SACTTI position statement of SARS-CoV-2/COVID-19 and the safety of blood, tissues and stem cells

Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a recently emerged coronavirus, a pathogen of the respiratory tract, the spread of which has resulted in a global pandemic. Although the virus has been officially named as SARS-CoV-2 by the International Committee on the Taxonomy of Viruses (ICTV), the World Health Organization (WHO) has named the disease caused by the virus as COVID-19. It is important that this distinction is understood.

SARS-CoV-2 transmission is by the respiratory route during close unprotected contact between infected and uninfected individuals, primarily through droplet contact with infected secretions, directly or on surfaces.

Although coronaviruses are usually found in the upper and lower respiratory tract, at some point during infection virus may be found in the bloodstream. There are now data on the presence of both SARS-CoV-2 nucleic acid and, what are assumed to be, virus particles in the bloodstream (viraemia) of symptomatic individuals. However, there are limited data available regarding the presence of viable virus in blood, bodily fluids and various tissues and organs; to date virus has not been cultured from blood samples taken from laboratory confirmed infected individuals. A recent review of published data estimated that SARS-CoV-2 RNA may be present at low copy numbers in approximately 10% of blood samples obtained from individuals with COVID-19 prior to day 28. In at least one recently published study SARS-CoV-2 RNA was detected in a significant proportion of hospitalised patients, including 100% of patients in ICU, and the levels of SARS-CoV-2 RNA associate with disease severity. SARS-CoV-2 RNA has also been found in a very small percentage asymptomatic blood donors; transfusion transmission has not been reported.

Asymptomatic SARS-CoV-2 infection is an important aspect of virus infection and interaction with its human host which needs to be better understood. Initial data suggested that only a small proportion of cases would be asymptomatic, but more recent ongoing studies, including those looking at the use of antibody testing, suggest that currently a significant percentage of infections are asymptomatic.

Based on precedent, transmission of a respiratory virus by transfusion is very unlikely to result in an infection in the transfused patient; nonetheless, SARS-CoV-2 is a new human agent and the possibility of transmission has to be considered. It is important that blood donor deferrals, and the deferral of donors of other donated products, to ensure safety are balanced with any negative impact on the ability to maintain a sufficient

supplies of blood and the other donated products, and that actions taken are proportionate to the level of potential risk.

Infection and viral persistence

Current estimates suggest a median incubation period from five to six days for SARS-CoV-2, with a range from one to up to 14 days. Comparisons with the two previous major coronavirus outbreaks (SARS from 2002 - 2004; MERS from 2007 and ongoing) have shown very similar incubation period distributions (3-10 days for SARS-CoV-1 and up to 14 days for MERS-CoV).

Virus can initially be detected in upper respiratory samples 1-2 days prior to symptom onset, demonstrating the potential for transmission from infected individuals who are not displaying any symptoms, or in whom the symptoms are so mild and non-specific to not be noticed. The viral load profile of SARS-CoV-2 appears to be similar to that of influenza, peaking around the time of symptom onset. This is different to both SARS-CoV and MERS-CoV which peak at around 10 and 14 days respectively, after onset of symptoms. Testing of upper respiratory tract swabs for SARS-CoV-2 RNA using molecular techniques (reverse transcription polymerase chain reaction [RT-PCR]) has found persistence of viral RNA for 28 days post symptom clearance in moderate cases and for longer periods in more severe cases. However, infectivity decreases after 7 days and the detection of non-infectious virus genomes for several months has been shown for other viruses.

Most laboratory investigations are based on the use of RT-PCR to detect viral RNA in upper respiratory swabs. As well as the respiratory tract, viral RNA has been found in whole blood, serum, plasma, saliva, urine, semen and faeces; however, the presence of viral RNA does not necessarily equate with infectivity, and to date only viral nucleic acid, not infectious virus, has been found in blood.

SARS-CoV-2/COVID-19 disease

Symptoms of SARS-CoV-2 infection are most commonly: cough, fever, loss or reduced sense of smell and taste, dyspnoea and tiredness, but other symptoms may occur, and include sputum production, headache, haemoptysis and diarrhoea. Clinical features include pneumonia, acute respiratory distress syndrome, acute cardiac and renal injury.

Most infected individuals experience no apparent or only mild symptoms, with recovery in 7 days. However, in other infected individuals, symptoms are more severe and life-threatening, with hospitalisation needed. In general, more severe symptoms and outcomes are associated with a range of pre-existing chronic conditions. Increasing age, male gender and ethnicity also appear to be associated with more severe

outcomes. Case fatality rate increases with severity of symptoms, the time from onset of symptoms to death can be as long as 41 days, but in most cases is around 14 days.

Blood phase and potential for transmission through blood, tissues and stem cells

At the time of publication of this Position Statement, there have not been any reports of the transmission of any respiratory virus via blood, tissues or stem cells, although the identification of such infections would be difficult in a pandemic situation when there is ongoing transmission in the community and within healthcare environments. Limited data from the very few published case reports suggest that asymptomatic blood donors do not transmit SARS-CoV-2 to recipients, however, it is acknowledged that SARS-CoV-2 is a recent human infection and that evidence regarding the risk through transfusion and/or transplantation is limited. *Well powered studies are needed to further evaluate the rate of detection of viral nucleic acids in donors, the viability of any virus detected in the blood of blood, tissue or cell donors and the potential risk of transmission via transfusion/transplantation. In the US many thousands of donations have been screened for SARS-CoV-2 RNA with very few showing any evidence or RNAaemia, and no infectious virus reported to date. Transfusion transmission studies in macaques, humanised ACE-2 receptor mice and other animal models are currently underway.*

Nonetheless, the presence of SARS-CoV-2 nucleic acid in the bloodstream of some infected individuals does indicate a potential risk, and the need for precautionary measures. Such measures include: the deferral of confirmed SARS-CoV-2 infected individuals until recovered, reminding donors to report post-donation illness, recall of donations from donors subsequently reporting confirmed infection or compatible symptoms and depending on the nature of the donors (e.g. live vs deceased) testing of the donor. In addition, for some tissue types, the processing of the tissue includes steps which may inactivate or physically remove any virus present. However, whilst Blood Services and Tissue Establishments may elect to test respiratory swabs/blood samples from donors of some product types for SARS-CoV-2 RNA it is noted that, at the time of review of this Position Statement, the ECDC have not currently recommended screening of blood or plasma samples for SARS-CoV-2 RNA. It is currently unknown whether SARS-CoV-2 RNA may persist in certain organs and tissues, as well as other body fluids, longer than it is detectable in plasma and serum.

Precautionary measures adopted by UK Blood Services

The UK Donor Selection Guidelines already include information on the identification and deferral of donors with acute infections. These are sufficient to deal with donors who provide information which would suggest recent or ongoing acute infection. It is unlikely that symptomatic live donors would attend to donate, but there is the potential for a live donor who is symptom free, but with virus circulating in the bloodstream, or a deceased donor with mild unidentified symptoms ante-mortem, to donate. Although there are no reports

of the transmission of respiratory virus through blood, tissues and stem cells, precautionary measures have been adopted by the UK Blood Services.

An important issue to be considered in relation to donations which may be stored for some time prior to issue for clinical use, primarily some tissue and stem cell donations, is the timing of the spread of SARS-CoV-2 infection in the UK. The first cases of imported COVID-19 in the UK were identified on 31st January 2020 in two holiday makers from China. The Standing Advisory Committee on Transfusion Transmissible Infections (SACTTI) identified the 28th February 2020 as the date from when the UK is to be considered a country with sustained community transmission of SARS-CoV-2. On this date, the first case of COVID-19 transmitted in the UK was identified. Sequence analysis of UK SARS-CoV-2 samples indicate that China, where the virus originated, had a less than 1% impact on cases in the UK and that 80% of all those who came to the UK and spread the virus arrived between 28 February and 29 March. Therefore, prior to the 28th February 2020, it is reasonable to consider that the majority of UK donors had not been exposed to SARS-CoV-2. UK Blood Services implemented specific measures to identify donors with a risk of carrying SARS-CoV-2, including geographical deferrals, from January 23rd 2020. The UK Blood Services have broadly aligned with the ECDC guidance on coronavirus disease and donation of substances of human origin, updated in December 2020, and the UK Government guidance on minimising transmission across the UK population.

The following measures apply to blood, living tissue and cord blood donors

Illness deferral

- Donors with symptoms and a positive test for SARS-CoV-2 are deferred for 7 days from symptom resolution
- Donors who are asymptomatic but have had a positive test for SARS-CoV-2, if remaining well, are deferred for 10 days since the last positive test was taken
- Donors with COVID-19 symptoms but who have not been tested for SARS-CoV-2 RNA, or who have been tested and are unaware of the result, are deferred for 7 days from symptom resolution
- Donors with upper respiratory tract symptoms but who have a negative SARS-CoV-2 PCR result are deferred until symptoms have resolved
- Donors with upper respiratory tract symptoms but who have a negative SARS-CoV-2 lateral flow test result are deferred for 7 days from symptom resolution

Contact deferral

- Donors who have been in contact with a confirmed or suspected case of COVID-19 are deferred for 10 days from the last day of contact
- Donors who have been in contact with a confirmed or suspected case of COVID-19 may be accepted without deferral if the donor remains well has been advised that:
    - isolation is now complete or not required AND
    - any post-contact testing is complete and negative AND
    - no further testing is required AND
    - the donor remains well and agrees to report any post-donation illness

Additional considerations for living tissue donors and cord blood donors

- Living tissue donors are treated in a similar fashion to blood donors, with no requirement for anything other than the standard donor questioning and deferral. However, as living tissue donors are all hospital inpatients at the time of donation, they are likely to have a respiratory swab taken and tested for SARS-CoV-2 RNA on admission, depending on national and/or local hospital policy applicable at the time of donation
- There will be a cohort of live tissue donors who donated during the early stages of the pandemic where donation proceeded in the absence of swab testing for the virus. As long as the donor has not reported a diagnosis of COVID-19 or symptoms suggestive of COVID-19 in the 2 weeks post-donation the donation can be released for clinical use
- Mothers who donate cord blood or amnion may also have been subject to testing of respiratory swabs for SARS-CoV-2 RNA on hospital admission and post donations history applies in the same way as blood donors
- Due to the severe immune-suppression that is likely in the setting of cord blood transplantation, the cord blood donation itself, depending on updated evidence in the intervening period, could be screened alongside the other screening performed when the donation is selected for use in the future - this may be some years after donation

The following measures apply to deceased tissue donors

Illness deferral

- Donors with symptoms and a positive test for SARS-CoV-2 are deferred for 7 days from symptom resolution
- Donors who are asymptomatic but have had a positive test for SARS-CoV-2, if remaining well, are deferred for 10 days since the last positive test was taken

- Donors with COVID-19 symptoms but who have not been tested for SARS-CoV-2 or who have been tested and are unaware of the result, are deferred for 7 days from symptom resolution
- Donors with upper respiratory tract symptoms but who have been tested and Covid-19 has been ruled out may be accepted

Contact deferral

- Donors who have been in contact with a confirmed or suspected case of COVID-19 are deferred for 10 days from the last day of contact
- Donors who have been in contact with a confirmed or suspected case of COVID-19 may be accepted, subject to individual risk assessment, if the donor remains well

Additional considerations for deceased tissue donors

- The standard donor selection process cannot be applied in the same way with deceased tissue donors. However, these donors going forward are likely to be subject to testing on a respiratory swab for SARS-CoV-2 RNA either on admission to hospital, or as part of the organ donation pathway. All organ donors have been tested for SARS-CoV-2 since 19th March 2020 (including islet donors), and about half of deceased tissue donors are also organ donors. However, a number of donations may have been progressed during the early stages of the pandemic when testing for SARS-CoV-2 RNA would not have been carried out prior to donation
- A number of tissue types undergo processing prior to clinical release. If the processing is considered to be effective in the inactivation of any virus that may be present testing respiratory swabs for SARS-CoV-2 RNA would not be necessary in the case of donors where only such processed products are being donated. However, if the testing of respiratory swabs from any deceased tissue donor for SARS-CoV-2 RNA is readily available, SACTTI considers that this information can be used. In these cases, a positive result is a contraindication for donation
- All deceased donors donating tissue types (e.g. heart valves) which do not undergo processing which would be considered to inactivate any virus present, should, going forward, have a respiratory swab tested for SARS-CoV-2 RNA
- Tissue donations progressed during the early stages of the COVID-19 pandemic where routine testing of deceased donors for SARS-CoV-2 on an upper respiratory tract was not carried out will require a case-by-case assessment and can be released for clinical use if the donor did not have symptoms suggestive of COVID-19

The following measures apply to bone marrow and stem cell donors

Illness deferral

- Donors with confirmed SARS-CoV-2 infection, with or without symptoms, are deferred for 14 days from symptom resolution; if urgent, donation at less than 14 days may be considered after clinical review
- Donors with suspected Covid-19 and who have been tested and advised that they do not have Covid-19 are deferred for 14 days from symptom resolution
- Donors with suspected Covid-19 and who have been tested and advised that they do not have Covid-19 may be accepted less than 14 days from symptom resolution subject to clinical review: if the donor remains well OR the donor has not been tested to exclude the diagnosis of Covid-19

Contact deferral

- Donors who have been in contact with a confirmed or suspected case of COVID-19 are deferred for 10 days from the last day of contact
- Donors who have been in contact with a confirmed or suspected case of COVID-19 may be accepted if less than 10 days since the last day of contact subject to clinical review

Additional considerations for bone marrow and stem cell donors

Stem cell donors are treated differently to blood and tissue donors, primarily because of considered potential increased risk to donors recently recovered from SARS-CoV-2 infection/COVID-19 receiving G-CSF. There is also the potential of increased risk to stem cell recipients if acquiring SARS-CoV-2 infection, because of their heavy immunosuppression.

- Stem cell donors have a respiratory swab taken and tested for SARS-CoV-2 RNA on the day of donation
- For stem cell donations collected in the early stages of the pandemic, before routine testing of stem cell donors for SARS-CoV-2 RNA was put in place, if the donation remains in storage, testing the blood sample taken at the point of donation for the virus would be a sensible approach

Travel deferral (applies to all donors)

Travel deferrals may be required because of any UK testing/self-isolation requirements for individuals arriving in the UK. These are applied in addition to any existing country specific travel related deferrals which may be in place:

- Donors returning to the UK may donate once any post-travel testing has been completed and is negative and/or once any post-ravel isolation has been completed, and the donor remains well

- Donors who are returning to the UK and have been laboratory confirmed to be infected with SARS-CoV-2 or who have COVID-19 symptoms must follow the illness deferral guidelines

An important safety measure which has been used for many years by the UK Blood Services is to ensure that any live donor with symptoms appearing in the 14 days post donation immediately contacts the appropriate Blood Service and reports the symptoms

- All donors are reminded to report any illness arising in the 14 days after donation. This reminder is given at the point of donation, and for blood donors, at every donation. Full details of the symptoms and accurate timings are required. This requirement applies to blood donors, living tissue donors and stem cell/cord blood donors
- All components/donations from donors who are laboratory confirmed infected with SARS-CoV-2 or have clear diagnostic symptoms of COVID-19, within 2 days of donation/harvest, will be recalled/removed from inventory. If the components/ donations have been administered/transplanted, the clinician responsible for the recipient should be informed unless a SARS-CoV-2 RNA test on the day of donation serum/plasma sample is negative. Confirmation of diagnosis should be attempted whenever possible
- It is recommended that the archive sample of the index donation be tested for SARS-CoV-2 RNA

This approach is precautionary, and predicated on the current, albeit limited, data available on duration of RNAaemia in infected individuals; viral load in respiratory tract peaking just prior to the appearance of symptoms and then starting to fall as symptoms appear. RNAaemia has been detected in 1-15% of clinical samples from hospitalised COVID-19 patients and to date has been reported to be associated with more severe symptoms. However, in those individuals in whom viral RNA has been detected, the viral load has been very low.

Retrospective testing (tissues/stem cells)

In the situation where donations have been retrieved/harvested, but not yet released and transplanted, there is the possibility of retrospective testing using the stored plasma archive sample. There are limited data on the presence and significance of viable virus in the bloodstream. It is considered likely that virus will not be present in the majority of cases as most donors are anticipated to be asymptomatic at the point of donation;

- Prior to the 28th February 2020, SACTTI considered that sustained community transmission in the UK was not present. Therefore, it is reasonable to consider that prior to the 28th February 2020 the majority of donors had not been exposed to the virus.

- Although SACTTI suggests that the retrospective testing of any donations collected before that date, and currently stored ready for release, is not mandatory, it acknowledges that individual UK Blood Services may elect to test for SARS-CoV-2 RNA to assist in their risk assessments to mitigate the risk of virus possibly being present in donations collected prior to 28th February 2020.
- For tissues collected from deceased donors after 28th February 2020, SACTTI considers that there are limited data on the presence and significance of virus in the bloodstream and there are no reports to date of transmission of the virus via tissue transplantation. Although, as SARS-CoV-2 is a new human agent and the ACE-2 receptors used by the virus to enter cells are present on certain tissue types, the possibility of transmission has to be considered. The processing applied to some tissue types should inactivate any virus present in those tissues, however, it is noted that processing may not be applied to all types of retrieved tissues e.g. no viricidal processing is applied to heart valve tissue. Individual risk assessment will be required to release non-processed tissues without a negative SARS-CoV-2 respiratory swab test. There are currently no CE-marked SARS-CoV-2 RNA assays for samples collected from deceased donors but if/when such an assay becomes available, individual UK Blood Services may elect to test for SARS-CoV-2 RNA to assist in their risk assessments to mitigate the risk of virus possibly being present in donations where the donor has not been tested for the virus on an upper respiratory swab. The caveat regarding possible persistence of SARS-CoV-2 RNA in tissues/other body fluids longer than it is detectable in plasma and serum applies.
- For stem cells collected after the 28th February 2020, because of the potential consequences of infection in such heavily immunosuppressed individuals, in addition to the pre-donation testing of a respiratory swab for SARS-CoV-2 RNA, SACTTI considers that, if fully validated testing of blood samples becomes available, testing a serum/plasma sample for SARS-CoV-2 RNA may be considered, particularly for any collections still in storage prior to routine respiratory swab testing having been put in place.

Immunisation

Donors having recently received vaccines may require deferral depending on the vaccine administered and the particular vaccination programme. Guidelines already in place defined vaccines on the basis of the nature of the vaccine, i.e. vaccines containing live or attenuated virus and those not containing live agents. However, although the SARS-CoV-2 vaccines in use at in the UK at the time of updating this Position Statement do not contain live material, there are limited data currently available on side-effects and adverse reactions in vaccine recipients.

- After vaccination with attenuated viruses (e.g. virus vector-based or live-attenuated virus vaccines) donors must be deferred for four weeks

- After vaccination with inactivated viruses or vaccines that do not contain live agents, excepting HBV and SARS-CoV-2 vaccines, if well do not require any deferral
- At this time, because of the limited information available and to minimise the impact of post-donation contact from donors who develop symptoms subsequent to a donation taking place soon after vaccination, a precautionary deferral period of 48 hours after the most recent immunisation within the UK coronavirus vaccination programme is advised
- In situations where information about vaccine type is missing, the vaccination is experimental or vaccination was given outside of the UK vaccination programme, a four-week deferral period should be applied and the donor should be well with no ongoing local or systemic reaction to the vaccine

Antibody response to SARS-CoV-2

Although specific SARS-CoV-2 antibody assays are now available, they have limited value in assuring the safety of donations at this stage.

However, the use of plasma from individuals who have recovered from SARS-CoV-2 infection, and who have developed sufficient level of antibody against the virus (convalescent OR immune plasma), is currently under investigation. There are clinical trials underway to determine if the antibody produced is neutralising and can help currently infected individuals to clear the virus more quickly.

Resources

The UK Government provides up to date UK coronavirus data
https://coronavirus.data.gov.uk/

ECDC produces regular situation updates for coronavirus in the EU/EEA
https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea

ECDC has produced guidance on coronavirus and the safety of SoHO, second update December 2020
https://www.ecdc.europa.eu/en/publications-data/coronavirus-disease-2019-covid-19-and-supply-substances-human-origin

WHO has a dedicated section to all aspects of the coronavirus pandemic
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

WHO has produced a document on maintaining a safe blood supply during the pandemic
https://www.who.int/publications-detail/maintaining-a-safe-and-adequate-blood-supply-during-the-pandemic-outbreak-of-coronavirus-disease-(covid-19)

The JPAC Geographical Disease Risk Index (GDRI) is regularly reviewed and updated with appropriate deferrals
https://www.transfusionguidelines.org/dsg/gdri/guidelines