Maintaining a safe and adequate blood supply and collecting convalescent plasma in the context of the COVID-19 pandemic

Interim guidance

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World Health Organization

Key points

- Transmission of SARS-CoV-2 via transfusion of blood and components has not been reported and is currently considered highly unlikely.
- The pandemic has had a negative impact on blood supplies through reduced blood donation and reduced availability of appropriate collection facilities due to operational disruptions.
- Blood services should take steps to avert potential shortages of blood and components.
- Individuals with confirmed COVID-19 or recent contact with a known infected person should be deferred temporarily from donating blood to reduce the risk of respiratory and contact- mediated contagion in blood collection facilities and as a precaution against potential transmission of SARS-CoV-2 through transfusion of blood or components.
- Effective public awareness campaigns on the importance of maintaining an adequate national blood supply, the need for blood donors and safety of the donation process should be disseminated continuously, using different communication platforms to reach all segments of the population.
- There is some evidence for favourable outcomes in patients who have received COVID-19 convalescent plasma, but it is not definitive. WHO recognizes COVID-19 convalescent plasma as an experimental therapy that is appropriate for evaluation in clinical studies or as a starting material for the manufacture of experimental hyper-immune immunoglobulins.

Introduction

This document provides guidance on the management of the blood supply in the context of the COVID-19 pandemic, including recommendations on collection of convalescent plasma. It is intended for:

- blood services, or other bodies directly responsible for the provision of blood and blood components within member states
- national health authorities and NGOs responsible for blood services and their activities
- groups responsible for the collection of SARS-CoV-2 convalescent plasma.

The document provides updates to the interim guidance published on 10 July 2020 (1). Updates include recommendations for deferring donors who have received vaccines against SARS-CoV-2, the virus that causes COVID-19. The document also provides scientific updates on reported experience with experimental use of convalescent plasma, including randomized controlled trials and several uncontrolled case series. Last, it reports on the availability of a newly established international standard reagent for normalization of assays for the binding and neutralizing activity of antibodies to SARS-CoV-2.

WHO will continue to update this guidance as new information becomes available.

Methodology for developing this guidance

This guidance and its recommendations are built on earlier WHO publications, in particular the WHO Guidance for National Blood Services on Protecting the Blood Supply during Infectious Disease Outbreaks (2) and risk assessment publications and practical interim guidance on COVID-19 from WHO, Regional networks and national and international bodies and institutions including the United States Food and Drug Administration, the European Centre for Disease Prevention and Control and the International Society of Blood Transfusion (3,4,5,6). Additionally, emerging literature, country experiences and expert opinions provided by the WHO

Expert Committee for Biological Standardization and the WHO Expert Panel in Transfusion Medicine were evaluated. Consideration also was given to the feasibility for implementation of the recommendations in resource-limited settings. Draft versions of this guidance document were reviewed through expert consultations prior to publication.

General considerations

Extensive literature searches have failed to identify any evidence of transmission of SARS-CoV-2 via transfusion of blood and components, and this risk is therefore currently theoretical and considered highly unlikely. Nevertheless, the current pandemic already has had an impact on blood supplies through reduced blood donation and reduced availability of appropriate collection facilities (7,8,9,10,11). Blood services should therefore take steps to assess, plan, and respond to the challenges appropriately and proportionately after undertaking a data-driven risk assessment.

This assessment should take into consideration:

- the level of transmission in the country or geographical area (12)
- risk of transfusion transmission (13)
- the quality of the health care
- the public health response
- sufficiency of the blood supply
- operational impacts
- cost effectiveness of blood safety interventions in reducing disease morbidity in relation to the overall situation in the country.

Blood services must be prepared to move quickly in response to changes in the pandemic situation. A national approach, rather than a sub-national or local approach, should be adopted for coherence and coordination, but taking into account any specific localised factors or needs. This type of approach will also ensure public confidence in the safety and sufficiency of the blood supply. Coordination and support should be fostered between all stakeholders in the blood system to help maintain blood and blood component availability. Blood services should be included in the national outbreak response through experts linked to the national emergency response team. Blood services should develop, implement and activate their emergency response plans.

Mitigating potential transmission of SARS-CoV-2 to patients through the transfusion of blood and blood components

Individuals with confirmed COVID-19 or recent contact with a known infected person should not be accepted as blood donors, despite a lack of evidence that SARS-CoV-2 is transmitted through blood or blood components. Reports to date indicate that despite detection of viral RNA in some cases, blood components collected from donors in the pre-symptomatic phase of SARS-CoV-2 infection did not transmit the infection (14,15,16,17,18). Therefore, any risk of virus transmission via transfusion of blood collected from asymptomatic individuals is theoretical, and any actions taken to mitigate that risk are precautionary. Testing of the blood supply is premature in the absence of cases of transfusion transmission or demonstrated infectivity of SARS-CoV-2 in blood collected from asymptomatic persons, including persons who are pre-symptomatic.

Considerations for risk mitigation include the following:

- Potential blood donors should be educated about the need to self-defer based on risk factors for SARS-CoV-2 infection or feeling unwell. It is essential to strictly comply with current pre-donation criteria for donor suitability that exclude symptomatic individuals who are unwell or with signs and symptoms of fever and respiratory disease (such as cough or breathlessness). Individuals whose symptoms meet standard definitions for COVID-19 should be deferred and referred for testing and isolation in line with national policies.
- Donors should be advised to inform the blood centre immediately if they develop a respiratory illness or are subsequently confirmed of being infected with SARS-CoV-2 through laboratory testing within 14 days following donation.
- Persons with possible direct exposure to SARS-CoV-2 through close contact with a confirmed case or care of an infected patient, and those who have travelled from areas with high levels of local transmission (e.g., as determined by national policy) (12), should refrain from blood donation for a period defined by a national standard. A minimum deferral period of 14 days (one incubation period) without illness is generally considered adequate to ensure absence of active SARS-CoV-2 infection.
- Persons who have infection with SARS-CoV-2 confirmed by laboratory testing in the absence of symptoms should be deferred for 14 days after the last positive test.
- Persons who have recovered from confirmed COVID-19 should be deferred from routine blood donation for 14 days after full resolution of symptoms and cessation of therapies for their illness.

- Donor deferral may take the form of self-deferral or deferral by the blood collection establishment. In the event of community transmission (12), donor restrictions may need to be modified to fit the local situations so as not to affect availability of blood for critical transfusion therapy.
- One option is to quarantine components and release them only following confirmation that a donor is free of SARS-CoV-2 infection. However, this approach is difficult to implement, disrupts existing processes and delays release of blood into available inventory. Quarantine of platelets is particularly challenging, given their short shelf-life.
- Blood and components collected within 14 days prior to disease onset or a positive virologic test for SARS CoV2 in the donor, or collected within 14 days subsequent to contact exposure, may be recalled as a precautionary measure. Notification of the clinician responsible for a transfusion may be considered if infection in the donor is confirmed.
- Pathogen reduction technologies (PRTs) have been demonstrated to be effective against SARS-CoV-2 in plasma and platelets (19,20) but require significant logistical and financial investment. Introduction of a PRT for SARS-CoV-2 in the absence of evidence for transfusion-transmission would not be cost effective or proportionate and is not recommended in settings where it is not already in practice.
- Current manufacturing processes for plasma derivatives can inactivate and remove enveloped viruses such as SARS-CoV-2. There is thus no presumed risk for transmission through these products.
- A haemovigilance system should be in place to capture any possible cases of transmission through blood and components. Haemovigilance is invaluable for helping to understand the risk from blood and components and the overall effectiveness of the measures taken by the blood service (21).
- The decision whether to implement precautionary measures with their resulting impact on blood sufficiency and operational resources must be carefully considered. Measures introduced during one phase of the pandemic may also become impractical or unsustainable during another phase.

Mitigating the risk of staff and donor exposure to SARS-CoV-2

Transmission from a donor is far more likely to occur through the respiratory route than through parenteral routes (including phlebotomy during blood donation). Strategies taken to mitigate this risk should follow the public health measures taken in the country. Blood donor centres and manufacturing premises are not patient care settings. Therefore, public health measures appropriate to community environments with frequent public contact should be applied and not those specific to medical clinics and hospitals. Measures include screening for COVID-19-related symptoms, social distancing, hand hygiene and use of personal protective equipment (12,22). Providing information to donors and the public about the measures taken will contribute to gaining their confidence in continuing to donate blood (6,9).

The safety of the donation process should be ensured by appropriate protective measures while ensuring proper workflow. Potential donors should be informed about the importance of self-deferral if they are feeling unwell or have COVID-19-related symptoms and about immediately reporting any illness within 14 days after donation to the blood service. Relevant information on websites and other forms of public communication or pre-selection procedures to identify potentially infected donors before entry into the donation area will help exclude individuals who should not donate blood (6,10).If coronavirus infection is suspected or confirmed in a potential blood donor or staff, national public health guidelines should dictate the management of the donor, staff and contacts.

To avoid crowding at the collection centre, efforts should be made to schedule blood donations by appointment and to maintain a minimally sufficient number of staff members (e.g., by reducing overlapping shifts and decreasing movement of staff members between sections of the facility). Minimizing contacts between donors and staff, regular environmental decontamination, temperature measurement at the entrance, providing entering donors with face masks and hand sanitizer and physical distancing should also be considered (7,8,9,10,12,23,24).

Standard laboratory biosafety practices, based on national or international guidelines, should be followed in all circumstances (25). If blood service laboratories provide any pre-transfusion investigations, samples from patients with suspected or confirmed COVID-19 should be handled in accordance with COVID-19 guidance (26).

Staff should be educated about SARS-CoV-2 and COVID-19 and advised not to come to work if they feel ill or may have been exposed. Infection prevention and control measures should be reinforced. During community transmission, staff may be reduced because of illness and national public health measures implemented to mitigate the impact of the pandemic on essential activities (11,12,27).

Temporary deferral of donors after vaccination against SARS-CoV-2

As prudent measures to protect donor health and to avoid the theoretical risk of unintentional transmission of vaccine agents to transfusion recipients the following deferrals are recommended.

- Initial safety data for the currently approved SARS-CoV-2 mRNA vaccines do not suggest any concerns for blood donation (28,29). Also, these liposome encapsulated mRNA vaccines do not contain any live virus, and any risk for use of blood components from recipients of these vaccines is theoretical and likely insignificant.
- Although, consistent with current general global practice, recipients of SARS-CoV-2 vaccines that do not contain live virus may donate blood if they feel well, as SARS-CoV-2 vaccines have been developed only recently, and in settings where deferrals would not compromise blood supply availability, a precautionary deferral period of up to seven days may be considered to minimize the impact of call-backs from donors who develop symptoms subsequent to donating soon after vaccination.
- Recipients of live virus vaccines (e.g., virus vector based or live-attenuated virus vaccines) should be deferred for four weeks, consistent with current practices.
- Persons who feel unwell after receiving a SARS-CoV-2 vaccine should be deferred for seven days after complete resolution of symptoms, or as specified after receipt of a virus vector-based or live-attenuated vaccine, whichever is the longer period.
- In situations where it cannot be established whether the donor received a live virus vaccine, a four-week deferral period should be applied.
- Persons participating in a clinical trial of a live virus vaccine against SARS-CoV-2 should not donate blood for 12 months after receipt of the experimental vaccine unless the vaccine subsequently is authorized or licensed by the relevant regulatory authority
- Persons participating in a clinical trial of a non-live vaccine against SARS-CoV-2 should not donate blood for 28 days after receipt of the experimental vaccine unless the vaccine subsequently is authorized or licensed by the relevant regulatory authority and an alternative policy regarding donor deferral is established by that authority

Although administration of some vaccines requires more than one vaccination, each vaccination should be regarded as an independent event for purposes of blood donor deferral. Where mass vaccinations are anticipated, the blood centre should work closely with local health authorities to minimize any impact this may have on the availability of blood donors.

Mitigating the impact of reduced availability of blood donors

Reduction of donor numbers during the COVID-19 pandemic is a major risk and should be considered early to enable preparedness and response. As these reductions may vary throughout the course of the pandemic, blood donation numbers should be closely monitored so that measures can be taken quickly to pre-empt any decline (8,11). This is particularly critical for components with short shelf life, such as platelets, where a constant supply is needed for patients dependent on platelet transfusions. Cooperation among hospitals and blood collection centres to monitor inventories (10) and to redistribute blood components to prevent wastage may help to balance local supply and demand.

A significant decline in donations occurs when individuals are unwilling to donate because of their fear of being infected during blood donation (7). A clear, proactive and consistent communication strategy is key to addressing and overcoming donor anxiety and fears, which often stem from lack of awareness or misinformation. Communications are most effective when they are part of national emergency response messaging (see below).

Pandemic control strategies may limit the ability of donors to attend donation sessions and prevent blood collection teams from visiting areas where public health restrictions on movement are in place. Mobile blood donation drives and group donations may be reduced due to closure of workplaces, schools and community organizations. Strategies to overcome these impediments include rapid switching of sites for blood collections, providing donor transportation, intensifying efforts to schedule appointments for donations or adjusting operating hours. Blood collection activities may be organized on a more targeted basis through focused (including blood-group specific) retention and recall of healthy repeat donors (7,8,10). Governmental authorities need to identify blood collection as an essential service and provide mechanisms to ensure that blood donors do not get penalized for coming out to donate.

Routine practices for donor management and infectious disease testing should not be changed. However, in the event of extreme blood shortages, changes in certain criteria – such as reduction of whole blood donation intervals for donors with robust haemoglobin levels who are able to tolerate more frequent donations – may be considered.

Systems should be in place to enable re-entry of previously infected and fully recovered donors after a minimum deferral period of 14 days post recovery. A standard deferral period also supports the collection of convalescent plasma at blood donor centres (see below).

Importation of blood and components from less affected areas of the country or a less affected country (if permitted by regulatory authorities) is a potential solution if there are insufficient local stocks; but there are logistical issues with safely transporting blood and components.

Managing the demand for blood and blood products

Blood services should continually assess their blood stocks carefully in anticipation of uncertainty in the scale of collection activities (30). Additionally, they should establish and maintain communication with public health officials charged with oversight of the blood supply so that actions can be taken as appropriate to strengthen the call for volunteer donors and to facilitate movement of available blood inventories to the areas of greatest need.

During community transmission, demand for blood and components may decrease as the health care system shifts towards treating increased numbers of COVID-19 patients, and elective surgeries and non-urgent clinical interventions are deferred. However, blood transfusions will still be necessary for emergency situations such as trauma, post-partum haemorrhage, severe infant anaemia, blood dyscrasias and urgent surgeries requiring blood. Although the rate of blood component utilization is low in the majority of COVID-19 patients, increased stocks may be needed to support COVID-19 patients with severe sepsis or disseminated intravascular coagulation or those requiring extracorporeal membrane oxygenation support (31,32,33,34). Convalescent plasma, now being evaluated as a treatment for COVID-19 in some countries, requires collection of plasma from recovered individuals with required minimum levels of neutralizing antibodies.

Good patient blood management will help safeguard sufficient blood stocks. The blood service must clearly communicate and coordinate with health care professionals responsible for transfusion activities to ensure that blood and components are only used when clinically appropriate (8,11).

Preventing disruption in supplies of critical material and equipment

Transport and trade restrictions, quarantine requirements, border control measures and production disruptions may decrease the global supply chain of critical materials and equipment used in blood and component collection and laboratory testing (including immunohaematology reagents and infectious disease screening assays). The blood service must take steps to ensure continuity of supplies both nationally and across all blood service facilities.

Communications

Public and stakeholder confidence in the blood system is important for maintaining an adequate blood supply. Effective public awareness campaigns on the importance of maintaining an adequate national blood supply, the need for blood donors and safety of the donation process should be disseminated continuously, using different communication platforms to reach all segments of the population (7,8,9,10,11,24). Governmental authorities and the blood service must communicate clearly to ensure that the national emergency response team, donors and recipients, and the public are properly informed and understand planned actions including recognition of blood collection activities as essential services. Messaging and actions should be consistent with overall national emergency response messaging (8,35,36).

Within the blood service, all staff should understand and be prepared to communicate about the actions taken to ensure safety and reliability of the blood supply and the safety of staff and donors.

Considerations for collection of COVID-19 convalescent plasma

Definitive evidence for safety and efficacy of COVID-19 convalescent plasma currently is lacking (37). However, in consideration of the available evidence and pending the outcome of ongoing studies, WHO recognizes COVID-19 convalescent plasma as an experimental therapy that is appropriate for evaluation in clinical studies or as a starting material for the manufacture of experimental hyper-immune immunoglobulins. While some controlled studies have failed to demonstrate a clinical benefit (38,39), reports from a randomized controlled trial and several uncontrolled case series of use of COVID-19 convalescent plasma have suggested favourable patient outcomes (40,41,42). A meta-analysis of multiple clinical studies and retrospective analysis of a large database of protocol driven, but uncontrolled experimental use of COVID-19 convalescent plasma in the United States of America also demonstrated favourable outcomes (44).

Various studies, including one involving treatment of 20 000 patients with COVID-19 convalescent plasma, have reported low rates of serious adverse reactions, that were similar in type and frequency to those seen with non-immune plasma infusions (45). There was also no evidence of antibody-dependent enhancement, a well-recognized effect in other viral illnesses (46,47). Positive historical experience with use of convalescent plasma to treat SARS and pandemic influenza further supports the plausibility of a clinical benefit in COVID-19 (48,49).

Further clinical evidence is needed before guidance can be provided on the clinical use of COVID-19 convalescent plasma. WHO strongly recommends randomized controlled trials as the most effective and efficient strategy to determine the efficacy and safety of this experimental therapy. In settings where randomization of patients is not feasible, structured observational studies linked to

randomized controlled trials can be considered. In this approach, standardized protocols consistent with the active arm of an established randomized controlled trial are used to generate data on the properties of the administered COVID-19 convalescent plasma, the characteristics of treated patients and pre-defined patient outcomes. Where structured clinical studies are also not possible, efforts nevertheless should be made to document patient outcomes and to obtain and archive blood samples from donors and recipients for future scientific study. Data on product preparation and use collected through close cooperation between treating physicians and blood establishments and reported to a central national authority can provide information that complements the findings of randomized controlled trials.

COVID-19 convalescent plasma can be made available on an experimental basis through local production provided that medical, legal and ethical safeguards are in place both for the donors of COVID-19 convalescent plasma and the patients who receive it. Detailed risk assessment must always be conducted to ensure that the blood service has sufficient capability to safely collect, process and store these specific blood components in a quality-assured manner in compliance with established standards and requirements for plasma for transfusion.

The WHO Blood Regulators Network has published a position paper that provides helpful considerations on use of convalescent plasma in an epidemic of an emerging virus (50). Regulatory agencies should enable progress by establishing appropriate conditions for the collection of convalescent plasma, the ethical conduct of clinical studies and the monitoring and reporting of assessable patient outcomes (51).

WHO encourages its international partners to obtain and share information on policies and protocols for studies of COVID-19 convalescent plasma that emerge in different countries and regions. A Cochrane rapid systematic review on the use of COVID-19 convalescent plasma and hyperimmune immunoglobulin provides information on case series and on studies that have been registered in clinical trial websites, and also reinforces the importance of using COVID-19 convalescent plasma in randomized controlled trials (37). Additional information relevant to studies of COVID-19 convalescent plasma can be found at an open access website of the International Society of Blood Transfusion (ISBT). However, WHO has not evaluated the statements or protocols listed at that website.

While no universal protocol exists for collection of COVID- 19 convalescent plasma, criteria for acceptance of donors of COVID-19 convalescent plasma should include:

- overall donor qualification based on standard criteria for blood or plasma donation
- laboratory-confirmed evidence of prior infection with SARS-CoV-2
- complete resolution of symptoms and cessation of treatments for COVID-19 for at least 14 days prior to the donation
- establishment of the minimum neutralizing antibody titre required for plasma to be suitable for use as convalescent plasma
- measurement of the neutralizing antibody titre in the unit of convalescent plasma.

Procedures for convalescent plasma collection

Several assays are available for determining the binding and neutralizing activity of SARS-CoV-2 antibodies, and their results may vary. To reduce inter-assay variation, WHO recommends the use of reference reagents that have been calibrated against the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136) (51,52) to express the assay results in International Units.

In settings where donor selection based on the titre of neutralizing antibodies is not feasible, retention of a blood sample from the convalescent donor for subsequent characterization of antibodies to the virus is strongly recommended. Potential donors may also be tested for presence of antibodies to SARS-CoV-2 in antigen binding assays (e.g., EIA or CLIA). Correlation with antibody neutralization titres is variable among binding assays, but some recently developed immunoassays have demonstrated reliable correlation of high levels of binding activity with neutralization titres (54). Although the WHO International Standard for anti-SARS-CoV-2 immunoglobulin has currently been assigned a value only for neutralizing antibody activity against SARS-CoV-2, work is ongoing to determine the utility of this material in the standardization of antigen binding assays.

Ideally, donations of convalescent plasma should be obtained by plasmapheresis to avoid unnecessary red blood cell loss in the donor and to optimize the volume of plasma that can be collected. Infection control precautions should follow WHO interim guidance on rational use of personal protective equipment, taking into consideration that the donor has fully recovered from COVID-19 (55). Red blood cell concentrates that are prepared as a by-product of preparation of COVID-19 convalescent plasma can be released for transfusion if the donor was asymptomatic for at least 14 days after full recovery from symptoms.

Data elements for reporting of outcomes in patients treated with COVID-19 convalescent plasma should include patient characteristics (e.g. sex, age, co-morbidities); timing of therapy in relation to disease onset; therapies administered, including number, volume and antibody titre of transfused units of COVID-19 convalescent plasma; clinical and laboratory indicators of

disease severity at baseline and at defined subsequent time points; adverse reactions linked to transfusions; and time to hospital discharge or fatality. In settings where donor selection based on the titre of neutralizing antibodies is not feasible, COVID-19 antibodies can be measured and characterized in retained samples of the convalescent plasma units. In post-trial analyses, outcomes from the treatment can be stratified by the dose (volumes and titres) of the units administered to determine the effect of the titre of the convalescent plasma on clinical outcomes.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire two years after the date of publication.

Declarations of interest

The current updates were developed by the following experts and WHO staff member: Dr Jay Epstein (ISBT Working Party for Global Blood Safety), Dr Alan Kitchen (WHO Expert Advisory Panel member for blood transfusion), Dr Yuyun Maryuningsih (Team Lead, Blood and other Products of Human Origin, Health Products Policy and Standards Department, WHO Headquarters, Switzerland), and Dr Diana Teo (Member of WHO Expert Committee on Biological Standardization).

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