

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

Scope of the document

This document aims to provide a risk assessment and management options for the safe and sustainable supply of substances of human origin (SoHO) to assist the European Union and European Economic Area (EU/EEA) Member States in responding to the threat posed by the coronavirus disease 2019 (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 published a set of rapid risk assessments and set out measures on how to maintain the safety and sustainability of SoHO supply. It has also been advocating for EU/EEA Member States to activate pandemic plans to prepare for large outbreaks and community transmission of COVID-19 [1-3].

This document is based on current knowledge concerning COVID-19 and 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 [4]. 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 procurement organisations and transplant centres in the EU/EEA.

Background

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, the capital of Hubei province, China. While the outbreak in China is almost over, 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 on a daily basis on the ECDC, US Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) websites [5-7].

On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (PHEIC) [8]. Based on the high levels of global spread and the severity of COVID-19, on 11 March 2020, the Director-General of the WHO declared the COVID-19 outbreak a pandemic [9].

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), has been 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* [10].

The virus is transmitted from human to human via droplets coughed or exhaled by infected persons and by touching droplet-contaminated surfaces or objects and then touching the eyes, nose or mouth [4,5]. The most commonly reported clinical symptom in laboratory-confirmed cases is fever (88%), followed by a dry cough (68%), fatigue (38%), sputum production (33%), dyspnoea (19%), sore throat (14%), headache (14%) and myalgia or arthralgia (15%) [11]. Less common symptoms are diarrhoea (4%) and vomiting (5%). Around 80% of the reported cases in China had mild-to-moderate disease (including non-pneumonia and pneumonia cases), 13.8% had severe disease and 6.1% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure) [12-14].

Cases of asymptomatic virus infection have also been reported [15-19]. Based on data from China, the international WHO mission report indicates that up to 75% of initially asymptomatic cases will progress to clinical disease, making true asymptomatic infection rather rare [11]. Modelling estimations of pre-symptomatic transmission have been reported to be between 48% and 62% [20]. Major uncertainties remain in assessing the influence of pre-symptomatic transmission on the overall transmission dynamics of the pandemic.

Population groups that have been more frequently reported as having severe disease and a higher mortality rate include people aged over 60 years, males, people with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer [21-23]. Pregnant women appear to experience similar clinical manifestations to non-pregnant adult patients with COVID-19 pneumonia. There is no evidence of severe adverse outcomes in neonates due to maternal COVID-19 pneumonia, and the virus has not been found in breastmilk [12,24]. Information currently available indicates that children are as likely to be infected as adults, and they mainly experience mild clinical manifestations [5,25]. Robust estimates of the final case fatality risk for COVID-19 are still lacking and biased due to incomplete outcome data and the fact that only severe cases were detected during the initial phase of the outbreak. In data on diagnosed COVID-19 cases in China, Italy and South Korea, the overall case-fatality rate (CFR) was 2.3%, 2.8% and 0.5%, respectively. This increased with age in all settings, with the highest CFR among people over 80 years of age (14.8%, 8.2% and 3.7%, respectively).

Current estimates suggest a median incubation period of five to six days for COVID-19, with a range of one to 14 days [26-28]. The majority (97.5%) of those with clinically manifest COVID-19 will develop symptoms within 11.5 days (CI 8.2 to 15.6 days) of infection [28]. The viral RNA has been identified in respiratory tract specimens [29], faeces, whole blood [30], serum [14,31] saliva [32] and urine [33] of symptomatic patients. COVID-19 patients with conjunctivitis had detectable viral RNA in tears and conjunctival secretions [34]. Chen et al. detected SARS-CoV-2 RNA in the blood of six out of 57 Chinese patients and found that RNAemia was associated with a more severe clinical course [35]. To our knowledge, data on the presence or absence of the infectious virus in blood, plasma or serum have not been reported.

Estimates of all of the above parameters will probably be revised and refined as more information becomes available. Data on the COVID-19 pandemic are being regularly updated in ECDC's rapid risk assessment.

Disease-specific pharmaceuticals and vaccine are still under research and development. The therapeutic use of convalescent plasma donated by patients recovered from COVID-19 might play a role in the efforts to find a possible treatment for COVID-19.

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 [36-38], and all of these substances when they are used as starting materials for the manufacture of medicinal products.

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 the context of the COVID-19 pandemic emergency and for the purposes of 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 manufacture of medicinal products and tissues for lifesaving transplantation (e.g. heart valves, skin, etc. in some cases) and plasma for fractionation 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**'.

This document relates to the safe and adequate supply of critical and essential SoHO.

In this document, the term 'SoHO establishment' refers to blood and tissue establishments, organ procurement organisations and transplant centres, as defined in the EU/EEA directives [36-38].

COVID-19 pandemic and 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 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.

Risks posed by COVID-19 to SoHO safety

Although SARS-CoV-2 virus is transmitted from human to human via droplets, uncertainties about the presence of the virus in the blood and bodily fluids of an asymptomatic SoHO donor may be considered a potential threat to the viral safety of SoHO. Available data show that:

- All respiratory viruses normally attach to receptors in the airways (with the exception of adenoviruses [39]) and therefore the feasibility of blood-borne transmission of respiratory viruses is unknown.
- A low level of viraemia has been detected in some symptomatic patients. Limited data have shown that viral RNA could be detected in plasma or serum of COVID-19 patients. Viraemia was detected in six of 41 patients (15%) [14] and one of six patients (15%) in China but only in one of 12 patients (8%) in the study from Singapore [30]. 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 [40]. The results of PCR testing of serum samples in six viraemic patients suggests a very low viral load in specimens [14]. Viral RNA has also been detected in the urine of symptomatic patients [33].
- Viraemia in the incubation period, asymptomatic course of infection and after symptom resolution has not been documented.
- The transmission of respiratory viruses (including SARS-CoV and MERS-CoV and other coronaviruses) by transfusion or transplantation has not been reported. Vertical transmission of SARS-CoV-2 has not been detected, although perinatal transmission was suspected in one case [12,41].
- Routine donor screening measures should prevent individuals with clinically manifest infections from donating SoHO.
- Large-size lipid-enveloped RNA viruses such as SARS-CoV-2 [6] should be removed and/or inactivated during the manufacturing of plasma derivatives [42-44], as has been demonstrated for other lipid-enveloped model viruses [45]. 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 a threat to the safety of plasma protein therapies applying established fractionation methods.

Based on current knowledge, the risk of COVID-19 transmission through SoHO appears to be theoretical. However, uncertainties surrounding viraemia during the incubation period, during an asymptomatic course of infection, or after symptom resolution continue to be of concern in relation to the viral safety of SoHO. Therefore, precautionary measures are suggested to mitigate the theoretical risk.

Risks posed by COVID-19 to transplant recipients

COVID-19 has not been described in organ or haematopoietic stem cell (HSC) transplant recipients. However, a fatal case of a liver transplant recipient with SARS-CoV infection and two renal transplant recipients with MERS-CoV infection have been reported [46,47]. 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 as super-spreaders [46]. A SARS case has been reported in a recipient of an allogeneic bone marrow transplant for acute myeloid leukaemia [48]. In hospital settings, the immunosuppressed transplant recipient may be exposed to the SARS-CoV-2 which increases the risk of being infected or developing severe illness. It is anticipated that COVID-19 may increase mortality in transplant recipients.

Risks posed by COVID-19 to the sufficiency and sustainability of SoHO supply

The nature of COVID-19 transmission, extensive spread and experiences from previous outbreaks of other respiratory viruses including SARS-CoV and MERS-CoV [49-51] 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 population, SoHO establishment staff and demand or supply of SoHO, 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 in general irreplaceable. Due to the inherent complexity and individualised donor/recipient approach, the transplantation of solid organs and haematopoietic stem cells (HSCs) is also sensitive to the impact of the pandemic on the organisation, co-ordination 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 of having COVID-19, being in isolation, self-isolating after contact with a confirmed case of COVID-19 or practising social distancing. Other factors which 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, although to a lesser extent. During the peak of the SARS epidemic in Singapore, a decrease of 60% was seen in donors coming forward to donate blood [50].

Temporary SoHO establishment staff absence

It is anticipated that absenteeism among staff working in SoHO establishments during a COVID-19 outbreak will be higher than routine daily absenteeism. Absence from work increases during epidemics or pandemics for a variety of reasons. Staff may not be able to come to work because of transportation restrictions, community measures, illness, isolation or 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 percent [52-54].

Clinical demand of 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 cell and tissue therapies. Implementation of patient blood management (PBM), 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 because of travel restrictions, quarantine requirements, border control measures and disrupted production. This may also decrease 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 use (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.

Mitigation measures

Until more information is available on the epidemiology and pathogenesis of COVID-19, SoHO safety authorities in the EU/EEA countries should consider precautionary actions to mitigate the potential risks to the microbial 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 focus and prioritise their efforts on managing 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.

Measures to mitigate risks posed by COVID-19 to 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.

Donor information

SoHO donors should be informed about the nature and clinical signs of COVID-19, transmission risks and related donation restrictions as this will help them take decisions on self-deferral from donation.

Donor selection

- Donors diagnosed with confirmed COVID-19 are not eligible for the donation of any type of SoHO.
- Donors recovering from confirmed COVID-19 should be deferred from donation for at least 14 days after symptom resolution and negative results of repeated testing.
- Donors of blood, cells and tissues should be deferred for at least 14 days after the last contact with a confirmed case of COVID-19 or returning from a country with sustained COVID-19 transmission.
- Living organ and HSC donors should defer from donation for at least 14 days after last contact with a person having confirmed COVID-19 or returning from a country with sustained COVID-19 transmission. 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 donation.
- Deceased donors who were infected with COVID-19 are not eligible for organ donation.
- Deceased donors without symptoms or diagnosis of COVID-19 in an area with sustained transmission should be tested for the presence of SARS-CoV-2 in the bronchoalveolar lavage (BAL) specimens collected 72 hours before organ procurement.
- Donors should preferably be called to schedule donation in order to regulate donor flow and provide them with information about triage measures.
- Promote triage at donor reception, including the measurement of body temperature. It is suggested that a temperature of 37.5 °C should act as a criterion for temporary donor deferral.

The deferral period of 14 days after last contact with a person having a confirmed diagnosis of COVID-19 or returning from an area with sustained COVID-19 transmission is based on the double median incubation period of six days.

The activation of donor triage is designed both to avoid the possible spread of the virus in waiting rooms and to help with donor pre-selection.

Post-donation information and haemovigilance/biovigilance reporting

SoHO 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. In the course of national haemovigilance/biovigilance activities, particular attention should be paid to the potentially adverse effects of transfusion and transplantation associated with infection transmission.

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 delayed release in the absence of a subsequent illness reported in the donor. 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 of donations in areas with sustained transmission may affect the sustainability of essential SoHO supply. Therefore, SoHO establishments and plasma donation centres should accommodate their donation activities to ensure the supply of essential SoHO to hospitals and plasma for fractionation. In order to maintain SoHO supply in areas with sustained transmission, consideration may be given to providing vital blood, cells and tissues 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 being applied to suit the local epidemiological situation and ensure sustainability of blood supply. For this pandemic, derogation of mandatory donor selection criteria is considered unnecessary.

Laboratory screening

There is no licensed test for the screening of blood, plasma for fractionation or cell and tissue donors/donations. Laboratory screening of donors/donations of blood, plasma for the manufacture of medicinal products, and cells and tissues is currently not recommended. This is because transmission of COVID-19 through SoHO has not been reported; levels of detected RNA in plasma coinciding with clinical symptoms are very low [14] and a screening policy has not been implemented for other viral respiratory illnesses for which transfusion transmission remains theoretical, including influenza. Testing of donors and recipients may be considered in organ and HSC transplantation settings.

Pathogen reduction

Several coronaviruses are susceptible to inactivation with amotosalen or riboflavin, ultraviolet light, methylene blue and light, and ultraviolet C light alone when applied to platelets and fresh frozen plasma [55-58]. 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 other known and emerging microbial threats to the safety of plasma and platelets [59]. Viruses may be inactivated during 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 the SARS-CoV-2 in tissues.

Measures to mitigate risks posed by COVID-19 to transplant recipients

Transplant recipients at risk of COVID-19 infection should be tested for the presence of SARS-CoV-2 in the nasopharyngeal swab before proceeding with the transplant procedure.

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; procedures for when the transplant centre is temporarily closed and isolation of recipients if transplanted during a potential incubation period or in an area with sustained community transmission in order 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 with the outbreak and possibilities for transplantation.

Measures to mitigate the risks posed by COVID-19 to an adequate and sustained supply of SoHO

The impact of the COVID-19 pandemic on the SoHO supply is likely to be significant for SoHO establishments and 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 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 sufficiency and sustainability of SoHO supply and in accordance with previously suggested principles [60], 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 cost impact of measures in the country.
- Ensure the inclusion of the SoHO national competent authorities (NCA) 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 social distancing rules and recommendations may apply;
 - national policies and guidance prioritise the supply of personal protective equipment, such as face masks 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 NCAs 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 and tissue 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. 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 and use personal protective equipment in accordance with national public health guidelines [61,62]. 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 [63]. In the event of an individual staff member developing acute respiratory illness, the person should leave the work place, self-isolate at home and immediately seek care, preferably first by phone, in

- accordance with 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. The 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 [64].
- 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 (BCP) related to the COVID-19 outbreak. This may include activities to:
 - Activate the BCP and set up a Business Continuity Management Team (BCMT) 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. Change how staff are deployed (i.e. arrangements in offices/laboratories, cease non-essential meetings, minimise gatherings of staff, have meetings by teleconference even when in the same building, review catering arrangements and stagger staff dining, consider splitting shifts in the laboratories, especially where there is no external contingency in place with no crossover to minimise the risk of passing on the virus, have as many of the critical staff work from home as is possible, retrain staff to provide extra cover, bring back recently retired staff if necessary to fill essential roles, cease non-essential travel etc.)
 - Make operational changes at blood, cell and tissue donations sites (adapt the type of blood donation sessions to local situation, use an appointment strategy in communicating with donors, etc.)
 - 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 who has tested positive for COVID-19, as well as the need for self-isolation and social distancing.
 - Regular and effective communication between SoHO establishments, NCA, national health authorities, ECDC and the European Commission is essential for facilitating 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 (RAB) and Rapid Alert Tissues and Cells (RATC) platforms may be used for communication between NCAs, the European Commission and ECDC in order to share data on measures implemented and difficulties with supply.

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