

REVIEW ARTICLE

Plasma procurement and plasma product safety in light of the COVID-19 pandemic from the perspective of the plasma industry

Peter L. Turecek¹  | Deborah Hibbett² | Thomas R. Kreil³

¹Plasma-Derived Therapies R&D, Baxalta Innovations GmbH, part of Takeda, Vienna, Austria

²Global Communications and Public Affairs, Takeda Pharmaceutical Company Limited, Zurich, Switzerland

³Global Pathogen Safety, Takeda Manufacturing Austria AG, Vienna, Austria

Correspondence

Peter L. Turecek, Plasma-Derived Therapies R&D, Baxalta Innovations GmbH, part of Takeda, Vienna, Austria.

Email: peter.turecek@takeda.com

Funding information

The work was sponsored by Baxalta Innovations GmbH, part of Takeda.

Abstract

This review, written from the perspective of the plasma industry, discusses plasma procurement and plasma product safety in light of the COVID-19 pandemic. The COVID-19 pandemic impacted the whole world and, therefore, not unexpectedly, the pharmaceutical industry too. In spite of this, the plasma protein industry has continued to provide life saving therapies to critically ill patients. Moreover, companies have collected COVID convalescent plasma (CP) to support development of investigational therapies, for example, hyperimmune globulins to potentially treat SARS-CoV-2 infection, and collaborated with those collecting COVID CP for direct transfusion, which has been made available under emergency use in the United States. For plasma that is fractionated to become a therapy, general knowledge of coronaviruses and numerous new studies on the structure and function of SARS-CoV-2 provide reassurance that existing industry precautions, including donor selection, as well as virus inactivation and removal steps during the manufacturing process are sufficient to maintain the high standards of virus safety of plasma products. The pandemic also revealed the vulnerability and inadequacy of the current plasma ecosystem. There is a need for more plasma to be collected around the world to meet the growing need for safe and efficacious plasma-derived therapies. This requires outdated regulatory and policy restrictions to be realigned with current scientific evidence. More countries around the world should be in a position to contribute to global supply of plasma so that patients with life-threatening conditions - and often no alternative therapeutic solutions - have better access to care.

KEYWORDS

COVID-19, pathogen safety, plasma for fractionation, plasma products, SARS-CoV-2

Highlights

- COVID-19 pandemic reemphasized the need for more plasma to be collected around the world to meet the growing need for safe and efficacious plasma-derived therapies.
- Although SARS-CoV-2 RNA was occasionally detectable in serum samples, the risk of transmission of infectivity by blood and blood products is considered negligible.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 Baxalta Innovations GmbH. Vox Sanguinis published by John Wiley & Sons Ltd on behalf of International Society of Blood Transfusion.

- Standard precautions for donor selection as well as virus inactivation and removal steps during the manufacturing process were sufficient to maintain the high standards of safety of plasma products, even during the COVID-19 pandemic.

INTRODUCTION

The production of plasma products depends on a diligently planned, complex system of willing donors, donation facilities, global manufacturing networks and pharmaceutical product distribution channels, which is largely robust under normal circumstances. However, since the advent of the coronavirus disease pandemic in late 2019 (COVID-19), the situation has been challenged. From early 2020, the pandemic significantly impacted the balanced and well-developed system of plasma procurement in ways not previously experienced, further hindering the industry's ability to keep pace with growing patient demand for these life-changing therapies. Challenges included the disruption of donor networks and blood/plasma donation, as well as supply chain networks, leading to reduced supply of plasma and plasma therapies. Local and global travel and trade restrictions hampered the acquisition of source plasma and reduced the available number of blood donations from which recovered plasma is obtained. In turn, this impacted pharmaceutical manufacturing and distribution by interfering with global supply channels of raw materials and devices, and affected the delivery of final drug products to the patients [1–3]. In parallel, global demand for plasma products has continued to grow across approved indications as a result of broader access in more countries and more patients with rare diseases being diagnosed. The notion that convalescent plasma (CP) and hyper-immune globulin products could be viable treatment options for COVID-19 patients has further increased the demand for plasma [4–6]. Moreover, with only a small percentage of the 3000+ proteins [7] circulating in plasma being used therapeutically today, research is currently under way to unlock the untapped potential in plasma to support treatment for many diseases such as rheumatoid arthritis, sickle cell anaemia and age-related macular degeneration [8–10]. Cumulatively, this is creating additional strain on sourcing this scarce life-changing resource.

In the early 1980s, recipients of biopharmaceuticals derived from human plasma were devastated by widespread infections with the human immunodeficiency virus (HIV) and hepatitis C virus (HCV), which were transmitted through plasma-derived concentrates sourced from virus-carrying donors. Recognition of this serious problem led to major changes in procedures for donor screening and testing and the validation of new process steps embedded into the manufacturing processes of plasma derivatives to remove or inactivate blood contaminants such as viruses and even prion agents [11]. The occurrence of new infectious and transmissible agents always alerts recipients, regulators, prescribers and manufacturers of blood products. This is what happened with SARS-CoV-2: The potential for transmission by transfusion and, therefore, blood derivatives prompted serious considerations towards the safety of blood and plasma products.

In this review, we assess the impact of the COVID-19 pandemic, and particularly the causing pathogenic SARS-CoV-2 on procurement of plasma for fractionation from the plasma industry perspective and focus specifically on sustaining supply of safe and efficacious plasma-derived medicines. Information was collected by literature search in PubMed® (<https://pubmed.ncbi.nlm.nih.gov/>; cut-off date, 10 January 2022), web search and personal communication of the authors who are connected to the specialist network of the plasma industries.

CORONAVIRINAE AND SARS-CoV-2

The severe acute respiratory syndrome (SARS) called COVID-19 is induced by SARS-CoV-2, which belongs to the group of β -coronaviruses. The virus has a single-stranded genome of about 26–32 kb (+ssRNA), which is the largest known genome size of an RNA virus. Coronaviruses belong to the order Nidovirales, family Coronaviridae and the subfamily Coronavirinae, which consists of α -, β -, γ - and δ -coronaviruses [12]. Coronavirus was first isolated from chicken in 1937. Before the SARS outbreak in February 2003, coronavirus was not considered highly pathogenic to humans [13]. Since 2002, three zoonotic outbreaks have been caused by β -coronaviruses: SARS-CoV in 2003 [14], MERS-CoV in 2012 [15] and the latest outbreak of SARS-CoV-2 at the end of 2019 [16]. There is ongoing debate about the origin of SARS-CoV-2 and a final assessment has not been made, but it seems likely that SARS-CoV-2 is a new evolutionary branch of coronaviruses originating from bats [17]. Despite their genomic differences, coronaviruses share a common structure. Human coronaviruses contain phosphorylated nucleocapsid (N) protein with genomic RNA as core enveloped by phospholipid bilayers to form spherical or pleomorphic particles of 80–120 nm size and outer surface-projected spike (S) proteins [18].

SARS-CoV-2 is a respiratory virus and primarily infects the airways. There is no reported evidence for the transmission of respiratory viruses, including the influenza viruses and the coronaviruses responsible for SARS (SARS-CoV) and Middle East respiratory syndrome (MERS) (MERS-CoV), by blood and blood components including plasma and plasma-derived medicinal products (PDMPs) [19–21].

BLOOD AND PLASMA DONATIONS

Testing of blood donations for the absence of infectious agents plays a vital role in providing safe blood for transfusion. Blood services are constantly on alert for the reported detection of emerging pathogens that may impact the safety of the blood supply [22]. When there is a risk that an infectious agent may be transmitted by blood transfusion,

this may trigger the implementation of additional screening of donors and testing of blood donations. The best example in this regard was the introduction of HIV testing in the 1980s. Other examples of potential risks to the safety of the blood supply occurred with the expanded geographic range of pathogens, including the West Nile virus (WNV), Zika virus and babesiosis.

To mitigate the impact of these emerging pathogens on the safety of the blood supply in a timely and effective manner, an effective interaction between all stakeholders, that is, blood services, regulatory authorities, public health institutions and industry, has been established. An example of this was the epidemic occurrence of the WNV, which first appeared in the United States in 1999 and has since spread across the entire country, resulting in thousands of cases of disease. By 2002, it was clear that the virus could be transmitted by blood transfusion, and by the middle of 2003, essentially all blood donations were being tested for WNV [23]. Subsequently, the resulting plasma products like immune globulins were tested for neutralizing antibody titers in plasma-derived intravenous immune globulin released in the United States during 2003–2008. Antibody titers correlated closely with the cumulative incidence of past WNV infection in blood- and plasma donors, with the lots released in 2008 indicating a seroprevalence of 1% [24]. Similarly, upon the occurrence of the corona pandemic, the discussion around testing of blood and blood derivatives for SARS-CoV-2 started early in 2020 [25].

While there was much uncertainty at the beginning of the pandemic, as it had been unclear whether SARS-CoV-2 could be transmitted from those with pre-symptomatic or asymptomatic infection, some tangible data have become available as of now. In May 2020, researchers from China found no evidence of SARS-CoV-2 RNA in the blood of donors in a multi-centre study in the province of Hubei [26]. They examined 98,342 blood donations including 87,095 whole-blood donations and 11,247 platelet donations by individual or minipool testing with the commercially available SARS-CoV-2 real-time RT-PCR assay from PerkinElmer (SYM-BIO LifeScience, Suzhou, China). All donations were negative for SARS-CoV-2 RNA over an observation period of 12 weeks. With a similar set-up, samples from 17,995 minipools of 6 or 16 donations corresponding to approximately 258,000 donations were tested for viral RNA (vRNA) in the United States from March to September 2020 [27]. In this study, a research-use-only transcription-mediated amplification (TMA) assay was used. Reactive results were confirmed using an alternate target region TMA assay. To estimate the viral load of reactive minipools, those were tested by TMA after serial dilution. Additionally, testing for anti-SARS-CoV-2 antibodies and infectivity was performed. Three confirmed reactive minipools from 16 donations were identified, which resulted in an estimated prevalence of vRNA reactive donations of 1.16/100,000 (95% CI 0.40–3.42). The vRNA-reactive samples were non-reactive for antibody. The estimated viral loads of the presumed single positive donations within each minipool ranged from <1000 to <4000 copies/ml. Most importantly though, for all these TMA-positive samples, no infectivity was observed in inoculated permissive cell cultures. At this point, it remains unclear why the study performed in China did not find any vRNA in blood donors while in

the United States, vRNA could be detected in a few minipools. Most relevant, though, is the fact that a positive TMA signal did not predict the presence of infectivity.

Diagnosis of SARS-CoV-2 infections has largely been based on RT-PCR tests from nose or throat swabs resembling the viral load in the upper respiratory tract [28]. However, detection of vRNA has also been reported in blood, serum and plasma [29, 30]. A study in the United Kingdom aimed to determine whether PCR-positive blood samples could pose an infection risk by investigating the frequency and determinants of vRNA detection in blood using 424 samples collected from acutely infected and convalescent patients infected with SARS-CoV-2 [31]. The study group also attempted virus isolation from a subset of RNA-positive samples to determine whether RNA detection could be a marker of infectious virus. The results of this study reported that among the PCR-positive samples, cycle threshold (ct) values were high (range 33.5–44.8), suggesting low vRNA copy numbers. PCR-positive sera inoculated into SARS-CoV-2-susceptible cell culture did not produce any cytopathic effect or yield an increase in detectable SARS-CoV-2 RNA. The authors concluded that vRNA was detectable at low viral loads in a minority of serum samples collected in acute infection but was not associated with infectious SARS-CoV-2.

These studies and similar other observations resulted in considerations around blood and plasma donor deferral criteria for COVID-19 patients. The US FDA published several points that responsible physicians who evaluate prospective donors for blood establishments may wish to consider. Among these, the agency suggested individuals diagnosed with COVID-19 or who are suspected of having COVID-19, and who had symptomatic disease, as well as individuals who had a positive diagnostic test for SARS-CoV-2 but never developed symptoms, should refrain from donating blood for at least 10 days after complete resolution of symptoms or 10 days following the date of the positive test result, respectively [20].

PLASMA FOR FRACTIONATION

Plasma for fractionation can be obtained as surplus plasma separated from whole blood (recovered plasma), plasma intended or repurposed for fractionation collected by apheresis concurrently with a cellular product (in some regions called concurrent plasma) and as plasma solely intended for fractionation (source plasma). The assessment of blood and plasma donor suitability and deferral, where appropriate, aims to exclude donations from individuals at risk of transfusion-transmissible infection. All blood components should be obtained from healthy voluntary donors who are carefully selected using a systematic and validated process comprising review of the donor's health assessment and social behaviour history assessed through a donor questionnaire, as well as a medical examination. Current guidelines require a clearly defined list of permanent or temporary deferral criteria used for potential donors. However, standards for donor selection have always differed for the different types of plasma resulting from the circumstances of collection, which is particularly

relevant for newly discovered pathogens. Emerging infections that may influence donor and patient safety should be monitored and may necessitate the revision and modification of donor selection criteria. Donor acceptance and deferral criteria and blood screening procedures need to be balanced to provide optimal safety for both donors and recipients while at the same time ensuring an adequate supply of blood products [32, 33].

Early in the corona pandemic, Chinese authors discussed evidence and understanding of the transmission of SARS-CoV-2 through blood products, and also pathogen inactivation methods on coronaviruses. Although coronaviruses usually infect the upper or lower respiratory tract, the presence of vRNA in plasma or serum is possible, although infectivity has never been detected. Therefore, the risk of transmission of coronaviruses through the transfusion of blood products is theoretical. Given that many asymptomatic infections are found among COVID-19 cases, donor selection would fail under the current circumstances. So far, donation testing for plasma has not been implemented. Testing has not even been required for blood donations, that is, directly transfused components without any virus reduction before application to recipients. Low amounts of vRNA were only rarely found in blood donations (~1:100,000) and did not result in transfusion transmission. No infectivity was observed in inoculated permissive cell cultures, indicating no risk of transmission of the infection by blood components including plasma [26].

In low- and middle-income countries, an increase of blood donations from voluntary, unpaid donors to cover the unmet demand for red blood cell concentrates was observed because of global efforts [34, 35]. However, there is a continuous but slow decline in demand for red blood cells in high-income countries, and with the economic developments across the world, the decline in blood collection will likely continue [36]. Consequently, the amount of available recovered plasma used for plasma fractionation appears to decline. Simultaneously with the rise of the first wave of infections of the corona pandemic, a substantial decrease in the blood supply was observed. For example, in the Hubei province in China, the number of donations was 86% lower in February 2020, dropping from 34,059 to 4778. In some cities in the province, the reduction could reach 90% or even 95% [26]. Until April 2020, the number of donations gradually recovered but did not reach the numbers of the corresponding period of the earlier years. Similar observations were reported from all parts of the world but with varied numbers [37–39]. This caused a dramatic call to action by the International Foundation of Patient Blood Management (IFPBM) and the Society for the Advancement of Blood Management (SABM) Work Group, urging regional and national shortage plans worldwide and, more vitally, dissemination of knowledge and immediate implementation of patient blood management to optimize medical and surgical patient outcomes by clinically managing and preserving a patient's own blood [40]. Along that line, the UK National Blood Transfusion Committee provided a framework and triage tool to guide the allocation of blood for patients with massive haemorrhage during severe blood shortage. The goal of this document was to provide blood transfusions in an ethical, fair and transparent

manner to ensure that the greatest number of life-years were saved [41].

Reduced or constant availability of recovered plasma before the corona pandemic was compensated by a steady increase of source plasma collections, which had improved by a factor of 3.4 from 2000 to 2017 [42]. Plasma supply and demand are held in fine balance. If demand exceeds supply, or in cases of disruptions in the supply chain, shortages of plasma-derived products can occur [43]. In the past, shortages of plasma-derived coagulation factors and albumin concentrates have altered medical practice. In recent years, intravenous immunoglobulin has been in short supply [44, 45], with the corona pandemic introducing additional stress on plasma supply and creating constraints across geographies ([46] and personal communication from plasma industry representatives).

At the same time, in absence of specific therapies, PDMPs have been proposed for the treatment of COVID-19, thereby further increasing plasma demand. Transfusions of CP have been used and are under investigation in approximately 200 studies worldwide with mixed results [47]. Some preliminary observations of treatment with CP therapy resulted in a clinically relevant increased risk of severe adverse events, prompting uncertainty whether CP would be beneficial for people admitted to hospital with COVID-19 [48]. In contrast, other studies have shown that CP could provide a safe and efficacious therapy, improving outcomes in severe SARS-CoV2 infection (e.g., [49]). A recent systematic review and meta-analysis of randomized clinical trials investigated the association between CP treatment and mortality and concluded that CP treatment of patients with COVID-19 did not reduce all-cause mortality [50]. Commonly, all studies have shown that most CP donations had high neutralizing antibody titers. Pre-testing of donations by ELISA which correlated to the neutralization titre with a certain threshold could be used to eliminate lower titre units, thus enabling an adequate pooling strategy of CP to level out variations of antibody titres and quality in the therapeutic units [51].

NEW PLASMA PRODUCTS AND SUPPLY

As plasma concentrates are the preferable alternative to whole plasma for safety, efficacy and convenience reasons, hyperimmune globulins (H-Igs) derived from CP have been produced for research use in clinical trials. Several attempts have been made around the world to produce such H-Igs, and studies on their use have been conducted in different centres. One global initiative was the CoVlg-19 Plasma Alliance, which comprised global and regional plasma product manufacturers who combined knowledge, resources and existing infrastructure to accelerate the collection of CP to produce a non-branded H-Ig. In parallel, two other plasma producers initiated similar development programmes independently. The four resulting investigational H-Ig products were clinically tested for safety, tolerability and efficacy in adult hospitalized patients at the onset of clinical progression of COVID-19 under the guidance of the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH) ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04546581).

Regrettably, the trial did not meet its endpoint to show meaningful improvement in the clinical status of hospitalized adult COVID-19 patients through treatment with an H-Ig when given with standard of care including remdesivir [52]. Importantly, this outcome should not be interpreted as negating the value of plasma in approved indications. The particular study design did not prove a clinical benefit of an H-Ig for this targeted COVID-19 patient population in a hospitalized setting. However, it has significantly contributed to scientific understanding and mirrors mixed experience with CP [53]. The antibody treatment approach has thus far demonstrated efficacy at an earlier stage, namely pre-hospitalization, of the disease through trials with monoclonal antibodies. This was not something that was so apparent when the clinical trial was designed and warrants more research for better understanding [54–57].

The plasma industry's response to the pandemic has forced new ways of thinking and greater collaboration, bringing into sharp focus what must change if we are to improve access to essential plasma-derived therapies for people with rare and complex diseases who often have few alternative treatment options, regardless of the pandemic.

PLASMA PRODUCTS

The COVID-19 pandemic has further exposed the gap between plasma supply and demand, as well as the fragility of a system that is dependent on a scarce resource and heavily reliant on plasma donations from relatively few countries.

Throughout the pandemic, we have seen challenges to plasma donation across the industry, fluctuating in line with restrictions on the movement of people and travel. In spite of significant industry-led investment in new donation and production facilities, as well as major awareness campaigns, industry donation volumes are still lagging pre-pandemic levels. Ultimately, this shortfall is impacting the supply of plasma-derived therapies, particularly immunoglobulins, those plasma-derived therapies that are in highest demand and for which demand grows year on year. This risks potentially compromising patient care. Many of those patients with life-long, life-threatening conditions who rely on immunoglobulins—and who are more vulnerable during a pandemic—have no alternative treatment option. Hundreds of donations are required to keep just one patient on treatment for one year and it takes several months to make these therapies, from donation through to delivery to the patient [58]. There is a lack of global infrastructure for collecting and fractionating plasma across the world and highly restrictive regulatory and legislative frameworks are in place based on limited understanding of the unique profile of plasma and the extent of its potential therapeutic value. Currently, source plasma collection for manufacturing plasma-derived medications is limited to very few countries, predominantly the United States, because of these constraints. For example, the plasma volume collected in Europe meets only approximately 63% of the European clinical need for PDMPs, with the rest being imported from the United States. Only six countries in Europe account for about 80% of all plasma donations to be

used for fractionation in Europe to manufacture PDMPs (Germany, France, Italy, Austria, Czechia and Hungary). However, since Italy, France and Spain use their collections exclusively for their own domestic clinical needs, only four countries (Austria, Czechia, Germany and Hungary) actually contribute more than 55% of the total plasma collected in Europe for use in manufacturing PDMPs [59]. Moreover, many of the policies and regulations that impede increased supply have not kept pace with current scientific understanding and should be revisited. The solution to increased availability lies in active collaboration between scientific researchers, the industry, policymakers and regulatory authorities to foster environments that encourage source plasma donation and support sustainable supply solutions. To this end, plasma fractionators are engaging broadly across the blood and plasma industries, with peers, researchers, professional associations, patient organizations, regulators and governments, to emphasize scientific developments and the critical importance of plasma sourcing for ensuring continuous supply of therapies for patients with chronic and complex conditions. Sustainable solutions include establishing or reviewing regulations to better encourage and incentivize donation as well as better global regulations, allowing collection and manufacture of plasma in a global network. Illustrative examples of changes in the scientific, societal, and regulatory environment of plasma collection can be found in the recently updated US guidance for reducing the risk of HIV transmission by blood and blood products [60]. As described in the document's background, the acquired immune deficiency syndrome (AIDS) was first identified in men who have sex with men (MSM). When it was recognized that AIDS could be transmitted through the transfusion of plasma-derived clotting factor concentrates, it was decided to indefinitely defer MSM from donating blood or plasma. Based on the implementation of pathogen inactivation and removal procedures for products manufactured from pooled plasma from the 1980s [61] and nucleic acid testing for HIV, HBV and HCV [62], it was concluded in 2015 that the indefinite deferral could be changed to a 12-month deferral. In 2021, with additional data on the effectiveness of the measures accumulated, the MSM deferral period was further shortened to three months, acknowledging though that it may not be possible to implement the change for all plasma collected in the United States, as it may be destined for fractionation elsewhere and thus different regulations may apply. Scientific advances have led to similar changes for other blood-transmissible infectious-agent risk factors, such as receipt of tattooing and piercing. In summary, regulations that are not harmonized across major geographies and not fully consistent with current science may still limit effective plasma collection. The ability to expedite the CoVlg-19 programme (explained above) in just one year was made possible only by temporary regulatory exemptions across the plasma value chain, which were granted by regulators and governments in the United States and European Union, in view of the urgent need and the available supporting scientific evidence. These included rapid approval of protocols to collect CP and to pool it for manufacture, regulatory exceptions to allow for faster processing and manufacture, for example, reduced inventory hold period, and facilitated import/export between the United States and the European

Union. CoVlg-19 serves as an important illustration of how the current plasma landscape in many countries cannot support rapid response with a potential plasma-derived therapy solution in times of crisis and, more importantly, limits access to potential life-saving and life-sustaining therapies for people with rare diseases. It is why the world relies so heavily on the United States to meet the growing need for plasma and plasma-derived therapies. This situation is likely not sustainable. It is hoped that heightened awareness of plasma-derived therapies and the positive engagement there has been with regulators and governments will help foster recognition and support for the urgent need to update laws and regulations supported by science that govern the donation and processing of human plasma for the production of these essential medicines. This will be vital towards ensuring sustainable patient access to safe and efficacious therapies for which demand is expected to grow for at least the next decade while new alternative synthetic solutions are being investigated to address the full gamut of approved indications.

PATHOGEN SAFETY

Safety of plasma-derived products relies on three complementary measures: (1) donor selection; (2) testing individual plasma donations and mini-pools and manufacturing pools using immunological and nucleic acid amplification technologies (NAT) and (3) manufacturing processes that include specific virus inactivation and removal steps. This is known as the Safety Tripod (Figure 1). The Safety Tripod effectively addressed safety concerns of plasma products, and today plasma products feature significant virus safety margins. The concept has proven so successful that it is now equally applied to and codified for cell-based biotechnology manufacturing platforms and increasingly

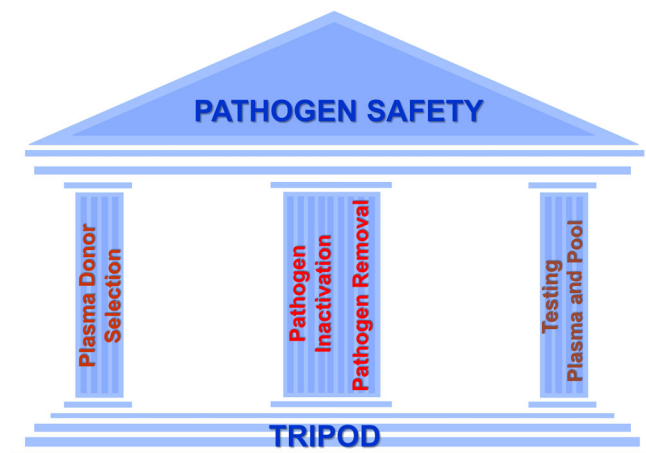


FIGURE 1 The so-called Safety Tripod best describes the safety of plasma-derived products relying on three complementary barriers: (1) selection of donors and plasma sources; (2) testing of individual plasma donations, and mini-pools and manufacturing pools using immunological and nucleic acid amplification technologies (NAT) and (3) manufacturing processes that include dedicated virus inactivation and removal steps

so for advanced therapy medicinal products, such as cell and gene therapies [63]. What does the Safety Tripod mean for SARS-CoV-2? Selection of lower-risk donors would be virtually impossible but also not necessary, as we have learned that blood donations and therefore also plasma would not transmit SARS-CoV-2. Consequently, also testing would not be required and would also not be helpful, as even the presence of SARS-CoV-2 vRNA would not result in infectious blood. Nevertheless, blood and plasma donor deferral criteria for individuals having recovered from COVID-19 have been applied as described above.

Coronaviruses are large lipid-enveloped viruses. Despite differences in their antigens, the main structural features regarding the size and lipid layer are conserved among all coronaviruses, meaning that their biochemical and physical properties are quite similar. Current regulations for plasma products require the use of at least two effective orthogonal virus reduction steps to eliminate infectious agents. The leading viral inactivation/removal technologies used today are solvent/detergent (S/D) treatment, heat treatments and nanofiltration. Given their envelope of phospholipid bilayers, coronaviruses are subject to effective inactivation by S/D treatment. A virus size of the spherical or pleomorphic particles of 80–120 nm size provides effective removal by nanofiltration with <35-nm virus-reduction nanofilter membranes.

To our knowledge, virus reduction validation studies for dedicated virus inactivation or removal steps for plasma products have not been performed with SARS-CoV-2. Nevertheless, the current situation with SARS-CoV-2 is comparable with the situation observed with other newly emerging pathogens. One recent example was the Zika virus (ZIKV), which caused large outbreaks in the Americas in 2015 and 2016, resulting in an increase in travel-associated cases in US states, which also raised concerns around the potential for ZIKV transmission via blood products. Before systematic virus inactivation and removal studies during the manufacture of PDMPs had been performed, risk assessments were made building on similarities between viruses, the so-called model virus concept. In the case of SARS-CoV-2, we do know its structure and function. As explained, the relatively large size and lipid envelope make SARS-CoV-2 highly susceptible to steps with virus inactivation and removal capacity used during the manufacturing processes, such as S/D [64], low-pH incubation, caprylate, pasteurization [65] or dry-heat treatments [66], nanofiltration or fractionation processes and others [67]. The effectiveness of these processes has been demonstrated on other lipid-enveloped model viruses that are quite similar to SARS-CoV-2, for example, human coronavirus 229E and OC43, SARS-CoV, and porcine coronavirus TGEV [68, 69]. In a recent publication, an array of effective coronavirus reduction steps during the manufacture of PDMPs was evaluated and discussed [70]. The authors concluded that, together with earlier reports that SARS-CoV and TGEV are effectively inactivated by pasteurization and standard S/D treatment conditions, these studies provide further evidence that various low-pH incubation and non-standard S/D treatment steps are also effective at inactivating coronaviruses, which, taken together with other safety measures, provide assurance of a high margin of virus safety against SARS-CoV-2 for

PDMPs. Thus, the Plasma Protein Therapeutics Association (PPTA) issued a statement in February 2020 - updated in April 2020 - that the SARS-CoV-2 outbreak is not a concern for the safety of plasma protein therapies manufactured by PPTA member companies [21].

DISCUSSION AND SUMMARY

Building on the historical use of plasma in earlier pandemics, the corona pandemic has substantially increased public awareness of the therapeutic use of plasma, although broader understanding of its use remains low. Use of CP and the potential for H-IgS made from CP to treat those at risk of serious complications from COVID-19 have been widely recognized, and this has drawn attention to the importance of blood and plasma as the source of life-saving human therapies.

Data obtained by in-depth investigations of the SARS-CoV-2 virus and derived from studies with highly similar viruses such as the human coronavirus 229E and OC43, SARS-CoV and porcine coronavirus TGEV confirmed that SARS-CoV-2 is not an issue for the safety of plasma derivatives. Several studies have suggested that infectivity will not be found in plasma donated by those individuals undergoing routine selection based on their health status.

There is a need for more plasma to be collected around the world to meet the growing need for safe and efficacious plasma-derived therapies—and this was evident even before the pandemic [71]. As an example, demand for immunoglobulin products is anticipated to grow steadily over the next few years, with an expected increase of 33% from 2017 to 2025. A key factor behind this growth is the growth in the use of immunoglobulins to treat secondary immunodeficiencies, or even cancer [72]. An increase in collections requires outdated regulatory and policy restrictions to be realigned with current scientific evidence. Specifically, several measures originally implemented with the intention to enhance the virus safety margins of PDMPs have now become redundant. This is largely a result of significantly enhanced and fully validated virus inactivation and removal processes that have been embedded into manufacturing processes, as well as advancements in the science of testing for infectious agents. The continued implementation of these measures limits collection of plasma for fractionation. By addressing this, as well as over-reliance on the few countries with regulatory frameworks conducive to effective plasma collection and shifting towards broader country contribution to global plasma supply, we can create a more sustainable plasma landscape. This means more patients around the world with life-threatening conditions—and often no therapeutic alternative solution— would be able to count on more reliable supply and, therefore, be more confident of access and continuity of care.

ACKNOWLEDGEMENTS

All authors conceived, wrote and edited the manuscript. We thank Wolfhard Erdlenbruch for critically reviewing the manuscript. We are also grateful to Roger Brinser, Bernhard Kohli, Ali Mardini, Robert Peter Weiss, Rob de With, Tineke Zuurbier and Ali Mardini for

providing additional information to give sound replies to some of the complex questions from the reviewers.

CONFLICT OF INTEREST

P.L.T, D.H. and T.R.K. are full-time employees of Takeda Pharmaceutical Company Limited, Takeda Manufacturing Austria AG and Baxalta Innovations GmbH, respectively.

ORCID

Peter L. Turecek  <https://orcid.org/0000-0002-6161-1556>

REFERENCES

1. Callaway Kim K, Tadrous M, Kane-Gill SL, Barbash IJ, Rothenberger S, Suda KJ. Changes in purchases for intensive care medicines during the COVID-19 pandemic: a global time series study. *Chest*. 2021;160:2123–34.
2. Kuo S, Ou HT, Wang CJ. Managing medication supply chains: lessons learned from Taiwan during the COVID-19 pandemic and preparedness planning for the future. *J Am Pharm Assoc*. 2003;2021:e12–5.
3. Schirolli D, Merolle L, Molinari G, Di Bartolomeo E, Seligardi D, Canovi L, et al. The impact of COVID-19 outbreak on the Transfusion Medicine Unit of a Northern Italy Hospital and Cancer Centre. *Vox Sang*. 2021;117:235–42.
4. Wendel S, Land K, Devine DV, Daly J, Bazin R, Tiberghien P, et al. Lessons learned in the collection of convalescent plasma during the COVID-19 pandemic. *Vox Sang*. 2021;116:872–9.
5. Russell WA, Grebe E, Custer B. Factors driving availability of COVID-19 convalescent plasma: insights from a demand, production, and supply model. *Transfusion*. 2021;61:1370–6.
6. Kaplon H, Reichert JM. Antibodies to watch in 2021. *MAbs*. 2021;13:1860476.
7. Schwenk JM, Omenn GS, Sun Z, Campbell DS, Baker MS, Overall CM, et al. The human plasma proteome draft of 2017: building on the human plasma PeptideAtlas from mass spectrometry and complementary assays. *J Proteome Res*. 2017;16:4299–310.
8. Song S. Alpha-1 antitrypsin therapy for autoimmune disorders. *Chronic Obstr Pulm Dis*. 2018;5:289–301.
9. Brittain JE, Parise LV. Cytokines and plasma factors in sickle cell disease. *Curr Opin Hematol*. 2007;14:438–43.
10. Limoli PG, Vingolo EM, Limoli C, Scalinci SZ, Nebbioso M. Regenerative therapy by suprachoroidal cell autograft in dry age-related macular degeneration: preliminary in vivo report. *J Vis Exp*. 2018;132:56469.
11. Kreil TR. Building blocks of the viral safety margins of industrial plasma products. *Ann Blood*. 2018;3:14.
12. Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, et al. Discovery of seven novel mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *J Virol*. 2012;86:3995–4008.
13. Fouchier RA, Kuiken T, Schutten M, van Amerongen G, van Doornum GJ, van den Hoogen BG, et al. Aetiology: Koch's postulates fulfilled for SARS virus. *Nature*. 2003;423:240.
14. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet*. 2003;362:263–70.
15. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367:1814–20.

16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
17. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. *Infez Med*. 2020;28:174–84.
18. Kirtipal N, Bharadwaj S, Kang SG. From SARS to SARS-CoV-2, insights on structure, pathogenicity and immunity aspects of pandemic human coronaviruses. *Infect Genet Evol*. 2020;85:104502.
19. Transfusion News. Risk of Transfusion Transmission of SARS-CoV-2 Is Only Theoretical. 2020 Mar 04 [cited 2021 Oct 21]. Available from: <https://transfusionnews.com/2020/03/04/risk-of-transfusion-transmission-of-sars-cov-2-is-only-theoretical/>
20. US Food & Drug Administration. Updated Information for Blood Establishments Regarding the COVID-19 Pandemic and Blood Donation. Bethesda. 2022 Jan 11 [cited 2022 Jan 11]. Available from: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-blood-establishments-regarding-covid-19-pandemic-and-blood-donation>
21. Plasma Protein Therapeutics Association (PPTA). New Coronavirus (SARS-CoV-2) and the Safety Margins of Plasma Protein Therapies. 2020 Apr 03 [cited 2021 Oct 21]. Available from: <https://www.pptaglobal.org/media-and-information/ppta-statements/1055-2019-novel-coronavirus-2019-ncov-and-plasma-protein-therapies>
22. Roman L, Armstrong B, Smart E. Donation testing and transfusion transmissible infections. *ISBT Sci Ser*. 2020;15:192–206.
23. Stramer SL, Fang CT, Foster GA, Wagner AG, Brodsky JP, Dodd RY. West Nile virus among blood donors in the United States, 2003 and 2004. *N Engl J Med*. 2005;353:451–9.
24. Planitzer CB, Modrof J, Yu MY, Kreil TR. West Nile virus infection in plasma of blood and plasma donors, United States. *Emerg Infect Dis*. 2009;15:1668–70.
25. Dodd RY, Stramer SL. COVID-19 and blood safety: help with a dilemma. *Transfus Med Rev*. 2020;34:73–4.
26. Chang L, Yan Y, Zhao L, Hu G, Deng L, Su D, et al. No evidence of SARS-CoV-2 RNA among blood donors: a multicenter study in Hubei, China. *Transfusion*. 2020;60:2038–46.
27. Bakkour S, Saá P, Groves JA, Montalvo L, Di Germanio C, Best SM, et al. Minipool testing for SARS-CoV-2 RNA in United States blood donors. *Transfusion*. 2021;61:2384–91.
28. Tang YW, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: current issues and challenges. *J Clin Microbiol*. 2020;58:e00512–20.
29. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323:1843–4.
30. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January–March 2020: retrospective cohort study. *BMJ*. 2020;369:m1443.
31. Andersson MI, Arancibia-Carcamo CV, Auckland K, Baillie JK, Barnes E, Beneke T, et al. SARS-CoV-2 RNA detected in blood products from patients with COVID-19 is not associated with infectious virus. *Wellcome Open Res*. 2020;5:181.
32. Custer B, Johnson ES, Sullivan SD, Hazlet TK, Ramsey SD, Murphy EL, et al. Community blood supply model: development of a new model to assess the safety, sufficiency, and cost of the blood supply. *Med Decis Making*. 2005;25:571–82.
33. Seifried E, Klueter H, Weidmann C, Staudenmaier T, Schrezenmeier H, Henschler R, et al. How much blood is needed? *Vox Sang*. 2011;100:10–21.
34. Report of the Fifth General Meeting of the Global Collaboration for Blood Safety, Geneva, 10–12 November, 2004. Available from: https://www.who.int/bloodsafety/GCBS_Report_NOV_2004.pdf
35. World Health Organization. Home/Newsroom/Fact sheets/Detail/Blood safety and availability [cited 2020 June 10]. Available from: <https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability>
36. Jones JM, Sapiano MRP, Savinkina AA, Haass KA, Baker ML, Henry RA, et al. Slowing decline in blood collection and transfusion in the United States - 2017. *Transfusion*. 2020;60:S1–9.
37. Pagano MB, Hess JR, Tsang HC, Staley E, Gernsheimer T, Sen N, et al. Prepare to adapt: blood supply and transfusion support during the first 2 weeks of the 2019 novel coronavirus (COVID-19) pandemic affecting Washington State. *Transfusion*. 2020;60:908–11.
38. Grandone E, Mastroianno M, Caroli A, Ostuni A. Blood supply and transfusion support in southern Italy: findings during the first four weeks of the SARS-CoV-2 pandemic. *Blood Transfus*. 2020;18:230–2.
39. Kumar S, Azim D, Nasim S, Hashmi SH. Dwindling blood reserves: an ominous downside of COVID-19 pandemic. *Transfus Apher Sci*. 2020;59:102818.
40. Shander A, Goobie SM, Warner MA, Aapro M, Bisbe E, Perez-Calatayud AA, et al. Essential role of patient blood management in a pandemic: a call for action. *Anesth Analg*. 2020;131:74–85.
41. Doughty H, Green L, Callum J, Murphy MF. Triage tool for the rationing of blood for massively bleeding patients during a severe national blood shortage: guidance from the National Blood Transfusion Committee. *Br J Haematol*. 2020;191:340–6.
42. Robert P. An analysis of the impact of international transfers of plasma on the availability of immunoglobulin therapies. Fall, 2019 [cited 2021 Oct 21]. Available from: https://www.pptaglobal.org/images/source/2019/Fall/An_Analysis_of_the_Impact_of_International_Transfers_of_Plasma_on_the_Availability_of_Immunoglobulin_Therapies.pdf
43. Hartmann J, Klein HG. Supply and demand for plasma-derived medicinal products - a critical reassessment amid the COVID-19 pandemic. *Transfusion*. 2020;60:2748–52.
44. Bayry J, Kazatchkine MD, Kaveri SV. Shortage of human intravenous immunoglobulin--reasons and possible solutions. *Nat Clin Pract Neurol*. 2007;3:120–1.
45. Hartmann J. Google Trends as an early indicator for shortages of intravenous immunoglobulin (IVIg). *Transfusion*. 2020;60:1656–7.
46. The United Kingdom Primary Immunodeficiency Network (UKPIN) Official Release. 2021 Nov 5. Available from: <http://www.ukpin.org.uk/>
47. Brown BL, McCullough J. Treatment for emerging viruses: convalescent plasma and COVID-19. *Transfus Apher Sci*. 2020;59:102790.
48. Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2020;10:CD013600.
49. Fodor E, Müller V, Iványi Z, Berki T, Kuten Pella O, Hornyák I, et al. Early transfusion of convalescent plasma improves the clinical outcome in severe SARS-CoV2 infection. *Infect Dis Ther*. 2022;11:293–304.
50. Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis*. 2021;21:1170.
51. Jungbauer C, Weseslindtner L, Weidner L, Gänsdorfer S, Farcet MR, Gschaidner-Reichhart E, et al. Characterization of 100 sequential SARS-CoV-2 convalescent plasma donations. *Transfusion*. 2021;61:12–6.
52. ITAC (INSIGHT 013) Study Group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. *Lancet*. 2022;399:530–40.

53. Hartmann J, Bloch EM, Burnouf T. Experience with COVID-19 convalescent plasma provides vital guidance to future pandemics. *Transfusion*. 2022 Jan 30. <https://doi.org/10.1111/trf.16810>. Epub ahead of print.
54. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384:229–37.
55. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021;325:632–44.
56. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med*. 2021;384:238–51.
57. So-Osman C, Valk SJ. High-dose immunoglobulins from convalescent donors for patients hospitalised with COVID-19. *Lancet*. 2022;399:497–9.
58. Plasma Protein Therapeutics Association (PPTA). Advocacy Toolkit [cited 2021 Oct 21]. Available from: <https://www.pptaglobal.org/advocacy/advocacy-toolkit>
59. Kluszczynski T, Rohr S, Ernst R. Key economic and value considerations for plasma-derived medicinal products (PDMPs) in Europe [cited 2020 Mar 5]. Available from: https://www.vintura.com/wp-content/uploads/2020/03/White-paper-key-economic-and-value-considerations-for-plasma-derived-medicinal-products-PDMPs-in-Europe_Vintura-and-PPTA.pdf
60. Guidance for Industry: Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products. August 2020. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reducing-risk-human-immunodeficiency-virus-transmission-blood-and-blood>
61. Klamroth R, Gröner A, Simon TL. Pathogen inactivation and removal methods for plasma-derived clotting factor concentrates. *Transfusion*. 2014;54:1406–17.
62. Custer B, Kessler D, Vahidnia F, Leparc G, Krysztof DE, Shaz B, et al. NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II). Risk factors for retrovirus and hepatitis virus infections in accepted blood donors. *Transfusion*. 2015;55:1098–107.
63. Barone PW, Wiebe ME, Leung JC, Hussein ITM, Keumurian FJ, Bouressa J, et al. Viral contamination in biologic manufacture and implications for emerging therapies. *Nat Biotechnol*. 2020;38:563–72.
64. Rabenau HF, Biesert L, Schmidt T, Bauer G, Cinatl J, Doerr HW. SARS-coronavirus (SARS-CoV) and the safety of a solvent/detergent (S/D) treated immunoglobulin preparation. *Biologicals*. 2005;33:95–9.
65. Gröner A, Broumis C, Fang R, Nowak T, Popp B, Schäfer W, et al. Effective inactivation of a wide range of viruses by pasteurization. *Transfusion*. 2018;58:41–51.
66. Yunoki M, Urayama T, Yamamoto I, Abe S, Ikuta K. Heat sensitivity of a SARS-associated coronavirus introduced into plasma products. *Vox Sang*. 2004;87:302–3.
67. Keil SD, Bowen R, Marschner S. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. *Transfusion*. 2016;56:2948–52.
68. Lamarre A, Talbot PJ. Effect of pH and temperature on the infectivity of human coronavirus 229E. *Can J Microbiol*. 1989;35:972–4.
69. Bucknall RA, King LM, Kapikian AZ, Chanock RM. Studies with human coronaviruses. II. Some properties of strains 229E and OC43. *Proc Soc Exp Biol Med*. 1972;139:722–7.
70. Schröder T, Koch J, Ross R, Schäfer W, Keiner B, Roth NJ, et al. Effective coronavirus reduction by various production steps during the manufacture of plasma-derived medicinal products. *Transfusion*. 2020;60:1334–5.
71. The Economist. Blood Money. May 2018. Available from: <https://www.economist.com/leaders/2018/05/12/lift-bans-on-paying-for-human-blood-plasma>.
72. Marketing Research Bureau. Forecast of the Global Immunoglobulin (IgG) Market 2025. Available from: <https://marketingresearchbureau.com/forecast-of-the-global-immunoglobulin-igg-market-2023-2/>

How to cite this article: Turecek PL, Hibbett D, Kreil TR. Plasma procurement and plasma product safety in light of the COVID-19 pandemic from the perspective of the plasma industry. *Vox Sang*. 2022;117:780–8.