnancy, the European Society of Human Reproduction and Embryology (ESHRE) has suggested postponing assisted reproduction treatments as a precaution, to avoid any unnecessary risk. However, ESHRE suggested continuing with the necessary cryopreservation of gametes, embryos or tissue in cases requiring urgent fertility preservation in oncology patients. It also suggested performing elective oocyte or embryo freezing for later embryo transfer for those patients who have started assisted reproduction treatment.

Then once the pandemic situation stabilised, ESHRE recommended restarting all ART treatments for any clinical indication [146].

Absence from work increases during epidemics or pandemics for a variety of reasons. Staff may not be able to go to work due to transportation restrictions, community measures, illness, isolation/self-isolation, or fear of being infected [147]. The magnitude of absenteeism will depend on the local extent of the COVID-19 outbreak. According to a media report quoting the Scottish government, at the beginning of April 2020, more than 14% of NHS Scotland's staff were off work. About 41% of those absences were related to COVID-19 (<https://www.bbc.com/news/uk-scotland-52133634>). An increase in absenteeism among staff during the COVID-19 pandemic will continue to be a risk factor that may hamper the work of SoHO establishments.

The COVID-19 pandemic will probably influence the supply chain of medical devices, critical material, reagents, technical equipment and personal protective equipment, causing potential disruptions in supply and shortages of critical products. The pandemic may also affect transportation and trade due to travel restrictions, quarantine requirements, border control measures and possibly disrupt production. This may also disrupt the national and global supply chain of critical materials and equipment used in the collection, laboratory testing, processing, storage, distribution and clinical use of SoHO. The disrupted supply chain may include goods that are sourced or manufactured in areas with COVID-19 sustained community transmission or in high demand due to increased usage (e.g. masks, gloves and hand sanitisers). The disrupted supply chain for medical products, critical material and equipment (including maintenance) therefore poses a risk to the sustainable and sufficient supply of SoHO.

Transportation and travel limitations may disrupt the supply of essential SoHO, including organs for transplantation, HSC (peripheral, bone marrow and cord blood), blood and blood components, tissues for lifesaving transplantation and plasma for manufacturing medicinal products both at the national and international level. In this respect, the EU Commission has published a Note for the Attention of National Competent Authorities, to facilitate cross-border shipments of SoHO as essential goods and services within the Community and from non-EU countries [148]. The situation affecting the donation and clinical use of SoHO may vary during the future course of the pandemic, and the consequences for SoHO supply and demand are still unpredictable. Therefore, close monitoring of the epidemiological situation, public health interventions and the timely implementation of SoHO-related responses remain crucial in balancing SoHO supply and demand.

Mitigation measures

According to available data on the epidemiology and pathogenesis of COVID-19, SoHO safety authorities in the EU/EEA countries should continue with precautionary actions to mitigate the potential risks to the viral safety of SoHO and infection of staff in SoHO establishments. With the increased spread of COVID-19, despite the extensive public health measures implemented in the EU/EEA, SoHO authorities and establishments should still prioritise efforts to manage the sustainability and sufficiency of the national SoHO supply. Measures taken should be in proportion to the evolution of the pandemic in real time and consistent with governmental and public health advice. Clinicians should pay special attention to mitigating the risk of COVID-19 in transplant recipients.

Common mitigation measures for SoHO

Given that the risk of COVID-19 transmission via SoHO is theoretical, the recommended risk mitigation measures are precautionary. The measures focus on preventing an infectious donor from donating SoHO and maintaining physical distance during the donation process. The goal is to protect staff and donors in SoHO establishments from possible COVID-19 infection by minimising the potential exposure to the virus. The measures should support public health action being taken in the country.

SoHO establishments should inform donors of the nature and clinical signs of COVID-19, transmission risks and related donation restrictions, as this will help them make decisions on a donation. The possibility of COVID-19 transmission during the SoHO donation process and infection prevention and control measures to be taken by SoHO establishments need to be specifically clarified. This may reduce the fear of infection in the process of SoHO donation.

Standard donor selection procedures involving the taking of medical and behavioural history and a physical examination should be adapted to prevent or minimise the possibility of respiratory transmission during the procedure and focus on possible exposure and travel, as well as clinical signs of acute respiratory infection in the donor.

Pre-selection measures are intended to regulate the donor flow at the collection/procurement facility, enable physical distancing and detect potentially infectious donors by triage. The exclusion of such donors may prevent the possible spread of the virus in waiting rooms and help with donor selection. However, health professionals should keep in mind that a relatively high proportion of the general population is asymptomatic.

Where applicable, SoHO establishments should consider applying the following physical distancing, hand hygiene and environmental cleaning measures during donation/procurement of some types of SoHO:

- schedule donations and undertake 'triage' when scheduling;
- complete donor questionnaires or interviews on-line if possible;
- limit the number of donors in waiting rooms;
- ensure that donors sanitise their hands before donation;
- offer surgical masks to donors if needed;
- apply recommended distancing during collection/procurement procedures;
- provide adequate personal protective equipment (PPE) to staff;
- limit close contact time between staff and donors < 15 minutes, when possible;
- sanitise rooms/mobile units after use;
- consider carrying out triage of donors at reception, including measurement of body temperature;
- ensure that disinfection procedures follow ECDC guidance on environmental cleaning in healthcare and non-healthcare settings during the COVID-19 pandemic [149] as well as complying with national and local recommendations;
- ensure that hand hygiene measures and use of disinfectant are in line with WHO recommendations on hand hygiene practices [150];
- ensure that the disinfectant complies with WHO-recommended Handrub Formulations [151];
- develop policies and procedures for identification, isolation and reporting of personnel experiencing symptoms and for advising rejected donors.

The criterion for temporary deferral for at least 14 days is a body temperature of 37.5°C or above. Advice to the rejected donor should follow the national public health recommendations for COVID-19.

When assessing donor eligibility, SoHO establishments may apply the following common donor selection criteria:

- donors with active confirmed COVID-19 are not eligible for the donation of SoHO;
- donors exposed to SARS-CoV-2 through close contact with a confirmed case of COVID-19 may donate SoHO after the end of the period nationally recommended for quarantine or isolation;
- donors returning from non-green COVID-19 risk areas¹ may donate SoHO if they meet national requirements for quarantine or entry testing for such travellers;
- donors may donate SoHO at least 14 days after testing positive for the presence of anti-SARS-CoV-2 antibodies if they have no clinical signs of disease or genomic/antigen testing results;
- donors who have recovered from confirmed COVID-19 may donate SoHO at least 14 days after symptom resolution or laboratory evidence of viral RNA clearance from the upper respiratory tract.

SoHO establishments and laboratories should use currently available CE marked tests. However, in the context of the pandemic crisis, some in-house tests may be used after appropriate national approvals.

SoHO donation and SARS-CoV vaccination

According to EU Directives, after vaccination with attenuated viruses (e.g. replication competent virus vector-based vaccines, live-attenuated virus vaccines) SoHO donors must be deferred for four weeks. Individuals vaccinated with inactivated/killed viruses or vaccines that do not contain live agents (i.e. mRNA vaccines, non-replicating/replication deficient virus vector-based vaccines and protein subunit vaccines) may be accepted as SoHO donors if they feel well [4-6].

In situations where information about vaccine type is missing or the vaccination is experimental, a four-week deferral period should be applied. Given that COVID-19 vaccines are newly developed and the effects on SoHO donation are unknown, Member States may take a precautionary approach and defer donors who develop symptoms directly after receiving a SARS-CoV-2 vaccine for up to seven days after symptoms have resolved. In addition, donors need to comply with the same general requirements for donation as non-vaccinated donors. Potential living donors of organs and HSCs, as well as transplant candidates, should have priority for vaccination. If the organ or HSC donors have been vaccinated with attenuated vaccines in the four weeks before donation, a risk assessment should be carried out and taken into account when deciding on transplantation and, if transplanted, the recipient should be monitored post-transplant.

Specific mitigation measures - blood and blood components

Blood donors should provide information on relevant changes in their health (including respiratory infection) within 14 days of donation by telephone or other means of communication. Donor information on the occurrence of confirmed or probable COVID-19 within 72 hours after blood donation should trigger the discarding of donated blood and blood components, unless they have been treated with approved pathogen reduction technology. Blood establishments should identify staff and donors having been in contact with the implicated donor and advise them to follow the

¹ <https://www.consilium.europa.eu/en/press/press-releases/2020/10/13/covid-19-council-adopts-a-recommendation-to-coordinate-measures-affecting-free-movement/>.

national public health recommendations for COVID-19. Haemovigilance staff should encourage clinicians to identify cases of COVID-19 in transfusion recipients and investigate the possibility of transmission via transfusion.

In the event of widespread transmission, blood establishments may need to adapt the blood safety and physical distancing measures applied to suit the local epidemiological situation and ensure the sustainability of blood supply.

Laboratory screening of blood donors for the presence of viral RNA or antigen in the upper respiratory specimens using RT-PCR or rapid antigen testing is currently not recommended because transfusion-transmitted COVID-19 has not been reported and published data show that blood-borne transmission of COVID-19 is unlikely. Case reports and lookback studies have shown that transfusion of blood products obtained from infected individuals who have not yet developed signs and symptoms of COVID-19 has not resulted in disease transmission [55-58]. Physical distancing and the use of personal protection equipment during the donation procedure appear to prevent exposure and respiratory transmission from asymptomatic COVID-19 donors to staff members and other donors. Therefore, laboratory screening of donors as an additional intervention to increase the safety of staff and donors seems unnecessary.

Blood establishments that use pathogen reduction technology may be able to decrease the theoretical risk of COVID-19 transmission through platelets and fresh frozen plasma. However, the implementation of pathogen reduction technology requires time and resources and has some limitations, which have to be weighed against the benefits, not only for the current pandemic but also for other known and emerging microbial threats to the safety of plasma and platelets [105].

Specific mitigation measures - non-reproductive cells and tissues

Living donors of non-reproductive cells and tissue should comply with the common SoHO mitigation measures.

- **HSC donation**
 - Within 14 days of donation, HSC donors should practice good hygiene and be as physically isolated as possible. Unnecessary travel should be avoided.
 - Routine testing of the donor/donated HSC is not recommended.
 - If local authorities require that an HSC donor is tested for the presence of viral RNA in an upper respiratory tract specimen, the most beneficial time for this is before the start of patient conditioning or donation procedure.
 - If donor/donation testing on the day of donation is required locally and produces a positive result, any decision to cancel or reject the donation must take into account the fact that the risk of contracting COVID-19 through HSCs is only theoretical and that in the absence of planned cryopreservation, patients may have already started the myeloablative conditioning regimen.
 - Donors of HSCs recovering from COVID-19 or exposed to SARS-CoV-2 may donate earlier than recommended if there is an urgent patient need and no suitable alternative donor. Such a donor must be without symptoms and have tested negative for the presence of viral RNA in the respiratory tract specimen.
 - Cryopreservation of HSC or provision of an alternative donor as back-up are recommended in situations where there is an increased risk of unpredictable logistical difficulties at a transplant centre, or a donor becoming unavailable at the time of planned transplantation due to community-acquired COVID-19, travel restrictions or logistical difficulties at a transplant centre.
- **Deceased donation**
 - Deceased donors with active confirmed COVID-19 at the time of death are not eligible for tissue donation.
 - Tissue donations may be retrieved from deceased donors who had recovered from COVID-19 if they tested negative for the presence of SARS-CoV-2 RNA in upper respiratory tract specimens or if they became asymptomatic at least 14 days before death. In order to resume tissue donation in Spain, donation of tissues from deceased donors with a previous diagnosis of COVID-19 (confirmed or suspected) is evaluated on a case-by-case basis. Deceased donors are eligible for donation if all three criteria are met: a) more than 14 days since the onset of symptoms (extended to 21 days if the absence of symptoms cannot be evaluated); b) more than 72 hours with no symptoms; c) negative result for SARS-CoV-2 by RT-PCR in a sample from the respiratory tract.
 - Tissues should not be collected from a deceased donor who did not have symptoms or a diagnosis of COVID-19, but who had lived in or visited a non-green COVID-19 risk area, unless a) the procured tissues are disinfected, sterilised or pathogen-inactivated using a procedure validated for enveloped viruses; b) the donor had completed the nationally required quarantine or been tested on entry when returning, or c) the donor tested negative for the presence of SARS-CoV-2 RNA in upper or lower respiratory tract specimens collected within 72 hours before procurement.

Tissue establishments should encourage living donors to provide information on relevant changes to their health status (including respiratory infection) within 14 days of donation by telephone or other means of communication. In the event of post-donation symptomatic or laboratory-confirmed COVID-19 in the donor, the transplant recipient should be monitored for COVID-19 and associated complications. Furthermore, pulmonary and other suitable

measures should be implemented to prevent the nosocomial spread of COVID-19 within a transplant unit. Tissue establishments and transplant centres should pay particular attention to biovigilance during data collection and analysis.

Viruses may be inactivated during the processing of some types of tissues (e.g. processed bone and decellularised tissues). Tissue establishments should assess the risk and evaluate the ability of such processes to inactivate/eliminate enveloped viruses in tissues.

Specific mitigation measures - reproductive cells and tissues and medically-assisted reproduction

Non-partner sperm and oocyte donors should comply with the common SoHO mitigation measures.

To mitigate the risk of COVID-19 transmission, the assisted reproduction technology (ART) centres in EU/EEA Member States should follow advice in the latest update from the European Society of Human Reproduction and Embryology (ESHRE) COVID-19 Working Group Guidance on ART treatments [152]. The guidance recommends the following mitigation measures to maintain safe ART services, depending on the incidence of infection:

- reduce the number of patients treated;
- limit access to treated patient only (no partners);
- increase patient and staff triage and testing;
- limit staff exposure and allow more time between patient appointments;
- enhance sanitation measures;
- use personal protective equipment (PPE) intensively;
- increase the use of telemedicine;
- reaffirm the ESHRE Code of Conduct;
- when clinically and epidemiologically indicated, consider avoiding embryo transfer and use a freeze-all strategy.

The Working Group also recommends that ART centres increase counselling and information to patients planning a pregnancy or already pregnant; monitor epidemiological data via national health systems and/or from ECDC; monitor internal and external risk factors which may have an impact on ART services, including but not limited to staff number and availability of supplies; gradually implement mitigation measures proportional to the COVID-19 incidence in the area and perceived impact on ART services (as suggested in the guidance). To simplify monitoring of the epidemiological data, the COVID-19 working group/ART centres may consider using the risk area classification recommended by the European Council [7].

Cryopreservation of gametes carries the risk of cross-contamination through cryogenic medium and thus calls for risk-mitigation strategies, including the testing of both partners for SARS-CoV-2 before initiating treatment, use of closed-carrier cryodevices, sanitary cryostorage protocols and efficient washing of gametes or embryos [153].

Specific mitigation measures - organs

Transplant candidates, recipients, and potential living donors should be informed of COVID-19 and aware of the importance of frequent hand washing, avoiding crowds and applying physical distancing.

Donor selection criteria

- **Living donation**
 - Organ donors should be tested for the presence of viral RNA in a respiratory tract specimen before the procedure to protect the staff of the transplant unit and other patients from COVID-19 infection.
 - Organ donors who have recovered from COVID-19 or have possibly been exposed to SARS-CoV-2 may donate earlier than recommended, if there is an urgent patient need and no suitable alternative donor. Such a donor must be without symptoms and have tested negative for the presence of viral RNA/antigen in the respiratory specimen.
- **Deceased donation**
 - Deceased donors with active COVID-19 at the time of death are not eligible for organ donation.
 - Deceased donors who were without symptoms or had not been diagnosed with COVID-19 at the time of death, but who had lived in or visited non-green COVID-19 risk areas may donate organs if they tested negative for the presence of SARS-CoV-2 RNA in upper or lower respiratory tract specimens collected 72 hours before organ procurement.
 - Deceased donors who had recovered from COVID-19 may donate organs if they had tested negative for the presence of SARS-CoV-2 RNA in upper respiratory tract specimens, or if they were asymptomatic at least 14 days before death.

In order to resume transplant activities, some centres have modified criteria for organ donation by deceased donors. Italian transplant centres are exploring the possible use of organs from deceased donors with active COVID-19 at the

time of death for recipients in need of life-saving organs with active COVID-19 or recipients who have recovered from COVID-19 [personal communication].

In Spain, donation of organs from donors who had previously been diagnosed with COVID-19 (confirmed or suspected) is evaluated on a case-by-case basis. Deceased donors are eligible for donation if all three criteria are met: a) more than 14 days since the onset of symptoms (extended to 21 days if the absence of symptoms cannot be evaluated and in the event of lung donation); b) more than 72 hours with no symptoms; c) negative result for SARS-CoV-2 by RT-PCR in a sample from the respiratory tract.

Clinical outcomes on the use of deceased donor organs will provide the necessary evidence to make evidence-based recommendations.

Transplant recipients

Transplant centres should follow infection prevention and control (IPC) measures implemented at hospital level and in accordance with the national strategy. The mainstays of IPC in all healthcare facilities are administrative measures, physical distancing, hand hygiene and the appropriate use of PPE [154].

Transplant centres may consider testing transplant candidates at risk of COVID-19 infection for the presence of SARS-CoV-2 via nasopharyngeal swab before proceeding with the transplant procedure. In principle, transplantation in candidates with active COVID-19 is not recommended. The final decision to transplant should be taken after taking into account the risk to the patient associated with delaying the procedure and the risk of COVID-19-associated complications. In general, if a transplant candidate is diagnosed with COVID-19, deferral of an HCT procedure is recommended. However, this is not always possible due to the high risk of progression of the underlying disease. This is a difficult risk-benefit assessment and must be made individually, with complete information given to the patient about the risks of transplant complications versus the risk for progression of the underlying disease [155]. To minimise the risk of being infected, transplant candidates/recipients and their immediate household contacts should avoid any non-essential travel and overcrowded situations, practice physical distancing and frequently wash their hands.

International and national transplantation bodies have developed measures for the management of transplant activities and recipients during the pandemic. These include managing transplant activities when the transplant centre is temporarily closed and isolating recipients if transplanted during a potential incubation period or in an area with sustained community transmission to protect the patient, family and hospital personnel.

It is also important for the national and international transportation of organs and cells and tissues intended for transplantation to proceed uninterrupted. In geographically-confined outbreaks, transplant authorities may consider putting transplant candidates on the waiting list at alternative centres for transplantation. Potential living donors and transplant recipients should be informed of the situation relating to the outbreak and possibilities for transplantation.

Staff in SoHO establishments

SoHO establishments should inform and educate staff on the nature of COVID-19, transmission routes, personal protection and other containment measures. During the donation process, medical staff should apply appropriate hand hygiene measures and use personal protective equipment in accordance with national public health guidelines [154,156]. Personal protective measures in the donation area of a SoHO establishment which is not located in a hospital environment should not be as stringent as in settings where staff take care of infected or potentially infected patients. However, the measures should still be consistent with national guidelines for community environments where there is frequent contact with the public. Infection control practices and measures should be in line with the national public health recommendations for COVID-19 [157]. As employees may be exposed to SARS-CoV-2, once a vaccine becomes available, consideration should be given to the prioritisation of staff working in these establishments for vaccination, together with other healthcare professionals, to ensure the continuity of supply. For deceased tissue and organ donation, standard protective garments (surgical mask, gloves and cap) required for routine procedures should provide adequate protection for procurement staff. Furthermore, exceptional measures can be taken, such as covering the donor's oral and nasal cavities and using of a face shield or protective glasses, respiratory protection masks (FFP3) and double gloves, to prevent exposure to possible droplets produced when handling procurement from deceased donors.

In the event of an individual staff member developing an acute respiratory illness, the person should leave the workplace, self-isolate at home and immediately seek care, preferably first by phone, as per local guidelines. Increased community transmission of COVID-19 may cause absenteeism due to illness, isolation or self-isolation, transportation restrictions and the need to care for sick family members. SoHO establishments must anticipate this early on and consider pre-emptive measures to mitigate the impact on essential activities. Laboratory staff should follow standard laboratory biosafety practices. In the event of diagnostic testing being provided for patients or suspected cases, procedures for handling and testing samples should be in line with laboratory biosafety guidance for COVID-19 [158]. In terms of organisation, SoHO establishments may consider changing arrangements in offices/laboratories, cancelling non-essential meetings, minimising staff gatherings, holding teleconference

meetings (even if in the same building), reviewing catering arrangements, staggering staff dining and arranging for as many critical staff as possible to work from home.

Adequate and sustained supply of SoHO

Experience with the current COVID-19 pandemic has had different but significant impacts on the SoHO supply chain, especially during the wave of widespread community transmission. SoHO establishments have applied contingency (preparedness) plans and undertaken a series of actions to ensure a continued supply of safe, high-quality, life-saving products and services at the level demanded by the healthcare community.

Given the unpredictable duration of COVID-19 pandemic, to maintain the safe and sufficient SoHO supply, SoHO establishments in EU/EEA Member States are encouraged to take the actions set out below.

- Continue implementing contingency plans based on principles recommended in the first update of the document 'Coronavirus disease - 2019 (COVID-19) and supply of substances of human origin in EU/EEA' [3] taking into account international and national guidelines provided by WHO [49], professional associations and authorities.
- Perform an intra-action review (IAR) to assess the impact of the pandemic on the SoHO supply and the effectiveness of measures taken to date, to identify strategic priorities and to exchange lessons learned. For this update, an intra-action review (IAR) is defined as a country-led, facilitated discussion that allows national and subnational stakeholders of the COVID-19 response to (i) reflect on actions being undertaken to prepare for and respond to COVID-19 outbreaks at the country level, to identify current best practices, gaps and lessons learned, and (ii) propose corrective action to improve and strengthen the continued response to COVID-19. Additionally, IAR findings and recommendations may contribute to improving the management of concurrent emergencies and long-term health security in general [159,160]. The IAR provides an opportunity to review the functional capacity of the national and subnational system of SoHO supply and to identify practical areas that need immediate remediation or can be targeted for sustained improvement of the outbreak response.
- Continue with regular and effective communication between SoHO establishments, national competent authorities, national health authorities, ECDC, the European Commission and other stakeholders to facilitate an adequate and proportional response to the COVID-19 outbreak at local, national and EU/EEA level. The alert platforms hosted by the European Commission for communication between Member States' SoHO authorities, Rapid Alert Blood and Rapid Alert Tissues and Cells platforms, may be used for communication between national competent authorities, the European Commission and ECDC in order to share data on measures implemented and difficulties with supply.
- Continue educating and creating awareness among the general population about the importance of donating SoHO and safety of the donation procedure.

Acknowledgments

This document was prepared by Dragoslav Domanović and reviewed by a panel of experts convened by the European Commission (DG Santé). The experts were nominated by Member State competent authorities for blood, tissues, cells and organs (Sophie Lucas Samuel – France, Kostas Stamoulis –Greece, Beatriz Dominguez-Gil, Anna Vilarrodona Serrat –Spain; Vincenzo de Angelis – Italy; Fewzi Teskrat – Malta), Paolo Antonio Grossi (University of Insubria, Italy) and the following SoHO stakeholder associations: US FDA (WHO consultant Jay Epstein), the European Society of Human Reproduction and Embryology (Anna Veiga, Nathalie Vermeulen), the European Blood Alliance (Ryenne Lieshout – Krikke), the European Society for Blood and Marrow Transplantation (Jan Styczynski), the European Eye Bank Association (Philip Maier), the International Plasma Fractionators Association (Paul Strengers), the World Marrow Donors Association (Mirjam Fetcher), and the European Plasma Alliance (Matthias Gessner).

References

1. European Centre for Disease Prevention and Control. Cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China 17 January 2020 [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Risk%20assessment%20-%20pneumonia%20Wuhan%20China%2017%20Jan%202020.pdf>
2. European Centre for Disease Prevention and Control. Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA. 2020 [18 April 2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-supply-substances-human-origin.pdf>
3. European Centre for Disease Prevention and Control. Coronavirus disease - 2019 (COVID-19) and supply of substances of human origin in EU/EEA - first update 2020 [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/COVID%2019-supply-substances-human-origin-first-update.pdf>
4. European Commission. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. 2003. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0098&from=EN>
5. European Commission. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. 30 March 2004. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32004L0033&from=EN>
6. European Commission. Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32010L0053&from=EN>
7. European Council. COVID-19: Council adopts a recommendation to coordinate measures affecting free movement. Press release 13 October 2020. [cited 31/10/2020]. Available from: <https://www.consilium.europa.eu/en/press/press-releases/2020/10/13/covid-19-council-adopts-a-recommendation-to-coordinate-measures-affecting-free-movement/>
8. European Centre for Disease Prevention and Control. Maps in support of the Council Recommendation on a coordinated approach to the restriction of free movement in response to the COVID-19 pandemic in the EU/EEA and the UK. 2020 [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/en/covid-19/situation-updates/weekly-maps-coordinated-restriction-free-movement>
9. European Centre for Disease Prevention and Control. COVID-19 pandemic. Available from: <https://www.ecdc.europa.eu/en/novel-coronavirus-china>
10. European Centre for Disease Prevention and Control. Increased transmission of COVID-19 in the EU/EEA and the UK – thirteenth update. Rapid risk assessment, 23 October 2020. [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/RRA-COVID-19-EU-EEA-UK-thirteenth-update-23-Oct-2020.pdf>
11. World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. Interim guidance 19 March 2020. [cited 13 March 2020]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/331329/WHO-COVID-19-laboratory-2020.4-eng.pdf?sequence=1&isAllowed=y>
12. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 11 March 2020
13. World Health Organization. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. 2020 [cited 31/10/2020]. Available from: https://www.google.com/search?q=sensitivity+and+specificity+of+rapid+antigen+test+for+covid+19&rlz=1C1GCEB_enSE874SE874&oq=sensitivity+and+specificity+of+rapid+antigen+test&aqs=chrome..69l69j69j57j0j22i30.16635j0j15&sourceid=chrome&ie=UTF-8#
14. Porte L, Legarraga P, Vollrath V, Aguilera X, Munita JM, Araos R, et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. International Journal of Infectious Diseases. 2020/10/01;99:328-33.
15. European Centre for Disease Prevention and Control. Strategies for the surveillance of COVID-19 [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-surveillance-strategy-9-Apr-2020.pdf>
16. European Commission. Commission Directive (EU) 2020/739 of 3 June 2020 amending Annex III to Directive 2000/54/EC of the European Parliament and of the Council as regards the inclusion of SARS-CoV-2 in the list of biological agents known to infect humans and amending Commission Directive (EU) 2019/1833 [cited 31/10/2020]. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32020L0739>
17. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PKS, Ng MHL, et al. ABO Blood Group and Susceptibility to Severe Acute Respiratory Syndrome. JAMA. 2005;293(12):1447-51.
18. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clin Infect Dis. 2020 Aug 4.

19. Zietz M, Zucker JE, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv. 2020:04.08.20058073.
20. Zeng X, Fan H, Lu D, Huang F, Meng X, Li Z, et al. Association between ABO blood groups and clinical outcome of coronavirus disease 2019: Evidence from two cohorts. medRxiv. 2020.04.15.20063107.
21. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. *British Journal of Haematology*. 2020;190(1):24-7.
22. Barnkob MB, Pottegård A, Støvring H, Haunstrup TM, Homburg K, Larsen R, et al. Reduced prevalence of SARS-CoV-2 infection in ABO blood group O. *Blood Advances*. 2020;4(20):4990-3.
23. Valenti L, Villa S, Baselli G, Temporiti R, Bandera A, Scudeller L, et al. Association of ABO blood group and secretor phenotype with severe COVID-19. *Transfusion*. 3/10/2020. Available from: <https://europepmc.org/article/pmc/pmc7675339>
24. Kolin DA, Kulm S, Elemento O. Clinical and Genetic Characteristics of COVID-19 Patients from UK Biobank. medRxiv. 2020.05.05.20075507.
25. Genome-wide Association Study of Severe COVID-19 with Respiratory Failure. *New England Journal of Medicine*. 2020;383(16):1522-34.
26. Dzik S, Eliason K, Morris EB, Kaufman RM, North CM. COVID-19 and ABO blood groups. *Transfusion*. 2020;60(8):1883-4.
27. Latz CA, DeCarlo C, Boitano L, Png CYM, Patell R, Conrad MF, et al. Blood type and outcomes in patients with COVID-19. *Annals of Hematology*. 2020/09/01;99(9):2113-8.
28. Guillon P, Clément M, Sébille V, Rivain J-G, Chou C-F, Ruvoën-Clouet N, et al. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology*. 2008;18(12):1085-93.
29. Hoiland RL, Fergusson NA, Mitra AR, Griesdale DEG, Devine DV, Stukas S, et al. The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. *Blood Advances*. 2020;4(20):4981-9.
30. Platton S, Mendes N, Booth C, Lancut J, Lee K, Regan F, et al. Positive direct antiglobulin tests in patients with COVID-19. *Transfusion*. doi.org/10.1111/trf.16156
31. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA*. 6 April 2020.
32. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 27 March 2020.
33. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest*. 2020/07/01;158(1):e9-e13.
34. Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *Proceedings of the National Academy of Sciences*. 2020;117(28):16587-95.
35. Chan JF-W, Zhang AJ, Yuan S, Poon VK-M, Chan CC-S, Lee AC-Y, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. *Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America*. 2020:325.
36. Sun J, Zhuang Z, Zheng J, Li K, Wong RL-Y, Liu D, et al. Generation of a Broadly Useful Model for COVID-19 Pathogenesis, Vaccination, and Treatment. *Cell*. 2020/08/06;182(3):734-43.e5.
37. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv. 2020.08.12.20169359.
38. Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews*. 2020 (10).
39. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nature Microbiology*. 2020/10/01;5(10):1185-91.
40. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science*. 2017;358(6365):929-32.
41. Bardina SV, Bunduc P, Tripathi S, Duehr J, Frere JJ, Brown JA, et al. Enhancement of Zika virus pathogenesis by preexisting ant flavivirus immunity. *Science*. 2017;356(6334):175-80.
42. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. 2019/02/21;4(4).
43. Agrawal AS, Tao X, Algaissi A, Garron T, Narayanan K, Peng B-H, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. *Human Vaccines & Immunotherapeutics*. 2016/09/01;12(9):2351-6.
44. Vennema H, de Groot RJ, Harbour DA, Dalderup M, Gruffydd-Jones T, Horzinek MC, et al. Early death after feline infectious peritonitis virus challenge due to recombinant vaccinia virus immunization. *Journal of Virology*. 1990;64(3):1407-9.
45. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill*. 2020 Feb;25(5).
46. Meffre E, Iwasaki A. Interferon deficiency can lead to severe COVID. *Nature*. 2020 Nov;587(7834):374-6.

47. European Commission. An EU programme of COVID-19 convalescent plasma collection and transfusion 2020 [15/04/2020]. Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/guidance_plasma_covid19_en.pdf.
48. World Health Organization. Protecting the blood supply during infectious disease outbreaks. Guidance for national blood services. 2019 [cited 31/10/2020]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/311443/9789241515214-eng.pdf?ua=1>.
49. World Health Organization. Maintaining a Safe and Adequate Blood Supply during Pandemic Influenza Guidelines for Blood Transfusion Services (July 2011). Available from: https://www.who.int/bloodsafety/publications/WHO_Guidelines_on_Pandemic_Influenza_and_Blood_Supply.pdf
50. Andersson M, Arancibia - Carcamo CV, Auckland K, Baillie JK, Barnes E, Beneke T, et al. SARS-CoV-2 RNA detected in blood samples from patients with COVID-19 is not associated with infectious virus. medRxiv. 2020.05.21.20105486.
51. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January–March 2020: retrospective cohort study. BMJ. 2020 Apr 21;369:m1443.
52. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
53. Corman VM, Rabenau HF, Adams O, Oberle D, Funk MB, Keller-Stanislawski B, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. medRxiv. 2020.03.29.20039529.
54. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nature Communications. 2020/10/30;11(1):5493.
55. Cho HJ, Koo JW, Roh SK, Kim YK, Suh JS, Moon JH, et al. COVID-19 transmission and blood transfusion: A case report. J Infect Public Health. 2020 Nov;13(11):1678-9.
56. Kwon S-Y, Kim E-J, Jung YS, Jang JS, Cho N-S. Post-donation COVID-19 identification in blood donors. Vox Sanguinis. 2 April 2020. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/vox.12925>
57. Chang L, Zhao L, Gong H, Wang L, Wang L. Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations. Emerg Infect Dis. 2020 Apr 3;26(7).
58. Cappy P, Candotti D, Sauvage V, Lucas Q, Boizeau L, Gomez J, et al. No evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation. Blood. 2020;136(16):1888-91.
59. Duan SM, Zhao XS, Wen RF, Huang JJ, Pi GH, Zhang SX, et al. Stability of SARS coronavirus in human specimens and environment and its sensitivity to heating and UV irradiation. Biomed Environ Sci. 2003 Sep;16(3):246-55.
60. Pinna D, Sampson-Johannes A, Clementi M, Poli G, Rossini S, Lin L, et al. Amotosalen photochemical inactivation of severe acute respiratory syndrome coronavirus in human platelet concentrates. Transfus Med. 2005 Aug;15(4):269-76.
61. Hindawi SI, Hashem AM, Damanhoury GA, El-Kafrawy SA, Tolah AM, Hassan AM, et al. Inactivation of Middle East respiratory syndrome-coronavirus in human plasma using amotosalen and ultraviolet A light. Transfusion. 2018 Jan;58(1):52-9.
62. Keil SD, Bowen R, Marschner S. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. Transfusion. 2016 Dec;56(12):2948-52.
63. Zhang Y, Bergelson JM. Adenovirus receptors. J Virol. 2005 Oct;79(19):12125-31.
64. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Letters. 2002;532(1-2):107-10.
65. Hashem AM, Hassan AM, Tolah AM, Alsaadi MA, Abunada Q, Damanhoury GA, et al. Amotosalen and ultraviolet A light efficiently inactivate MERS-coronavirus in human platelet concentrates. Transfus Med. 2019 Dec;29(6):434-41.
66. Ragan I, Hartson L, Pidcock H, Bowen R, Goodrich R. Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light. PLoS One. 2020;15(5):e0233947.
67. US Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) 2019. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/index.html>
68. Rabenau HF, Biesert L, Schmidt T, Bauer G, Cinatl J, Doerr HW. SARS-coronavirus (SARS-CoV) and the safety of a solvent/detergent (S/D) treated immunoglobulin preparation. Biologicals. 2005 Jun;33(2):95-9.
69. Groner A, Broumis C, Fang R, Nowak T, Popp B, Schafer W, et al. Effective inactivation of a wide range of viruses by pasteurization. Transfusion. 2018 Jan;58(1):41-51.
70. Yunoki M, Urayama T, Yamamoto I, Abe S, Ikuta K. Heat sensitivity of a SARS-associated coronavirus introduced into plasma products. Vox Sang. 2004 Nov;87(4):302-3.
71. Burnouf T. An overview of plasma fractionation. Annals of Blood. 2018 (1).
72. Ropa J, Cooper S, Capitano ML, Van't Hof W, Broxmeyer HE. Human Hematopoietic Stem, Progenitor, and Immune Cells Respond Ex Vivo to SARS-CoV-2 Spike Protein. Stem Cell Reviews and Reports. 2020/10/21.
73. Ratajczak MZ, Bujko K, Ciechanowicz A, Sielatycka K, Cymer M, Marlicz W, et al. SARS-CoV-2 Entry Receptor ACE2 Is Expressed on Very Small CD45– Precursors of Hematopoietic and Endothelial Cells and in Response to Virus Spike Protein Activates the Nlrp3 Inflammasome. Stem Cell Reviews and Reports. 2020/07/20.

74. Banerjee A, Nasir JA, Budyłowski P, Yip L, Aftanas P, Christie N, et al. Isolation, Sequence, Infectivity, and Replication Kinetics of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg Infect Dis.* 2020 Sep;26(9):2054-63.
75. Anurathapan U, Apiwattanakul N, Pakakasama S, Pongphitcha P, Thitithanyanont A, Pasomsub E, et al. Hematopoietic stem cell transplantation from an infected SARS-CoV2 donor sibling. *Bone Marrow Transplantation.* 2020/06/11.
76. Lázaro Del Campo P, de Paz Arias R, Ramírez López A, de la Cruz Benito B, Humala Barbier K, Sánchez Vadillo I, et al. No transmission of SARS-CoV-2 in a patient undergoing allogeneic hematopoietic cell transplantation from a matched-related donor with unknown COVID-19. *Transfus Apher Sci.* 2020 Aug 24:102921.
77. 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.* 26 Feb 2020.
78. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, et al. Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 31 Mar 2020.
79. Colavita F, Lapa D, Carletti F, Lalle E, Bordini L, Marsella P, et al. SARS-CoV-2 Isolation From Ocular Secretions of a Patient With COVID-19 in Italy With Prolonged Viral RNA Detection. *Ann Intern Med.* 17 April 2020.
80. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 28 Feb 2020.
81. Seah IYJ, Anderson DE, Kang AEZ, Wang L, Rao P, Young BE, et al. Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients. *Ophthalmology.* 2020 Jul;127(7):977-9.
82. Güemes-Villahoz N, Burgos-Blasco B, García-Feijó J, Sáenz-Francés F, Arriola-Villalobos P, Martínez-de-la-Casa JM, et al. Conjunctivitis in COVID-19 patients: frequency and clinical presentation. *Graefes Archive for Clinical and Experimental Ophthalmology.* 2020/11/01;258(11):2501-7.
83. Zhou Y, Duan C, Zeng Y, Tong Y, Nie Y, Yang Y, et al. Ocular Findings and Proportion with Conjunctival SARS-COV-2 in COVID-19 Patients. *Ophthalmology.* 2020 Jul;127(7):982-3.
84. Lang J, Yang N, Deng J, Liu K, Yang P, Zhang G, et al. Inhibition of SARS Pseudovirus Cell Entry by Lactoferrin Binding to Heparan Sulfate Proteoglycans. *PLOS ONE.* 2011;6(8):e23710.
85. Collin J, Queen R, Zerti D, Dorgau B, Georgiou M, Djidrovski I, et al. Co-expression of SARS-CoV-2 entry genes in the superficial adult human conjunctival, limbal and corneal epithelium suggests an additional route of entry via the ocular surface. *Ocul Surf.* 3 June 2020.
86. Paoli D, Pallotti F, Colangelo S, Basilico F, Mazzuti L, Turriziani O, et al. Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive naso-pharyngeal swab. *J Endocrinol Invest.* 2020 Apr 23:1-4.
87. Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, et al. No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. *Fertility and Sterility.* 2020;113(6):1135-9.
88. Song C, Wang Y, Li W, Hu B, Chen G, Xia P, et al. Absence of 2019 novel coronavirus in semen and testes of COVID-19 patients. *Biol Reprod.* 2020 Jun 23;103(1):4-6.
89. Holtmann N, Edimiris P, Andree M, Doehmen C, Baston-Buest D, Adams O, et al. Assessment of SARS-CoV-2 in human semen; a cohort study. *Fertility and Sterility.* 2020;114(2):233-8.
90. Guo L, Zhao S, Li W, Wang Y, Li L, Jiang S, et al. Absence of SARS-CoV-2 in semen of a COVID-19 patient cohort. *Andrology.* 29 June 2020.
91. Kayaaslan B, Korukluoglu G, Hasanoglu I, Kalem AK, Eser F, Akinci E, et al. Investigation of SARS-CoV-2 in Semen of Patients in the Acute Stage of COVID-19 Infection. *Urologia Internationalis.* 2020;104(9-10):678-83.
92. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019. *JAMA Network Open.* 2020;3(5):e208292-e.
93. Douglas GC, O'Bryan MK, Hedger MP, Lee DK, Yarski MA, Smith AI, et al. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. *Endocrinology.* 2004 Oct;145(10):4703-11.
94. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem.* 2000 Oct 27;275(43):33238-43.
95. Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, Santos RA. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. *Fertil Steril.* 2011 Jan;95(1):176-81.
96. Singh M, Bansal V, Feschotte C. A Single-Cell RNA Expression Map of Human Coronavirus Entry Factors. *Cell Reports.* 2020/09/22;32(12):108175.
97. European Society of Human Reproduction and Embryology. Assisted reproduction and COVID-19. An updated statement from ESHRE 2020 [cited 19/04/2020]. Available from: https://www.eshre.eu/Press-Room/ESHRE-News#COVID19_April2
98. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020 Mar 7;395(10226):809-15.
99. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. *Emerg Infect Dis.* 2020 Jun 17;26(6).
100. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. *JAMA Pediatr.* 26 March 2020.

101. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible Vertical Transmission of SARS-CoV-2 from an Infected Mother to Her Newborn. *JAMA*. 26 March 2020.
102. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA*. 26 March 2020.
103. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. *PLoS One*. 2020;15(4):e0230295.
104. Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. *Nature Communications*. 2020/10/12;11(1):5128.
105. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine*. 2020/03/12.
106. Gembardt F, Sterner-Kock A, Imboden H, Spalteholz M, Reibitz F, Schultheiss HP, et al. Organ-specific distribution of ACE2 mRNA and correlating peptidase activity in rodents. *Peptides*. 2005 Jul;26(7):1270-7.
107. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020 Feb 24;12(1):8.
108. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med*. 12 March 2020.
109. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv*. 2020.01.26.919985.
110. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCoV infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv*. 2020.01.30.927806.
111. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv*. 2020.02.03.931766.
112. Huang J, Lin H, Wu Y, Fang Y, Kumar R, Chen G, et al. COVID-19 in post-transplantation patients- report of two cases. *Am J Transplant*. 3 April 2020.
113. Zhu L, Xu X, Ma K, Yang J, Guan H, Chen S, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant*. 17 March 2020.
114. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020 Feb 15;395(10223):514-23.
115. Wang J, Li X, Cao G, Wu X, Wang Z, Yan T. COVID-19 in a Kidney Transplant Patient. *Eur Urol*. 6 April 2020.
116. Marx D, Moulin B, Fafi-Kremer S, Benotmane I, Gautier G, Perrin P, et al. First case of COVID-19 in a kidney transplant recipient treated with belatacept. *Am J Transplant*. 13 April 2020.
117. Zhang H, Chen Y, Yuan Q, Xia QX, Zeng XP, Peng JT, et al. Identification of Kidney Transplant Recipients with Coronavirus Disease 2019. *Eur Urol*. 2 April 2020.
118. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int*. 2020. Jun; 97(6): 1076–1082.
119. Huang JF, Zheng KI, George J, Gao HN, Wei RN, Yan HD, et al. Fatal outcome in a liver transplant recipient with COVID-19. *Am J Transplant*. 10 April 2020.
120. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 9 April 2020.
121. Bin L, Yangzhong W, Yuanyuan Z, Huibo S, Fanjun Z, Zhishui C. Successful Treatment of Severe COVID-19 Pneumonia in a Liver Transplant Recipient. *Am J Transplant*. 3 April 2020.
122. Farfour E, Picard C, Beaumont L, Lesprit P, Ballester M-C, Ackermann F, et al. COVID-19 in lung-transplanted and cystic fibrosis patients: Be careful. *J Cyst Fibros*. 2020;19(3):e16-e7.
123. Varma A, Kosuri S, Ustun C, Ibrahim U, Moreira J, Bishop MR, et al. COVID-19 infection in hematopoietic cell transplantation: age, time from transplant and steroids matter. *Leukemia*. 2020/10/01;34(10):2809-12.
124. Kumar D, Tellier R, Draker R, Levy G, Humar A. Severe Acute Respiratory Syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening. *Am J Transplant*. 2003 Aug;3(8):977-81.
125. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? *Am J Transplant*. 20 March 2020.
126. Coll E, Fernández-Ruiz M, Sánchez-Álvarez JE, Martínez-Fernández JR, Crespo M, Gayoso J, et al. COVID-19 in transplant recipients: The Spanish experience. *American Journal of Transplantation*. 23 October 2020. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.16369>
127. Scandiatransplant. COVID-19 status in Scandiatransplant 2020 [cited 27/11/2020]. Available from: <http://www.scandiatransplant.org/data/covid-19-status-in-scandiatransplant>
128. Cai X, Ren M, Chen F, Li L, Lei H, Wang X. Blood transfusion during the COVID-19 outbreak. *Blood Transfus*. 2020 Mar;18(2):79-82.
129. Fan BE, Ong KH, Chan SSW, Young BE, Chong VCL, Chen SPC, et al. Blood and blood product use during COVID-19 infection. *American Journal of Hematology*. 2020;95(7):E158-E60.
130. Berzuini A, Bianco C, Paccapelo C, Bertolini F, Gregato G, Cattaneo A, et al. Red cell-bound antibodies and transfusion requirements in hospitalized patients with COVID-19. *Blood*. 2020 Aug 6;136(6):766-8.

131. Velázquez-Kennedy K, Luna A, Sánchez-Tornero A, Jiménez-Chillón C, Jiménez-Martín A, Vallés Carboneras A, et al. Transfusion support in COVID-19 patients: Impact on hospital blood component supply during the outbreak. *Transfusion Clinique et Biologique*. 17 October 2020.
132. Stanworth SJ, New HV, Apelseth TO, Brunskill S, Cardigan R, Doree C, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. *The Lancet Haematology*. 2020;7(10):e756-e64.
133. Wang Y, Han W, Pan L, Wang C, Liu Y, Hu W, et al. Impact of COVID-19 on blood centres in Zhejiang province China. *Vox Sang*. 2020 Aug;115(6):502-6.
134. Masser BM, Hyde MK, Ferguson E. Exploring predictors of Australian community members' blood donation intentions and blood donation-related behavior during the COVID-19 pandemic. *Transfusion*. 9 Sep 2020.
135. Angelico R, Trapani S, Manzia TM, Lombardini L, Tisone G, Cardillo M. The COVID-19 outbreak in Italy: initial implications for organ transplantation programs. *Am J Transplant*. 3 April 2020.
136. Parekh M, Ferrari S, Romano V, Myerscough J, Jones GLA, Griffoni C, et al. Impact of COVID-19 on corneal donation and distribution. *European Journal of Ophthalmology*. 2020:1120672120948746.
137. Trigaux C, Salla S, Schroeter J, Tourtas T, Thomasen H, Maier P, et al. SARS-CoV-2: Impact on, Risk Assessment and Countermeasures in German Eye Banks. *Current Eye Research*. 2020:1-6.
138. Toro MD, Brézin AP, Burdon M, Cummings AB, Evren Kemer O, Malyugin BE, et al. Early impact of COVID-19 outbreak on eye care: Insights from EUROCOVCAT group. *European Journal of Ophthalmology*. 2020:1120672120960339.
139. Thuret G, Courrier E, Poinard S, Gain P, Baud'Huin M, Martinache I, et al. One threat, different answers: the impact of COVID-19 pandemic on cornea donation and donor selection across Europe. *British Journal of Ophthalmology*. 2020:bjophthalmol-2020-317938.
140. Guha C, Tong A, Baumgart A, Scholes-Robertson N, Isbel N, Kanellis J, et al. Suspension and resumption of kidney transplant programmes during the COVID-19 pandemic: perspectives from patients, caregivers and potential living donors – a qualitative study. *Transplant International*. 2020;33(11):1481-90.
141. Manara AR, Mumford L, Callaghan CJ, Ravanan R, Gardiner D. Donation and transplantation activity in the UK during the COVID-19 lockdown. *Lancet*. 2020 Aug 15;396(10249):465-6.
142. Spanish National Transplant Organization. COVID-19: Impact on donation and transplant activity. 2020 [22/04/2020]. Available from: http://www.ont.es/infesp/Paginas/Impacto_tx.aspx
143. Domínguez-Gil B, Fernández-Ruiz M, Hernández D, Crespo M, Colmenero J, Coll E, et al. Organ donation and transplantation during the COVID-19 pandemic: a summary of the Spanish experience. *Transplantation*. 5 November 2020. Available from: <https://europepmc.org/article/med/33165237>
144. Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. *The Lancet*. 2020;395(10237):e95-e6.
145. Chadban SJ, McDonald M, Wyburn K, Opdam H, Barry L, Coates PT. Significant impact of COVID-19 on organ donation and transplantation in a low-prevalence country: Australia. *Kidney Int*. 2020 Dec; 98(6): 1616–1618.
146. Group EC-W, Vermeulen N, Ata B, Gianaroli L, Lundin K, Mocanu E, et al. A picture of medically assisted reproduction activities during the COVID-19 pandemic in Europe. *Hum Reprod Open*. 2020(3). Available from: <http://europepmc.org/article/MED/32821857>
147. Brooks SK, Dunn R, Amlôt R, Rubin GJ, Greenberg N. Protecting the psychological wellbeing of staff exposed to disaster or emergency at work: a qualitative study. *BMC Psychol*. 2019 Dec 10;7(1):78.
148. European Commission. COVID-19 and Substances of Human Origin. Cross-Border shipments of SoHO as essential goods and services. Note for the attention of national competent authorities [18/04/2020]. Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2020_soho_crossborder shipments_en.pdf
149. European Centre for Disease Prevention and Control. Disinfection of environments in healthcare and non-healthcare settings potentially contaminated with SARS-CoV-2. [cited 15/11/2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Environmental-persistence-of-SARS-CoV-2-virus-Options-for-cleaning2020-03-26_0.pdf
150. World Health Organization. Recommendation to Member States to improve hand hygiene practices widely to help prevent the transmission of the COVID-19. [cited 15/11/2020]. Available from: <https://www.who.int/docs/default-source/inaugural-who-partners-forum/who-interim-recommendation-on-obligatory-hand-hygiene-against-transmission-of-covid-19.pdf>
151. World Health Organization. Guide to Local Production: WHO-recommended Handrub Formulations [cited 15/11/2020]. Available from: https://www.who.int/gpsc/5may/Guide_to_Local_Production.pdf?ua=1
152. European Society of Human Reproduction and Embryology. Safe ART services during the third phase of the COVID-19 pandemic. Guidance from the ESHRE COVID-19 Working Group [cited 31/10/2020]. Available from: https://www.eshre.eu/-/media/sitecore-files/Guidelines/COVID19/ESHRE-guidance_Safe-ART-services-during-the-third-phase-of-the-COVID19-pandemic.pdf?la=en&hash=2CB99F64F1D017FE441FE47BC6CA9BC66F729E5D
153. Adiga SK, Tholeti P, Uppangala S, Kalthur G, Gualtieri R, Talevi R. Fertility preservation during the COVID-19 pandemic: mitigating the viral contamination risk to reproductive cells in cryostorage. *Reprod Biomed Online*. 2020:S1472-6483(20)30518-6.

154. European Centre for Disease Prevention and Control. Infection prevention and control and preparedness for COVID-19 in healthcare settings. Fifth update – 6 October 2020 [cited 31/10/2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Infection-prevention-and-control-in-healthcare-settings-COVID-19_5th_update.pdf
155. Ljungman P, Styczynski J, Mikulska M, de la Camara R. Coronavirus disease COVID-19: EBMT recommendations Version 11. 2 November 2020. [cited 22/11/2020]. Available from: <https://www.ebmt.org/covid-19-and-bmt>
156. World Health Organization. Advice on the use of masks the community, during home care and in healthcare settings in the context of the novel coronavirus (2019-nCoV) outbreak. Available from: [https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-\(2019-ncov\)-outbreak](https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak)
157. European Centre for Disease Prevention and Control. Interim guidance for environmental cleaning in non-healthcare facilities exposed to SARS-CoV-2. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/coronavirus-SARS-CoV-2-guidance-environmental-cleaning-non-healthcare-facilities.pdf>
158. European Commission. Communication from the Commission. Guidelines on COVID-19 in vitro diagnostic tests and their performance 2020 [17/04/2020]. Available from: https://ec.europa.eu/info/sites/info/files/testing_kits_communication.pdf
159. World Health Organization. Guidance for conducting a country COVID-19 intra-action review (IAR). WHO: Geneva; 2020 [cited 31/10/2020]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Country_IAR-2020.1
160. European Centre for Disease Prevention and Control. Conducting in-action and after-action reviews of the public health response to COVID-19 [cited 31/10/2020]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/In-Action-and-After-Action-Reviews-of-the-public-health-response-to-COVID-19.pdf>