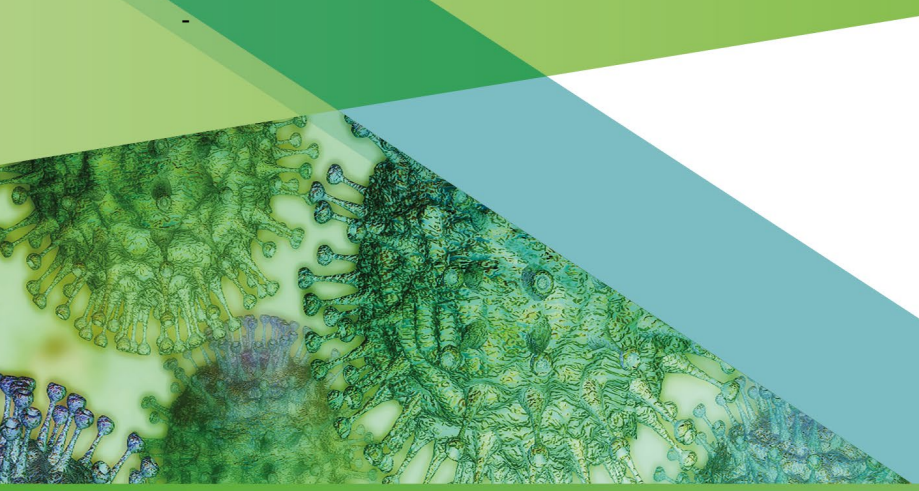

April 2020

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

Scope of the document

This first update of the original document is prompted by the recent scientific developments and evolution of the coronavirus 2019 (COVID-19) pandemic and the need to include types of substances of human origin (SoHO) that were not addressed in the first version (e.g. reproductive and some non-reproductive tissues and cells). The document aims to provide a risk assessment and management options for the safe and sustainable supply of SoHO to assist the European Union and European Economic Area (EU/EEA) Member States in responding to the threat posed by the COVID-19 pandemic. Following the rapid spread of COVID-19 in the EU/EEA and worldwide, the European Centre for Disease Prevention and Control (ECDC) has been publishing rapid risk assessments and setting out measures on how to maintain the safety and sustainability of SoHO supply [1-4]. These documents have also advocated the activation of pandemic plans to prepare for large outbreaks and community transmission of COVID-19. The first version of this document and the current update also consider the current evidence available on other viral respiratory pathogens, mainly the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), the Middle East Respiratory Syndrome-related coronavirus (MERS-CoV), and seasonal or pandemic influenza viruses [5]. ECDC will update the document as and when new relevant information becomes available, or as required by the epidemiological situation.

Target institutions

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

Definitions

Substances of human origin (SoHO) include human blood, blood components, tissues, reproductive and non-reproductive cells and organs, as defined in EU/EEA Directives [6-8], and all of these substances when they are used as starting materials for the manufacture of medicinal products. In the context of the COVID-19 pandemic emergency and for this document, the following prioritisation is applied:

- blood and blood components, organs and haematopoietic stem cells are considered to be '**critical SoHO**', as there are usually no alternative therapies, they are often life-saving and there are limited possibilities for storage;
- plasma for the manufacturing of medicinal products and tissues for life-saving transplantation (e.g. heart valves, skin, etc. in some cases) are considered to be '**essential SoHO',** as they can be stored; and
- other types of cells and tissues used to enhance the quality of life are considered to be '**common SoHO**'.

To safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures possible need to be taken in order to maintain the supply of safe and high-quality SoHO.

In this document, the term 'SoHO establishment' refers to blood and tissue establishments, organ, tissue and cell procurement organisations and transplant centres, as defined in the EU/EEA directives [6-8].

Background

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, the capital of Hubei province, China. This highly contagious disease is currently spreading across the world and throughout EU/EEA Member States, with a daily increase in the number of affected countries, confirmed cases and infection-related deaths. Updated data are published daily on the ECDC and World Health Organization (WHO) websites [9,10].

On 30 January 2020, WHO declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (PHEIC) [11]. On 11 March 2020, based on the high levels of global spread and the severity of COVID-19, WHO's Director-General declared the COVID-19 outbreak a pandemic [12].

COVID-19 is an acute respiratory disease caused by a newly emerged zoonotic coronavirus. A positive-sense enveloped single-stranded RNA virus, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), was isolated from a patient with pneumonia and connected to the cluster of acute respiratory illness cases from Wuhan. Genetic analysis has revealed that it is closely related to SARS-CoV and genetically clusters within the genus *Betacoronavirus*, subgenus *Sarbecovirus* [13].

Detailed information about 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 [9,14] and is regularly updated in ECDC's rapid risk assessment [15].

Laboratory testing

The recommended diagnostic test method for SARS-CoV-2 infection is viral RNA detection with nucleic acid amplification tests (NAT), such as a real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) [16]. Testing specimens to be collected from symptomatic patients and contacts are listed in WHO's laboratory guidance [16]. When necessary, results can be confirmed by genome sequencing. The European Commission working document on the current performance of COVID-19 test methods and devices and proposed performance criteria recommend using RT-PCR tests that follow one of the WHO protocols [20]. Although the project group working on the document has identified 78 CE-marked RNA detection tests for which manufacturers have claimed good performance, WHO has only shortlisted three molecular detection assays through the Emergency Use Listing Procedure (EUL) and the Foundation for Innovative New Diagnostics (FIND) has provided validation results for another five assays [18,19]. The project group concluded that 13 antigen detection tests are CE-marked but that information on their performance in scientific literature is scarce. In addition, the group identified 101 CE-marked SARS-CoV-2 antibody tests for which good sensitivity and specificity are claimed by manufacturers although this is not validated by third parties. Once validated, commercial antibody tests will be essential for assessing the seroepidemiological profile of a population and the immune status of first-line responders or healthcare personnel, and for guiding infection prevention and control (IPC) measures. Preliminary reports on the use of enzyme-linked immunosorbent assays (ELISA) have shown a good correlation of antibody titration results with virus-neutralising antibodies [21,22]. In general, specimen handling for molecular testing requires BSL-2 or equivalent facilities. Attempts to culture the virus require BSL-3 facilities as a minimum. Laboratories performing diagnostic testing for COVID-19 should follow national guidelines on laboratory biosafety which need to comply with WHO biosafety guidance for COVID-19 [23]. Laboratory testing data are regularly updated in ECDC's rapid risk assessments [15].

Immunity

Current data show that IgM and IgG antibodies to SARS-CoV-2 develop between 6–15 days after disease onset [21,24-28]. However, we do not know whether the detected antibodies indicate that the person has acquired protective immunity against the disease, or how long this immunity will last. Longitudinal serological studies that follow patients' immunity over an extended period will provide the relevant information.

Prophylaxis and treatment options

While several potential COVID-19 vaccines are under development, the European Medicines Agency (EMA) expects that it may take at least one year before a vaccine is approved and available for widespread use [29].

Medical treatment for COVID-19 is symptomatic. Moderate to severely ill patients require supportive care and sometimes oxygen supplementation. At present, no medicine has demonstrated itself to be effective in the treatment of COVID-19. Pharmaceuticals are undergoing clinical trials to assess their safety and efficacy as potential treatments for COVID-19 and include the antiviral nucleotide analogue remdesivir; systemic interferons (in particular interferon β-1a); the antiviral combination lopinavir/ritonavir; the antimalarial chloroquine/hydroxychloroquine and monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) and IL-4 [29]. The potential treatments must be carefully assessed in randomised controlled trials (RCTs). EMA has published recommendations on compassionate use of the investigational antiviral agent

remdesivir [30] and on clinical trials or emergency programmes for the use of chloroquine/hydroxychloroquine [31]. Systemic use of steroids for COVID-19 pneumonia is not recommended because they might increase the viral replication and shedding of the virus, along with other steroid-related side effects [32].

Convalescent plasma (plasma of patients recovered from COVID-19 which contains specific anti-SARS-CoV-2 antibodies) is under investigation for the treatment of patients with COVID-19. Despite some study limitations, the improved outcomes in recipients of convalescent plasma obtained in two recent small studies in China [33,34] support investigating this therapy further in adequately designed clinical trials. Blood services and academic hospitals in several EU countries and the USA [35,36] have reported activities for collection and transfusion of convalescent plasma [37]. The EU Commission, in cooperation with ECDC, national competent authorities for blood safety and national blood establishments, has published an EU programme of COVID-19 convalescent plasma collection and supply [36]. It aims to launch a coordinated and effective approach to the collection of convalescent plasma across the EU, supporting the possible treatment of seriously ill patients within observational studies or randomised clinical trials and case-controls studies and, in the longer term, the development of immune globulin concentrates by industry. The programme includes the development and hosting of a database to monitor convalescent plasma donation and use. The database will be developed and hosted by the European Commission (DG DIGIT), in compliance with Regulations 2016/679 and 2018/17/25 and will be designed in collaboration with the European Blood Alliance (EBA).

COVID-19 pandemic and SoHO

Maintaining a safe, sufficient and accessible SoHO supply during a pandemic is vital for public health. It is therefore critical that SoHO establishments recognise the potential impact of the pandemic on the safe and sufficient supply of SoHO and adequately respond to ensure the maintenance of core services.

In assessing the risk posed by the COVID-19 pandemic to SoHO supply, it is necessary to consider the extent of geographical spread, level of community circulation and local epidemiology of COVID-19 in parallel with the given public health response and healthcare system capacities of the country in question [38]. Taking into account the above-mentioned considerations, we identified the following risks to SoHO posed by the COVID-19 pandemic:

- risk to the viral safety of SoHO
- risk to SoHO recipients
- risk to staff in SoHO establishments,
- risk affecting sufficiency and sustainability of SoHO supply.

Risk to the viral safety of SoHO

Although SARS-CoV-2 is transmitted from human to human via respiratory droplets, the potential presence of the virus in the blood and bodily fluids, cells, tissues and organs may be considered a threat to the viral safety of SoHO.

Blood and blood components

Respiratory viruses generally attach to receptors in the airways (except adenoviruses [39]) and therefore the feasibility of blood-borne transmission of respiratory viruses is unknown. Furthermore, the cell-entry molecules for SARS-CoV-2, the human angiotensin-converting enzyme 2 (hACE 2) receptors, are not detected in red blood cells, and are absent or present in very limited amounts in immunocytes and lymphatic cells [40]. This implies that SARS-COV-2 infection of blood cells is unlikely.

Limited data have shown low levels of viral RNA detected in plasma or serum from some COVID-19 symptomatic patients. SARS-CoV-2 RNA was detected in six of 41 patients (15%) [41] and one of six patients (15%) in China but only in one of 12 patients (8%) in the study from Singapore [42]. Another study from China, on PCR laboratory testing of different types of clinical specimens from COVID-19 patients, reported only three PCR positive samples (1%) out of 307 blood samples [43]. The results of PCR testing of serum samples in six viraemic patients suggest a very low viral load in specimens [41]. Viral RNA has also been detected in the urine of symptomatic patients [44].

Cases of asymptomatic COVID-19 have been reported [39-42], although their proportion among all infected persons remains unknown. Pre-symptomatic transmission may occur 1–3 days before the source patient develops symptoms [47].

Four SARS-CoV-2 RNA-positive blood donations from asymptomatic donors were detected during a routine and retrospective laboratory screening in Wuhan Blood Centre, China [45]. While two donors were asymptomatic at the time and after donation, another two developed symptoms after donation. One of the donations was discarded. The transfusion history of the other three donations is missing. At the time of donation, donors tested negative for specific IgG and IgM against SARS-CoV-2 by ELISA. Since the RNA-positive results have not been confirmed by another reliable PCR test, or tested for the presence of infectious SARS-CoV-2 virions, it is unclear whether this occurrence of SARS-CoV-2 RNA-positive donations from asymptomatic and pre-symptomatic blood donors also

implies the possibility of COVID-19 transmission via transfusion. Data from Germany on a small sample of patients showed that no SARS-CoV-2 genome could be detected in the blood of asymptomatic patients or patients with less pronounced symptoms. Virus genome was only found in the serum of a seriously ill patient. Therefore, the authors concluded that the risk of SARS-CoV-2 transmission through blood components in asymptomatic SARS-CoV-2 infected individuals seems negligible, but further studies are needed [46].

As of the time of this update, cases of transfusion-transmitted COVID-19 or other respiratory viruses (including SARS-CoV and MERS-CoV and other coronaviruses) have not been reported.

Cells and tissues

The risk assessment of COVID-19 transmission through cells and tissues is based on the possible presence of the virus in particular cells, the distribution of such infected cells in the tissues and organs, and possible viraemia of vascularised tissues.

The absence of hACE2 receptors in immune cells in all haemato-lymphoid organs suggests that direct viral infection of haematopoietic stem cells (HSC) and cord blood is unlikely [41]. However, since SARS-CoV-2 RNA has been detected in blood [41-43,45] and there are uncertainties about the vertical transmission of COVID-19 from mother to child, the risk of the SARS-CoV-2 being present in HSC and cord blood donated by infected asymptomatic donors cannot be excluded.

The presence of SARS-CoV-2 RNA has been detected and the virus isolated in tears and conjunctival secretions of patients with COVID-19 [47-49]. In a study from China, one-third of 38 COVID-19 patients had conjunctivitis, including conjunctival hyperaemia, chemosis, epiphora, or increased secretions. However, only two of the patients with conjunctivitis were positive for the presence of SARS-CoV-2 RNA from both conjunctival and nasopharyngeal swabs [48]. This indicates the possibility of ocular transmission of the disease through contact with infected secretions or transplantation of ocular tissues donated by an infected donor. Corneal transplants are usually disinfected with PVP iodine (before removal and often before preparation of the tissue bank) and then stored in organ culture at ~ 30–37° degrees for at least 14 days [50]. The presence of viruses capable of reproduction after this procedure seems very unlikely. These data and the absence of known ocular transmission cases indicate that the risk of COVID-19 cases entering the eye donor pool and subsequent transmission is theoretical.

As of the time of this update, there were no reports of sexual transmission of COVID-19. No published evidence supports the presence or transmission of SARS-CoV-2 via sperm or oocytes. It is assumed that the virus cannot infect gametes because they lack hACE2 receptors, the cell-entry points for the virus. These receptors are expressed only in the testicular Leydig and Sertoli cells [51,52] and in ovary cells [53]. Whether hACE2 is present in spermatozoids and oocytes is unclear. The repeated washing steps required for the culture and freezing of gametes and embryos will result in high dilution of any possible secondary contaminations in the IVF laboratory [54].

Clinical manifestations of COVID-19 in pregnant women range from asymptomatic to mild symptoms, sometimes with atypical findings such as leucocytosis and higher prevalence of consolidation lesions in the computed tomography (CT) images [55-57]. There are reports of pregnant women being admitted to ICUs [58].To our knowledge, only two maternal deaths due to acute respiratory distress syndrome (ARDS) have been reported [59]. Overall, it seems that pregnancy and delivery do not aggravate the severity and maternal outcomes of COVID-19 pneumonia.

A recent study on 38 neonates delivered by women with COVID-19 showed no SARS-CoV-2 infection in the neonates; even though some of the neonates had perinatal complications with SARS-CoV-2 positive placenta [60,61] . Reports of perinatal transmission of COIVID-19 are emerging [62-64]. Although neonatal cases of COVID-19 have been confirmed [64-66] and IgM and IgG antibodies against the virus have been detected in three new-borns [67,68], more evidence is necessary to support the possibility of vertical transmission of COVID-19 infection from mother to child [62,69].

Organs

The organs that have a high expression of hACE2 receptors are the lungs, heart and kidneys [70-73]. High hACE2 expression was identified in type II alveolar cells (AT2) of lung [74,75], oesophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon [75], cholangiocytes [76], myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [70]. These findings indicate that organs with high hACE2-expressing cells should be considered as a potentially high risk for SARS-CoV-2 infection [70]. Nevertheless, donor-derived COVID-19 in solid organ transplant recipients has not been reported.

Based on current knowledge of hACE2 distribution in human cells, the absence of evidence for infectivity of SARS-CoV-2 RNA detectable in blood or serum and a lack of reports of transfusion and transplantation-transmitted cases, the risk of COVID-19 transmission through SoHO appears to remain theoretical. Routine donor screening should prevent individuals with clinically manifest respiratory infections, including COVID-19, from donating SoHO. However, uncertainties surrounding viraemia during the incubation period, during an asymptomatic course of infection, or after symptom resolution continues to be of concern in relation to the viral safety of SoHO.

Risk to SoHO recipients

During a pandemic, SoHO recipients are at increased risk of being infected and developing severe illness after exposure to the virus in the community or hospitals. Donor-derived COVID-19 in transplanted or transfused patients has not been reported yet. 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 [77-83], liver [84-86] or haematopoietic stem cell (HSC) [77] transplant recipients. Preliminary data collected by the European Society of Blood and Marrow Transplantation (EBMT) among 34 allogeneic and 10 autologous HSC transplant patients show that early mortality (at about two weeks after diagnosis) was approximately 20% in allogeneic HSC transplant recipients and 10% in autologous HSC transplant recipients (Webinar EBMT-ASTCT 15 April 2020). Deaths have previously been reported in a liver transplant recipient with SARS-CoV infection and two renal transplant recipients with MERS-CoV infection [87,88]. A SARS case has been reported in a recipient of an allogeneic bone marrow transplant for acute myeloid leukaemia [89]. Due to immunosuppression, transplant recipients may have increased and prolonged shedding of virus, thus potentially increasing the risk of transmission to contacts, including healthcare workers [87]. Solid-organ transplant recipients may present atypical COVID-19 symptoms, starting with gastrointestinal signs and fever, which then progresses to respiratory symptoms [90]. Current data show that organ and HSC transplant recipients are a high-risk population for infection with SARS-CoV-2 that may affect their morbidity and mortality. The risk of non-immunosuppressed recipients of blood, cell and tissues seems to be same as for other patients in hospital care.

The management of COVID-19 in the post-transplant setting presents complex challenges, emphasising the importance of strict prevention strategies. In these high-risk populations, protocols for screening for SARS-CoV-2 may need to be re-evaluated.

Risk to staff in SoHO establishments

In SoHO establishments, organ procurement organisations and transplant centres, employees may be exposed to SARS-CoV-2 via close contact with other staff members, touching contaminated surfaces, and during the donation/transplant process through contacts with living donors, deceased donors and potential recipients (and their relatives), and with 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 this update, SoHO establishments have not reported any such cases. Although it seems that that such a route of transmission is not very likely, responsible management and employees should not neglect these risks.

Risk to sufficiency and sustainability of SoHO supply

The nature of COVID-19 transmission, the extensive spread and experience from previous outbreaks of other respiratory viruses, including SARS-CoV and MERS-CoV [92-94], indicate that the COVID-19 pandemic may pose a significant risk to maintaining a sufficient and sustainable supply of SoHO. COVID-19 may affect both donor and recipient populations, SoHO establishment staff and demand or supply of SoHO, and critical materials and equipment. Blood supply is particularly vulnerable as it requires daily frequent blood donations, and labile blood components have limited storage time and are generally irreplaceable. Due to the inherent complexity and individualised donor/recipient approach, the transplantation of solid organs and HSC is also sensitive to the impact of the pandemic on the organisation, coordination and control of all crucial activities and services at local, regional, national and international level. During the pandemic, a decrease in the availability of donors and staff may have an impact on the donation of plasma for fractionation which is a precious biological resource used as a raw material to manufacture essential, life-saving, plasma-derived medicinal products (PDMPs), including clotting factors, albumin, and immunoglobulins. The main factors that may have an impact on the sufficiency and sustainability of SoHO supply are listed below.

Temporary loss of donors

Living donors may be unable to donate because they have COVID-19, are in isolation, are self-isolating after contact with a confirmed case of COVID-19 or are practising physical distancing. Other factors that may play a role are restrictions placed on public transportation, work commitments, the need to care for family members, or a reluctance to donate due to fear of being infected. COVID-19-specific donor selection criteria may also contribute to the decrease of donors, although to a lesser extent. During the peak of the 2003 SARS epidemic in Singapore, a decrease of 60% was seen in donors coming forward to donate blood [93]. Since the start of the COVID-19 pandemic, several countries across Europe have experienced a drop in the number of blood donations. So far, there have been no reports of serious disruptions in the supply of blood or blood components in the EU/EEA Member States. In March, the UK experienced a 15% decrease in the weekly number of blood donations at

national level [95]. Italy had a regional drop in Lombardy and other heavily affected regions. These shortages have been largely mitigated by a drop in demand due to the cancellation of elective operations and increased/adapted donor recruitment activities. The latest data show that there has been a decrease in the number of donors of plasma for manufacturing medicinal products. This drop may have an impact on the supply of PDMPs later this year. A restriction in the number of ICU beds available for both donors and transplant recipients may unfavourably influence overall donation activity, and eventually lead to a reduced number of transplants. 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 [96]. During the first five weeks of the pandemic, Spain reported a decrease in organ donation and transplantation by 85% [97].

Temporary SoHO establishment staff absence

It is anticipated that absenteeism among staff working in SoHO establishments during the COVID-19 pandemic will be higher than normal. 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. The magnitude of absenteeism will depend on the local extent of the COVID-19 outbreak. Published employee absenteeism rates estimated during an influenza pandemic have ranged from 10 to 40 per cent [98]. According to a media report quoting the Scottish government, at the beginning of April 2020 more than 14% of NHS Scotland staff were off work. About 41% of those absences were related COVID-19 (https://www.bbc.com/news/uk-scotland-52133634).

Clinical demand for SoHO

The hospital response to the COVID-19 outbreak should include the following two goals: to facilitate the care of patients with known or suspected COVID-19, and to reduce the risk of intra-hospital viral transmission to healthcare workers and other patients. These measures may reduce demand for some essential SoHO due to a probable reduction in elective healthcare and the postponing of non-essential SoHO therapies. Implementation of patient blood management (PBM), a thorough evaluation of the appropriateness of blood component requests and a reduction in elective surgery/healthcare with medium-high consumption of blood components is strongly advisable.

Supply of critical material and equipment

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 disrupted production. This may also affect 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 those that are 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

Transportation and travel limitations may disrupt 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 [4] within the country and internationally. 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 [99].

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. With the increased spread of COVID-19 and 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 should be as proportionate as possible to the evolution of the pandemic in real time and consistent with governmental and public health advice. Authorities should pay special attention to mitigating the risk of COVID-19 in transplant recipients. As some countries are starting to gradually ease measures to contain the COVID-19 epidemic, it is crucial that SoHO establishments, remain vigilant and keep precautionary measures in force until the pandemic is declared over.

Mitigation of risks to the safety of SoHO

Measures to prevent the theoretical risk of COVID-19 transmission through SoHO are precautionary. The measures set out below can be implemented by SoHO establishments and plasma collection centres.

Blood, blood components and plasma for manufacturing of medicinal products

Donor information

Blood establishments and plasma collection centres should inform blood and plasma donors of the nature and clinical signs of COVID-19, transmission risks and related donation restrictions, as this will help them make decisions on self-deferral from a donation.

Donor selection

Standard donor selection procedures involving the taking of medical and behavioural history and a physical examination should focus on possible exposure and travel as well as clinical signs of acute respiratory infection.

Pre-selection measures

- Contacting donors by telephone to schedule donation and to inform about the selection procedure
- Considering the triage of donors at reception, including measurement of body temperature
- Temporary deferral of donors with a body temperature of 37.5°C or above and counselling to act in accordance with the national public health recommendations for COVID-19.

Donor selection criteria

- Donors with confirmed COVID-19 are not eligible for blood or plasma donation.
- Donors possibly exposed to SARS-CoV-2 may donate blood or plasma at least 14 days after the last contact with a confirmed case of COVID-19 or after returning from a country with sustained COVID-19 transmission.
- Donors who have recovered from confirmed COVID-19 may donate blood/plasma at least 14 days after laboratory evidence of viral RNA clearance from the upper respiratory tract or at least 28 days after symptom resolution.

Pre-selection measures are intended to regulate the donor flow at the collection 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.

Post-donation information and haemovigilance reporting

Blood establishments should also encourage donors to provide information on their health (including respiratory infection) by telephone or other means of communication within 14 days of donation.

Quarantine of blood and blood components with delayed release

In the event of widespread and sustained transmission of COVID-19, one option is a quarantine of blood components, with a delayed release once the donor has confirmed an absence of subsequent illness. However, due to the disruption of existing processes and workflows, this may lead to an increase in the number of errors. Therefore, this approach is not recommended.

Temporary interruption or rescheduling of donations

Introducing a temporary interruption in donations in areas with sustained transmission may affect the sustainability of essential blood supply. Therefore, blood establishments and plasma donation centres should accommodate their donation activities to ensure the blood supply to hospitals and plasma for fractionation. In order to maintain blood supply in areas with sustained transmission, consideration may be given to the sourcing of essential blood and blood components from non-affected parts of the country, or from other countries, if feasible.

Derogation of mandatory donor selection criteria

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

Laboratory screening

There is no licensed test for the screening of donated blood or plasma for the presence of the SARS-CoV-2 RNA. Screening is currently not recommended because transfusion-transmitted COVID-19 has not been reported; levels of detected RNA in plasma coinciding with clinical symptoms are very low [41] and a screening policy has not been implemented for other viral respiratory illnesses for which transfusion transmission remains theoretical, including influenza.

Pathogen reduction

Several coronaviruses are susceptible to inactivation with amotosalen or riboflavin and ultraviolet light, solvent-detergent, methylene blue and light, and ultraviolet C light alone when applied to platelets and fresh frozen plasma [100-103]. A recent study shows that a method using riboflavin and ultraviolet light may reduce SARS-CoV-2 in plasma and platelets below the limit of detection in tissue culture [104]. Therefore, those blood establishments

which 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 outweighed 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].

Large-size lipid-enveloped RNA viruses such as SARS-CoV-2 [106] should be removed and/or inactivated during the manufacturing of plasma derivatives [107-109], as has been demonstrated for other lipid-enveloped model viruses [110]. Thus, regular screening procedures for plasma donors showing clinical symptoms and the established processes of virus inactivation and removal during manufacturing should mitigate COVID-19 transmission through plasma derivatives. Therefore, the COVID-19 outbreak is not considered to be a threat to the safety of plasma protein therapies applying established fractionation and virus inactivating methods.

Non-reproductive cells and tissues

Donor interview

A trained interviewer should inform the potential living donor of cells and tissues of the nature and clinical signs of COVID-19, transmission risks and related donation restrictions.

Donor selection

Standard donor selection procedures involving the taking of medical and behavioural history and a physical examination should focus on possible exposure and travel as well as clinical signs of acute respiratory infection.

Donor selection criteria

Living donation

- Living donors with active confirmed COVID-19 are not eligible for donation.
- Living donors possibly exposed to SARS-CoV-2 may donate cells and tissues at least 14 days after the last contact with a confirmed case of COVID-19 or after returning from a country with sustained COVID-19 transmission.
- Living donors recovering from confirmed COVID-19 may donate cells and tissues at least 14 days after laboratory evidence of viral RNA clearance from the upper respiratory tract or 28 days after symptom resolution.
- Donors of HSC recovering from or possibly 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 the viral RNA in the upper respiratory tract.
- Cryopreservation of HSC or provision of an alternative donor as back-up are strongly recommended in situations where there is an increased risk that a donor would become unavailable at the time of planned transplantation due to community-acquired COVID-19, travel restrictions or logistical difficulties at a transplant centre. If the use of non-frozen HSC is planned, a potential donor must be tested for the presence of the viral RNA in the upper respiratory tract prior to starting the mobilisation procedure [111].

Deceased donation

- Deceased donors with active confirmed COVID-19 at the time of death are not eligible for tissue donation.
- Deceased donors who have recovered from COVID-19 may donate tissues if they tested negative for the presence of SARS-CoV-2 RNA in upper respiratory tract specimens at least 14 days before death or if they became asymptomatic at least 28 days before death.
- Tissues should not be collected from deceased donors who are without symptoms or diagnosis of COVID-19, and who have lived in or visited areas of sustained community transmission of the virus unless:
  - procured tissues are disinfected, sterilised or microbially inactivated using a procedure validated for enveloped viruses, or
  - donors tested negative for the presence of SARS-CoV-2 RNA in upper or lower respiratory tract specimens collected within 72 hours before procurement.

Post-donation information and biovigilance reporting

Tissue establishments should encourage living donors to provide information on their health (including respiratory infection) by telephone or other means of communication within 14 days of donation.

Temporary interruption or rescheduling of donations

Given the stringent community isolation and quarantine measures, a tissue establishment may consider a temporary suspension of cells and tissues donations that are intended for non-urgent transplantation and thus can be postponed.

Pathogen reduction

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 SARS-CoV-2 in tissues.

Reproductive cells and tissues and medically assisted reproduction

Non-partner sperm and oocyte donation

Donor information and selection

Collection centres should inform donors about the nature and clinical signs of COVID-19, transmission risks and related donation restrictions. Standard donor selection procedures involving the taking of medical and behavioural history and a physical examination should focus on possible exposure and travel, as well as clinical signs of acute respiratory infection.

Donor selection criteria

- Donors with active confirmed COVID-19 are not eligible for donation.
- Donors possibly exposed to SARS-CoV-2 may donate sperm or oocytes at least 14 days after the last contact with a confirmed case of COVID-19 or after returning from a country with sustained COVID-19 transmission.
- Donors who have recovered from confirmed COVID-19 may donate sperm or oocytes at least 14 days after laboratory evidence for viral RNA clearance from the upper respiratory tract or at least 28 days after symptom resolution.

Assisted reproduction technologies

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 necessary cryopreservation of gametes, embryos or tissue in cases of urgent fertility preservation in oncology patients and performing elective oocyte or embryo freezing for later embryo transfer for those patients having started assisted reproduction treatment [54].

Given the current stabilisation of the pandemic, ESHRE recommends restarting all ART treatments for any clinical indication. Centres planning to restart ART treatments should follow the ESHRE guidance on recommencing ART treatments [112].

Solid organs for transplantation

Transplantation information

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

Living donation

- Living donors with active COVID-19 are not eligible for organ donation.
- Living donors possibly exposed to SARS-CoV-2 may donate organs at least 14 days after the last contact with a confirmed case of COVID-19 or after returning from a country with sustained COVID-19 transmission.
- Living donors who have recovered from confirmed COVID-19 may donate organs at least 14 days after laboratory evidence for viral RNA clearance from the upper respiratory tract or at least 28 days after symptom resolution.
- If organ transplant procedure cannot be delayed, the donor's nasopharyngeal swab specimens should be tested for the presence of the viral RNA no longer than seven days before the donation.

Deceased donation

- Deceased donors with active COVID-19 at the time of death are not eligible for organ donation.
- Deceased donors who are without symptoms or diagnosis of COVID-19, and who have lived in or visited areas of sustained community transmission may donate organs if they tested negative for the presence of SARS-CoV-2 RNA in upper or lower respiratory tract specimens collected within 72 hours before organ procurement.
- Deceased donors who have recovered from COVID-19 may donate tissues if they tested negative for the presence of SARS-CoV-2 RNA in upper respiratory tract specimens at least 14 days before death or if they became asymptomatic at least 28 days before death.

Temporary interruption or rescheduling of donations

During very high local COVID-19 transmission, temporary suspension of elective living donor transplantation or deceased donation may need to be considered to protect the potential donor as well as the recipient.

Mitigation of risks to transplant recipients

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. Due to immunosuppression, it is probable that transplant recipients are at increased risk of serious COVID-19. 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.

Experience with previous coronavirus epidemics has shown that organ and HSC transplantation authorities should develop measures for the management of organ recipients with COVID-19. These measures 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 national and international transportation of organs and other 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.

Mitigation of risks to 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 [113,114]. 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. Infection control practices and measures should be in line with the national public health recommendations for COVID-19 [115]. 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, such as covering the donor's oral and nasal cavities and using a face shield or protection glasses, respiratory protection masks (FFP3) and double gloves, can be adopted to prevent exposure to possible droplets produced when handling the procurement in 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 blood samples should be in line with laboratory biosafety guidance for COVID-19 [116]. 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.

Mitigation of risks to an adequate and sustained supply of SoHO

The impact of the COVID-19 pandemic is likely to be significant for SoHO establishments and will potentially affect the SoHO supply chain. It is therefore important that SoHO safety authorities and establishments update or develop and activate contingency (preparedness) plans and define actions that must be executed before, during and after the outbreak in order to maintain the sustainability of supply. The main objective is to make every effort to ensure a continued supply of safe, high-quality, life-saving products and services at the level demanded by the healthcare community.

In order to respond to the risk posed by the COVID-19 pandemic to maintaining a sufficient and sustainable supply of SoHO and in accordance with previously suggested principles [117], EU/EEA Member States are encouraged to undertake the measures set out below.

- Assess the risk posed by COVID-19 to the safety and sufficiency of SOHO supply, taking into account the extent and epidemiology of COVID-19 spread, public health measures implemented, status of SoHO supply and operational costs.
- Ensure the inclusion of the SoHO national competent authorities and/or SoHO establishment representatives in the national COVID-19 outbreak contingency planning body. This will ensure that:
  - SoHO contingency planning will be included in and compatible with the national plan and also that communications to citizens clarify that regular blood and plasma donation are essential activities that are still permitted even though physical distancing rules and recommendations may apply;

  - national policies and guidance prioritise the supply of personal protective equipment, such as facemasks and gloves, for SoHO collection facilities and SoHO establishments, in the same way as for hospitals;
  - national border controls facilitate the passage of critical and essential SoHO.
- Establish a mechanism for the SoHO national competent authorities and establishments to receive regular, up-to-date epidemiological information on the spread of COVID-19 in the country and abroad. Daily outbreak situation updates are available on ECDC's website.
- Develop national/regional contingency plans for blood, cells, tissue and organ supplies which are reviewed and updated constantly, in relation to the following areas:
  - risk of transmission of COVID-19 by SoHO which remains theoretical but cannot be completely excluded;
  - temporary loss of donors resulting in a reduced supply;
  - temporary loss of staff due to COVID-19;
  - changes in the clinical demand for SoHO;
  - working with national health authorities, hospitals and other responsible bodies to determine and monitor expected blood, plasma-derived medicinal products, cells and tissues, and organ usage during the COVID-19 outbreak and to plan donation activities accordingly;
  - changes in the local and general epidemiological situation in the country.
- Support SoHO establishments and plasma collection centres in developing and implementing business continuity plans related to the COVID-19 outbreak. This may include activities to:
  - activate the business continuity plan and set up a business continuity management team representing the key functions and decision-makers in accordance with national requirements;
  - implement measures to reduce transmission of COVID-19 among employees, customers/clients, and partners;
  - make operational changes at blood, cell, tissue and organ donation sites (adapt the type of blood donation sessions to the local situation, use an appointment strategy in communicating with donors, extend the opening hours, etc.;
  - increase the collection of plasma for manufacturing in Europe to mitigate the risk of mid- and long-term PDMP supply interruptions caused by the COVID-19 pandemic;
  - maintain critical operations and services by reviewing stocks of critical supplies and increase supplies where possible. Regularly check with contingency partners to ensure that they can fulfil their commitments;
  - communicate regularly with staff so that they feel assured that the situation is being managed and inform them as the situation changes. Staff should be clearly informed about procedures after direct contact with a staff member, donor or patient who has tested positive for COVID-19, as well as the need for self-isolation and physical distancing.
- Continue with the 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.

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