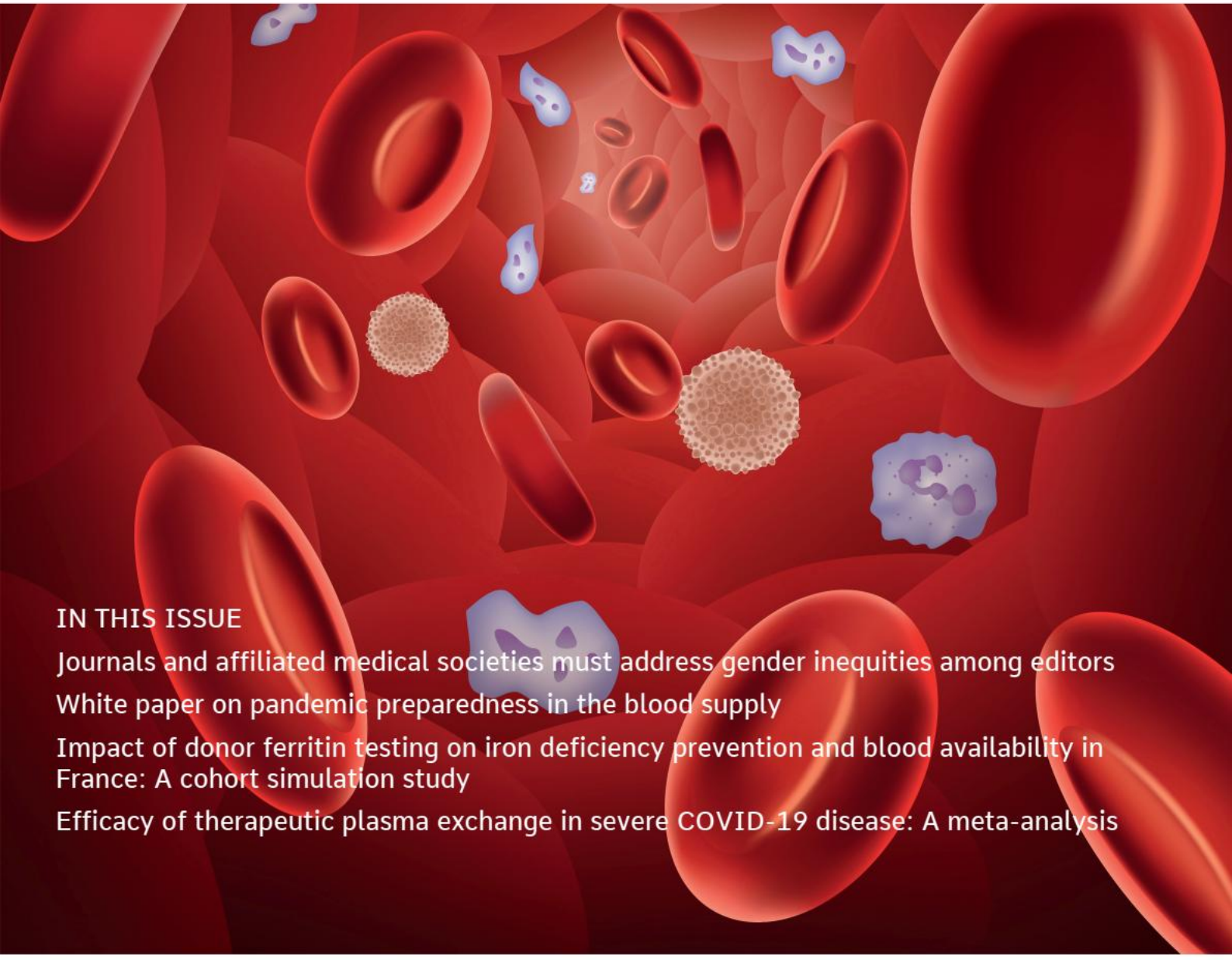
ISSN 0042-9007 (Print)
ISSN 1423-0410 (Online)

Volume 119 Number 2 FEBRUARY 2024

Vox Sanguinis

The International Journal of Transfusion Medicine



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International Journal of Blood Transfusion

Official Journal of the International Society of Blood Transfusion

Founded 1956 by J. J. van Loghem, L. P. Holländer, J. Dausset, A. Hässig and J. Julliard (formerly Bulletin of the Central Laboratory of the Blood Transfusion Service of the Dutch Red Cross, founded 1951)

Vox Sanguinis

International Journal of Blood Transfusion

Aims and Scope

Vox Sanguinis reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies. Comments, reviews, original articles, short reports and international fora are published, grouped into eight main sections:

1. Donors and Donations: Donor recruitment and retention; Donor selection; Donor health (vigilance, side effects of donation); Big data analysis and blood donation.
2. Blood Component Collection and Production: Blood collection methods and devices (including apheresis); Blood component preparation and storage; Inventory management; Collection and storage of cells for cell therapies; Quality management and good manufacturing practice; Automation and information technology; Plasma fractionation techniques and plasma derivatives.
3. Transfusion-transmitted Disease and its Prevention: Identification and epidemiology of infectious pathogens transmissible by blood; Donor testing for transfusion-transmissible infectious pathogens; Bacterial contamination of blood components; Pathogen inactivation.
4. Transfusion Medicine and New Therapies: Transfusion practice, thresholds and audits; Transfusion efficacy assessment, clinical trials; Non-infectious transfusion adverse events; Therapeutic apheresis.
5. Haemovigilance: Near misses, adverse events and side effects throughout the transfusion chain; Monitoring, reporting and analysis of those adverse events and side effects; Activities aiming at increasing the safety of the whole transfusion chain; Standardization of the definition of adverse events and side effects.
6. Patient Blood Management: Caring for patients who might need a transfusion; Transfusion indication decision-making process; Search for the optimal patient outcomes; Study of transfusion alternatives; Autologous blood transfusion.
7. Immunohaematology: Red cell, platelet and granulocyte immunohaematology; Blood phenotyping and genotyping; Molecular genetics of blood groups; Alloimmunity of blood; Pre-transfusion testing; Autoimmunity in transfusion medicine; Blood typing reagents and technology; Immunogenetics of blood cells and serum proteins: polymorphisms and function; Complement in immunohaematology; Parentage testing and forensic immunohaematology.
8. Cellular Therapies: Cellular therapy (sources; products; processing and storage; donors); Cell-based therapies; Genetically modified cell therapies; Stem cells (sources, collection, processing, storage, infusion); Cellular immunotherapy (e.g., CAR-T cells, NK cells, MSC); Cell-based regenerative medicine; Molecular therapy; In vitro manufacturing of blood components.

Vox Sanguinis also publishes the abstracts associated with international and regional congresses of the ISBT. (Abstracts from meetings other than those held by the ISBT are not accepted.)

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Abstracting and Indexing Services: The Journal is indexed by Abstracts in Anthropology (Sage); Abstracts on Hygiene & Communicable Diseases (CABI); Academic Search (EBSCO Publishing); Academic Search Alumni Edition (EBSCO Publishing); Academic Search Premier (EBSCO Publishing); AGRICOLA Database (National Agricultural Library); BIOBASE: Current Awareness in Biological Sciences (Elsevier); Biological Abstracts (Clarivate Analytics); BIOSIS Previews (Clarivate Analytics); CAB Abstracts® (CABI); CABDirect (CABI); CAS: Chemical Abstracts Service (ACS); CSA Biological Sciences Database (ProQuest); CSA Environmental Sciences & Pollution Management Database (ProQuest); CSA Virology & AIDS Abstracts (ProQuest); Current Contents: Life Sciences (Clarivate Analytics); Embase (Elsevier); Global Health (CABI); HEED: Health Economic Evaluations Database (Wiley-Blackwell); Index Veterinarius (CABI); Journal Citation Reports/Science Edition (Clarivate Analytics); MEDLINE/PubMed (NLM); Nutrition Abstracts & Reviews Series A: Human & Experimental (CABI); Pig News & Information (CABI); ProQuest Central (ProQuest); ProQuest Health & Medical Complete (ProQuest); ProQuest Research Library (ProQuest); Protozoological Abstracts (CABI); PubMed Dietary Supplement Subset (NLM); Review of Medical & Veterinary Entomology (CABI); Review of Medical & Veterinary Mycology (CABI); Rural Development Abstracts (CABI); Science Citation Index (Clarivate Analytics); Science Citation Index Expanded (Clarivate Analytics); Tropical Diseases Bulletin (CABI); Veterinary Bulletin (CABI).

VOX SANGUINIS (Online ISSN: 1423-0410 Print ISSN: 0042-9007) is published monthly. Postmaster: Send all address changes to VOX SANGUINIS, Wiley Periodicals LLC, C/O The Sheridan Press, PO Box 465, Hanover, PA 17331, USA. For submission instructions, subscription and all other information visit: www.wileyonlinelibrary.com/journal/vox. Printed in the UK by Hobbs the Printers Ltd.

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119/2/2024

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The special issue has been made free to read online through support from Abbott Laboratories. Abbott's support is not to be interpreted as an endorsement of the independent views and conclusions of the authors.

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Received: 25 January 2024 | Accepted: 25 January 2024

DOI: 10.1111/vox.13597

EDITORIAL

Vox Sanguinis ISBT International Society of Blood Transfusion

Advancing resilience and sustainability in plasma collections and plasma-derived medicinal product accessibility

The importance of a resilient and sustainable plasma supply cannot be overstated. Even before the COVID pandemic, plasma-derived medicinal product (PDMP) demands were rising, and discussions on how to organize more strategically independent local or regional plasma collections were ongoing. The pandemic further highlighted the value of plasma, as well as the importance of strategic independence. This special issue of *Vox Sanguinis* delves into the challenges of safely collecting plasma from donors and explores strategies to build resilient and more sustainable plasma collections, as well as to ensure accessibility to PDMPs.

Donor recruitment and retention are mainstays of a successful plasma collections programme. This issue delves into the need for more plasma donors and an innovative strategy for recruiting and retaining donors, emphasizing the need for stakeholder engagement, improved understanding of sentiments around donor incentives, and the implementation of ethical practices. By understanding the motivations and concerns of donors, we can establish a more robust and sustainable foundation for plasma collections. However, rising demands for PDMPs put a growing burden on donors to donate at higher frequencies while potential health implications remain inadequately understood. Ensuring the wellbeing of these volunteers is paramount, building a foundation of trust that their health is being protected. The research papers on donor health protection in this issue offer some reassuring data, but also underscore the potential risks associated with very frequent donations. Furthermore, two comprehensive reviews not only present a detailed overview of known health effects but crucially highlight the considerable gaps in our understanding, emphasizing the need for continued exploration of health effects of high-frequency plasma donations.

An important step towards sustainable plasma collections involves fostering international collaborations. As an example, the SUPPLY project is co-funded by the European Union (EU) and aims to strengthen the resilience of plasma collection in the EU to enable a stable and adequate supply of PDMPs [1]. SUPPLY shows the importance of such collaborations for comparing policies and legislations, reviewing evidence, and assessing risks and opportunities in order to build towards improved, unified plasma collections. This special issue includes reports on some of the challenges that became more evident with SUPPLY, and also on challenges in low- and middle-income countries and potential solutions to these. Together, these studies and commentaries emphasize the importance of sharing best practice, technological advancements, and regulatory frameworks to ensure the safety, quality, and ethical conduct of plasma collections.

To conclude, this special issue of *Vox Sanguinis* provides a snapshot of a journey towards unraveling the complexities of collecting plasma from donors and building resilient, sustainable systems on a global scale. The articles presented here aim to inspire dialogue, collaboration, and action to meet the growing demand for PDMPs. Let this be a call to action for the scientific community, policymakers, and stakeholders to unite in the pursuit of a resilient, healthy, and sustainable plasma collection and PDMP accessibility.

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REFERENCE

1. SUPPLY project. Strengthening voluntary non-remunerated plasma collection capacity in Europe Available from: https://supply-project.eu/. Last accessed 12 Jan 2024.

Received: 4 May 2023 | Revised: 26 July 2023 | Accepted: 27 July 2023

DOI: 10.1111/vox.13512

REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

A donor safety evidence literature review of the short- and long-term effects of plasmapheresis

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Funding information
Australian Governments

Abstract

Many blood establishments are expanding plasmapheresis collection capacity to achieve increasing plasma for fractionation volume targets, driven by immunoglobulin product demand. Some adverse events occur in both apheresis and whole blood collection, such as venepuncture-related trauma and vasovagal reactions. Others are specifically related to the apheresis procedure, such as citrate reactions, haemolysis, infiltration and air embolism. Whilst plasmapheresis procedures are generally well tolerated, theoretical longer term donor health considerations, such as the effects on donor plasma protein levels, bone mineral density, iron deficiency and malignancy also require consideration. An evidence-based framework that supports a safe and sustainable increase in the collection of plasma is essential. Our review demonstrates a lack of high-quality evidence on risks and outcomes specifically in plasmapheresis. Whilst conservative procedural controls and donor harm minimization policies will mitigate risk, high-quality evidence is needed to facilitate practice change that is safe and sustainable and maximizes the potential of individual donor differences.

Keywords

donor safety, plasmapheresis

Highlights

- This evidence review demonstrates that plasmapheresis is generally well tolerated, and that risk can be reduced with procedural controls and donor harm minimization policies.
- Donor attributes, donor selection, choice of apheresis technology, the plasmapheresis protocol, the collection environment and staff expertise all influence the rate of donor adverse events. Blood establishments should provide advice to donors regarding how to prepare for apheresis donation as well as post-donation care.
- Collection of immediate donor adverse events and long-term health data will contribute to safe and sustainable plasma collection.

INTRODUCTION

The demand for plasma-derived products has increased significantly worldwide, primarily due to increasing immunoglobulin demand. For most blood establishments, the collection of 280–320 mL of plasma, 'recovered' from a whole blood (WB) donation, has been the main plasma source. However, red cell transfusion demand has declined [1], so upscaling WB donations to meet fractionated plasma demand is neither ethically justified nor cost-effective. The United States has predominantly collected fractionated plasma by plasmapheresis, referred to as 'source plasma' [1].

Many blood establishments are now expanding plasmapheresis collection capacity, allowing greater plasma collection volumes per procedure and higher donation frequency. Donor health must be

protected by minimizing donor adverse events (DAEs) to as low as reasonably achievable and plasma quality optimized. Some adverse events occur in both apheresis and WB collection, such as venepuncture-related injuries and vasovagal reactions (VVRs). Others are specifically related to the apheresis procedure, such as citrate reactions, haemolysis and infiltration. Whilst donor attributes (donor experience, gender and age) influence DAE rates, the choice of apheresis technology and the plasmapheresis protocol also influence DAEs. There are other important potential donor health considerations, such as the effects on donor plasma protein levels, bone mineral density (BMD), iron deficiency (ID) and malignancy. This article reviews the evidence for donor safety and the procedural controls and policies that can be implemented to minimize plasmapheresis donor harm.

MATERIALS AND METHODS

Two authors completed independent literature reviews using OVID and PubMed databases. Initially, the search included plasmapheresis and adverse events (386 papers, 17 full-text), which was then expanded to include plasmapheresis, blood donation/donors and other keyword combinations including haemoglobin (179 results, 25 full-text), iron deficiency (5 results, 2 full-text), citrate (29 results, 9 full-text), extravasation (0 articles, 69 if plasmapheresis excluded), compartment syndrome and blood donation (33 results 1 full-text), haemolysis (18 results, nil, 1 full-text if expanded to apheresis), immunoglobulin (421 articles, 7 full-text), frequent plasmapheresis (nil new), gammaglobulin (5 articles 2 full-text), VVR (7 results, 3 new full-text), saline (15 results, 1 new full-text), cancer (3 articles, 0 full-text) and anaphylaxis (7 articles, 0 full-text). Titles were reviewed, concentrating on plasmapheresis. Articles that referenced therapeutic plasmapheresis were excluded. A summary of each relevant article was developed. Because of the poor quality of the evidence, a decision was made to write this up as an evidence review to guide best practice with relevant articles cited in the sections. All authors reviewed the evidence. New articles published beyond 2021 were evaluated as published, repeating the search up to July 2023.

RESULTS

Plasmapheresis venepuncture-related injuries

Because of the longer procedure and multiple draw and return cycles, there is more opportunity for needle displacement resulting in venepuncture-related injuries including haematoma, painful arm, arterial puncture and nerve irritation/injury, compared with WB. First-time plasma donors are demonstrated to have higher rates of venepuncture injury per donation than first-time WB donors (24 vs. 8 per 1000, respectively) [2]. Venepuncture-related injury may lead to early donation termination and higher unsuccessful donation rates [3], which impacts collection efficiency, donor experience and return. The rate of nerve injury lasting at least 12 months is increased in plasmapheresis, reported as 1 in 2.37 million per donation, being six times the rate in WB donations [4]. Anatomical variation means that the residual risk of nerve injuries cannot be reduced to zero [5].

VVRs and plasma volume collection limits

Donor inexperience is the largest risk factor for VVRs; females and younger donors are also at higher risk [6]. Many countries have policies that require donors to complete a successful WB donation prior to apheresis [7], resulting in an overall lower rate of VVRs in plasmapheresis donors than WB donors.

The plasmapheresis volume removed is an important consideration contributing to VVRs. Plasma collection volume limits, based on a collection volume cap or a total blood volume (TBV) estimate, are in place to prevent VVRs precipitated by hypovolaemia. For example, the European *Guide* includes a collection volume cap of 880 mL including anticoagulants and also states that collection volume limits should be based on an estimated TBV (not exceeding 16%) and/or body mass index (BMI) [8].

Schreiber et al. [9] reviewed safety data on over 12 million US donations. The data represented about 72% of the US plasma industry donations and showed an overall rate of DAEs of 15.85 per 10,000 donations with allowed plasma donation volumes (690, 825 or 880 mL) based on the donor's weight. DAEs were evaluated by categorizing donations by the percentage of donated plasma volume per estimated blood volume (EBV). EBV was calculated using Nadler's formula, which takes to account sex, weight and height [10]. The cohort of female donors who donated less than 16% of the EBV had higher DAEs in all donation volume categories (690, 825 and 880 mL) than cohorts who donated more than 16% of their EBV. In males, the cohort donating less than 16% of the EBV had the highest DAEs rate in the volume categories of 825 and 880 mL. In the smallest donation volume category (625 mL), the cohort donating 20%–24% of EBV had higher DAEs than cohorts donating <16%, 16%–19% or 25%–29% of EBV. Based on these results, the authors concluded that %EBV collected may not be the best predictor of DAE risk.

Their data are consistent with that published by Pink et al [11] in Figure 1. These data demonstrated that for both males and females, the VVR rate was highest at the 13% TBV collection tier and progressively reduced as the TBV collection tier increased from 16% to 18%. Several factors explain this finding. The incidence of reactions is highest in first-time donors, all of whom start at 13% TBV. Only donors who tolerate the lower collection volumes (i.e., physiologically less likely to be vulnerable to VVRs) are permitted to progress to higher TBV limits, hence the 16% and 18% TBV cohort includes more experienced donors. Larger, particularly male donors are limited by the collection volume cap and donate at a lower TBV. Finally, donors who experience a VVR are less likely to return.

Plasma nomograms, based on the donor's gender, height and weight, are often used to determine plasma volume collected, however, have limitations in obese donors, and in donors at the upper and lower ranges of height. Nomograms may overestimate TBV in obese blood

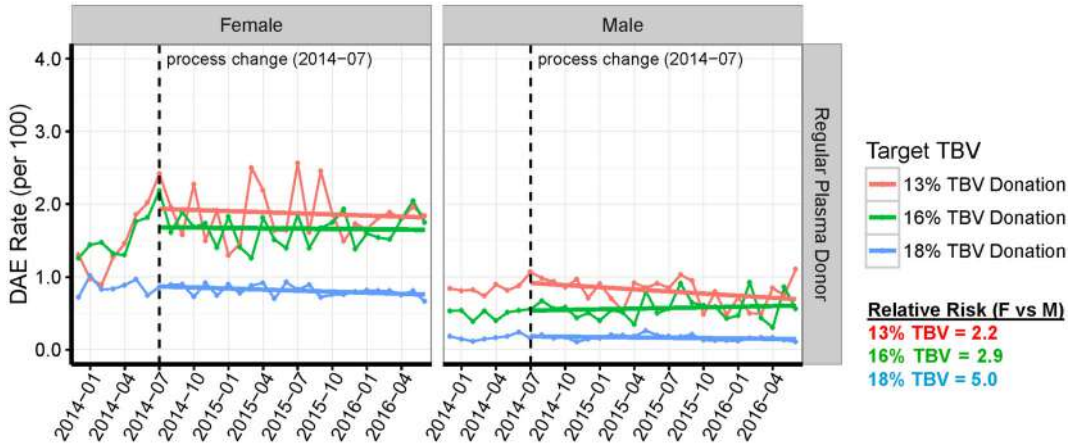

FIGURE 1 Adverse events by percentage of estimated total blood volume (TBV) in Australian plasma donors 2014–2016. DAE, donor adverse event.

donors. Obesity is known to increase blood volume in terms of absolute values but decrease blood volume per body weight kilogram [12]. Comparing weight, a disproportionately high volume of plasma is collected relative to available TBV in lighter donors [13].

In addition, some individuals can comparatively tolerate a greater volume of blood loss. Using a human laboratory model of haemorrhage, the model showed that individuals could be classified as having a high or low blood loss tolerance, and they demonstrated significant differences in physiological compensatory responses [14]. Karger et al. [15] found extracorporeal volumes exceeded 15% of TBV in more than 60% of males and 90% of female donors and concluded that a fixed volume limit would not avoid VVR circulatory reactions.

Whilst fear is a recognized predictor of VVRs [16] positive emotions are associated with a decreased risk. The use of techniques such as applied muscle tension (AMT) has been shown to reduce VVRs in WB donations but not plasma donations specifically [17]. There is an association between saline replacement and lower VVRs during the procedure [18]. In a before and after study, a pre-donation salty snack and water resulted in less VVRs overall by approximately 15%, but this reduction was evident in WB only and not apheresis [19].

Citrate complications

Acute citrate reactions

Citrate is mixed with extracorporeal blood and prevents clotting during apheresis by complexing with calcium. If ionized calcium decreases significantly it can result in spontaneous depolarization of nerve membranes, resulting in the classical symptoms of a citrate reaction which include perioral paraesthesia, acral paraesthesia, shivering, light-headedness, twitching and tremors. Less commonly donors also experience nausea and vomiting. VVRs can be triggered. If the ionized calcium levels fall further, symptoms could progress to carpopedal spasm and tetany [20].

Donors are only exposed to citrate during return cycles [21]. Whether citrate causes a systemic reaction in the donor is dependent on its concentration in the returned component (citrate is predominantly in non-returned plasma) and the return speed [22]; this means that the citrate dose in plateletpheresis where plasma is returned is materially higher than what occurs in plasmapheresis. During the rapid return cycle of citrate-containing red cells, the citrate infusion rate is likely to peak at three times the overall 'average' rate [21]. Because citrate exposure is intermittent, symptoms are typically transient and the small citrate dose returned is probably promptly buffered away by compensatory physiology [21]. Decreasing or pausing the plasmapheresis return rate should therefore reverse mild citrate symptoms.

Risk of metabolic bone disease

When a donor is exposed to higher citrate amounts, metabolic changes such as acute hypocalcaemia, hypomagnesemia and an increase in parathyroid hormone levels can occur [23]. Therefore, concern has been raised that repeated apheresis may impact bone health. A small randomized controlled trial in high-frequency platelet donors powered to detect a 3% difference did not demonstrate a BMD difference compared with controls [24]. Grau et al. [25] interrogated the Scandinavian Donations and Transfusions (SCANDAT2) database, which includes information on over 1.6 million blood donors from Sweden and Denmark. Using Swedish data information on fractures was obtained by linking SCANDAT2 to hospital registers. In total, 140,289 apheresis donors (67,970 women and 72,319 men) were identified from the SCANDAT2 database and were followed for up to 23 years. The authors observed no association between the apheresis frequency and fracture risk. The results were similar in analyses stratified by sex and restricted to postmenopausal women and whilst over 90% were plasmapheresis donors, there was no detectable difference between platelet and plasma donors.

Protein and immunoglobulin G levels

Immunoglobulin G (IgG) is the main circulating immunoglobulin, which plays a major role in humoral immunity and infection prevention. Plasmapheresis removes plasma proteins. Therefore, an acute decrease in plasma protein levels is expected immediately post-donation in line with the content collected. In a study of 54 experienced donors, the total IgG decreased by 13% immediately post-donation [26].

What are the potential clinical consequences of removing plasma proteins? First, does the acute reduction of IgG increase infection risk. Second, how long does it take for IgG to return to pre-donation levels. Third, does repeated plasmapheresis lead to a sustained drop, given subnormal IgG unrelated to plasmapheresis is associated with an increased infection risk [27].

An early study of 41 frequent plasma donors [28] found most of the changes in protein and IgG occurred in the initial 6 months. Over one quarter of donors experienced levels below the normal limit in the first 6 months but these were erratic and some rebounded. If plasmapheresis ceased, IgG returned to baseline levels after approximately 2 months.

Two early studies support maintaining IgG long term. At a donation interval of 2–3 weeks, ranges for total protein, albumin, IgG, IgA and IgM did not differ markedly from the first-time donor normal ranges [29]. In the second study [30], although the mean protein level of weekly donors fell significantly during the first 3 months, the values returned to almost baseline levels at the end of the 6-month study.

Riggert et al. [31] performed a single measurement of IgG subclasses 1–4 in 413 non-donor controls and 403 regular plasmapheresis donors who were donating low weekly volumes and found IgG values were not significantly lower. However, 113 donors had a second measurement 3–6 months later with a significant drop in total IgG, concluded to be donation related. Since there was no drop in IgG subclasses below the normal range, they concluded no likely clinical impact. Whilst the mean values were only slightly impacted, donors with a higher number of total donations tended to values below the normal. The authors concluded that this would not result in immunocompromise.

A 2-year Swedish study [32] investigated the effects of increasing the volume of plasma collected per donation to 16% TBV. There were no significant changes in protein patterns and no increase in adverse effects.

A prospective multi-centre study on the safety of long-term intensive plasmapheresis recruited [33] 3783 donors who donated up to 60 donations per year. Higher initial IgG levels and a lower donation frequency strongly protected against low IgG. The authors concluded that this intensive plasmapheresis regime is safe with careful monitoring. However, IgG fell with increasing plasmapheresis and resulted in a 12.5% deferral rate, therefore, intensive plasmapheresis did decrease IgG.

Moog et al. [34] investigated whether donors identified to have an IgG level below 6.0 g/L on at least three occasions should be permanently deferred for donor health. Three or more IgG measurements below the threshold occurred in 38.2% of 1462 control arm donors (donation protocol in accordance with national German guidelines) and in 20.9% of 14,281 individualized arm donors (donation protocol stratified by initial IgG and donor weight). However, there were no increased rates of infections in donors with ≥3 IgG measurements below the threshold.

Taborski and Laitinen [35] published interim donor safety results of an individualized plasma programme involving nearly 2 million donations. This prospective, multi-centre study aims to assess donor safety during an individualized plasma donation regime according to pre-donation IgG levels and body weight, compared with current German plasma donation guidelines monitoring DAEs and IgG levels. Most of the withdrawals with known causes were due to non-medical reasons. After an initial drop, IgG levels remained stable for up to 10 years. The results showed no significant difference in donor safety for donors on an individualized programme and those who donated under current guidelines, supporting the concept of donor stratification by pre-donation IgG levels.

The main consideration for determining a minimum donation interval is adequate time for endogenous IgG synthesis to replace removed plasmapheresis IgG. Whilst antibodies have the capacity to feedback regulate the production of themselves, the synthesis and catabolic rates of IgG vary between individuals. Some donors will maintain IgG levels on a particular donation regime; others will deplete on the same regime. Donors with lower levels are more likely to decrease below the reference range, but there is no difference overall between new and repeat donors [36].

Haemoglobin and iron levels

ID and ID anaemia are potential risks for plasmapheresis donors because of red cell loss associated with blood sampling for routine testing, retention of end-procedure residual red cells in the apheresis harness tubing and because of incidents requiring the procedure to be aborted before donor red cell return.

In a retrospective cross-sectional study of almost 53,000 donations [37], donors were stratified by donation type and the analysis concentrated on apheresis donors. In the analysis, apheresis donation frequency did not influence female ferritin values, but a significant male correlation was found. Whilst the authors concluded that both groups are at risk of ID attributed to residual blood loss and testing, in females iron compensation occurred whereas in males they developed ID. Haemoglobin screening and ferritin testing mitigated the risk of anaemia but resulted in a high rate of suspension for males and females, 21% and 50% of the totals, respectively.

A randomized placebo-controlled, double-blind study of iron supplementation for 59 female menstruating donors, scheduled for weekly plasma donations over 24 weeks, Bier-Ulrich et al. [38] demonstrated that the risk of ID with frequent plasmapheresis can be prevented with iron supplementation. The average total blood loss was 526–546 mL. Haemoglobin was measured before each plasmapheresis procedure and ferritin, transferrin and reticulocyte count every 4 weeks. At commencement, 8.4% of the donors had ID whilst at

completion 37.9% of the placebo group and 3.4% of the study group had ID.

Despite the two studies above that demonstrate plasmapheresis ID with no mitigation, there are other studies that are supportive of donors maintaining their iron and haemoglobin. An Australian study [39] demonstrated that the prevalence of ID in a plasma-only cohort (with saline infusion), did not exceed that for new donors, nor did it change with donation frequency.

A study of 1254 [40] plasma donors demonstrated a ferritin increase with increased donation frequency. For donors with 70 plus donations, ferritin was 13 ng/mL higher than in new donors ($p < 0.02$). Frequent donors may be more aware of the ID risk and act to risk mitigate; some donors may cease donation if symptoms or test results indicated anaemia or low ferritin. The authors concluded frequent plasma donation in the United States does not adversely impact iron stores in donors and therefore, it was not necessary to monitor iron status or give iron supplementation.

Procedural factors such as the extra-corporeal volume of the machine, use of end-donation saline infusion and sample requirements have a significant impact on blood loss and hence the risk of ID. With end-donation [41] saline and residual red cell return, the WB loss of almost weekly plasmapheresis could be reduced from almost 2.5 WB equivalent donations to less than one-third of a WB equivalent.

Haemolysis

Haemolysis is the rupture or destruction of red cells releasing haemoglobin. In apheresis, mechanical damage to the red cells can occur if there are malfunctioning valves, kinks or obstructions in the tubing [42]. If the haemolysed cells and free haemoglobin are returned to the donor, potential adverse effects such as vascular dysfunction, injury and inflammation occur [43]. The most common symptom in donors is pink urine.

In a recent international review, haemolysis was reported to occur in 0.14 per 100,000 apheresis donations, with 23% considered severe [44]; however, there were no further details. Young et al. [4] reported a lower rate of 0.02 per 100,000 donations.

Likely, there is variation in the rate of haemolysis between blood establishments, in part influenced by apheresis platform. In Australia, the rate of haemolysis increased from zero cases to a peak of 3.6 per 100,000 donations following the implementation of a new platform (Australian Red Cross Lifeblood internal data). All implicated donors were followed up and symptoms recovered quickly. Staff education, the introduction of routine checks to ensure no kit tube kinking and ensuring red cells are not returned when a haemolysis alarm is triggered or with pink plasma, significantly reduced the haemolysis rate.

Air embolism

Air embolism occurs when air enters the circulation due to machine malfunction or incorrect set-up. Air can occlude pulmonary arteries. Symptoms typically are respiratory and include dyspnoea, chest pain and tachycardia. For air embolism to result in a fatality, large volumes (200 mL plus) of air are required [45]. Fatalities associated with the use of older apheresis technology occurred in the 1940s/1950s due to positive pressure in the circuit, resulting in air being sucked into the circulation [46]. Modern apheresis machines make significant air embolism unlikely given standard alarms and inbuilt controls. A recent international surveillance study reported a rate of 1 in 2 million donations. Further details were not provided except that 38% ($n = 6$) were considered 'severe' [44]. Young et al. [4] reported a negligible risk of air embolism, 1 in 3.26 million donations. Schreiber et al. [9] did not report a single event in over 12 million donations.

Infiltration and compartment syndrome

Infiltration may occur during the return apheresis phase if fluid (saline or cellular components) is infused into the surrounding tissues following needle dislodgement. Swelling will occur and the donor may complain of pain or discomfort. Infiltration was reported to occur at a rate of 0.71 per 100,000 donations with none classified as severe [44]. Internal unpublished data from Australia reports rates of 280 per 100,000, demonstrating the difficulty of comparing international DAE rates, noting that this includes any swelling during the return cycle, including haematomas and minor events.

Compartment syndrome may occur if fluid leakage is within an anatomical compartment, resulting in high pressure and compromised tissue perfusion. It is a medical emergency requiring surgical intervention to prevent tissue necrosis. Compartment syndrome may also occur with arterial puncture and haematoma. Whilst in large data sets compartment syndrome has been described as rarely occurring with a rate of 1 in 7.6 million donations, further details and whether these cases represented true compartment syndrome is not known [4].

Risk of malignancy

It is hypothesized that frequent plasmapheresis donations could result in immune system alterations that could influence the proliferation of abnormal lymphocytes or result in gammopathies. Edgren et al.'s [47] study of Swedish and Danish blood donors found that the odds of non-Hodgkin lymphoma were higher among frequent plasma donors (>25 vs. 0 donations, odds ratio [OR] = 2.14, 95% confidence interval [CI] = 1.22–3.74). However, there was not a clear dose–response, there was no confounding factor information and the authors concluded this finding should be interpreted with caution.

A large Canadian cohort [48] found no correlation between plasma donation number or the frequency of donations per annum and the incidence of monoclonal gammopathies. Overall gammopathy rates were below the general population.

Other rare events

Other rare events may occur, such as anaphylaxis in response to exposure to apheresis consumables including the sterilizing agent ethylene oxide [42], with the last literature report of allergic-type reactions in plasma donations being from 1986 [49]. Donors may however experience acute health problems during or shortly after a plasmapheresis procedure purely by chance, with the event being unrelated to plasmapheresis. For example, isolated thrombotic and cardiac events are reported post-donation in case series as a potential donation complication [50, 51]. The background population rate of such events should always be considered before concluding a causal relationship. Case reports should not be relied on as evidence [52]. The donor may have other predisposing factors, which should be considered when determining causality.

A small cohort study demonstrated temporary drops in blood pressure [53] in hypertensive donors with less than 2-weekly donations and significant drops in total cholesterol [54] in donors who donated every 2–4 days. However, there are no studies that suggest these translate into lower cardiovascular events outside of the 'healthy donor effect' [55].

With modern apheresis machines, the risk of omitted anticoagulants resulting in harm to a donor is low. Whilst it is not known whether there is a thrombogenic cardiovascular risk with apheresis, citrate could theoretically lower this. Schulzki et al. [33] demonstrated a lower donor cardiovascular risk, also consistent with the healthy donor effect.

DISCUSSION

This evidence review demonstrates that plasmapheresis is generally well tolerated. However, there is a lack of high-quality evidence on risks and outcomes and the efficacy of interventions specifically in plasmapheresis. Whilst conservative procedural controls and donor harm minimization policies will support risk mitigation, the lack of large follow-up data sets limits conclusion on potential long-term health effects.

The medical supervision and care of apheresis donors should be managed by healthcare providers specifically trained in apheresis techniques. Best practice venepuncture can reduce the risk of phlebotomy injury. An upper collection volume limit is required for both physiological and manufacturing reasons (i.e., blood bag limits). However, research [9, 11, 14] suggests that there are individuals who can tolerate higher collection volumes than others. Some donors develop symptoms before collection commencement because of anxiety or pain precipitating a VVR. Whilst plasma collection volumes based either on nomograms or BMI both have limitations, using such methodologies to calculate the collection volume is pragmatic and, based on the limited available data, appears reasonable. Evidence of the safety of collection volumes above 880 mL is lacking and therefore blood establishments do not routinely collect above this cap. However, if nomograms are safe for smaller donors, there is no evidence to suggest larger collection volumes would not be safe for larger donors who are donating less of their TBV. The optimal way to collect adequate plasma being either increasing collection volume per donation versus increasing collections per donor over time has not been established.

Blood establishments should provide donors with blood donation preparation advice as well as post-donation care. Advice regarding adequate hydration and food pre- and post-donation should reduce the risk of volume-related VVRs, despite the fact there is not good evidence in plasma donors specifically. Given AMT decreases VVRs in WB donations due to an immediate blood pressure increase, it would be expected to decrease the plasmapheresis rate. Ensuring the donation environment is calm and welcoming is important to reduce VVRs secondary to fear.

Whilst an acute decrease in ionized calcium and associated hormonal changes from citrate anticoagulation are well documented in platelet donors [56, 57], data on longer term impacts are limited. Oral prophylactic calcium supplementation (at least 30 min before the procedure) could theoretically prevent some citrate reactions, but optimal timing, dose and formulation have not been determined. Reducing the return rate has an immediate effect of decreasing citrate with a resultant recovery of ionized calcium. The available evidence relating to bone metabolism and BMD in plateletpheresis and plasmapheresis donors, whilst limited in evidence strength; does not demonstrate a significant reduction in BMD, or an increase in bone fractures. Given the lower citrate load in plasmapheresis compared with plateletpheresis, altered bone metabolism is unlikely to be a significant plasmapheresis issue.

The available research on donor IgG levels and immune responsiveness is generally reassuring but further research is needed. Whilst plasmapheresis results in an acute, short-term reduction in IgG, and in some donors, an IgG level below the lower limits of the normal reference range, there is no evidence of increased infection risk. A decrease below the reference range is more likely in donors who have lower starting levels. Most studies show an initial fall in the donor's IgG level for a period of months, following which the IgG level increases towards the donor's pre-donation levels or stabilizes. Numerous studies have shown that as plasma IgG levels reduce, so does IgG catabolism, thereby extending IgG half-life. There is significant normal variation in IgG synthesis and catabolism rates, so a major limiting factor in plasmapheresis is the capacity of donors to restore their plasma proteins; this will also influence tolerable donation frequency.

Measurement of the donor's total protein and IgG level at the first donation can be used to tailor donation frequency [36]. IgG levels should be regularly monitored and, if the donor's IgG level falls below the lower reference range, the donor should be deferred or donation frequency reduced. The levels of proteins in the collected plasma also impact yield and product quality.

There is conflicting evidence on whether plasmapheresis impacts iron stores. Machine differences such as extracorporeal volume and hence maximum possible red cell loss, sample requirements, ferritin testing, advice regarding iron replacement and end-donation saline

can lead to profound differences in cumulative iron loss and may explain some of the evidence variation. Policies to decrease red cell loss can minimise risk including end-donation saline infusion to rinse back residual red cells and using the plasma bag for mandatory infectious disease samples.

For the haemolysis risk, with machine alarms and staff oversight, the volume of haemolysed red cells returned to a donor is small and unlikely to result in significant health complications. Whilst engineering controls are gold standard, introducing checks to ensure no kinking and ensuring red cells are not returned to donors if the plasma is tinged pink will reduce the complication risk.

Whilst there is no convincing evidence of an increased risk of malignancy or gammopathy, other rare events may occur.

CONCLUSION

Many blood establishments are expanding plasmapheresis collection capacity to achieve increasing plasma volume targets, driven by immunoglobulin product demand.

A framework to safely increase plasma collection should balance donor health with collection efficiency. Collection of DAEs and long-term health data and high-quality studies including clinical trials for interventions will contribute to safe and sustainable plasma collection and improve the limited evidence base. Large, linked databases are needed to evaluate longer term health effects. Evidence-based donor selection criteria and appropriate donor care are key factors in managing plasma supply [58] and more individualized donor assessment may facilitate balancing safety and supply.

ACKNOWLEDGEMENTS

Australian Governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian Community.

V.C.H. and J.P. primarily did the formal literature evaluation. However, all authors contributed to the literature review, drafting of the manuscript, critical review and approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. 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.
2. Thijsen A, Davison TE, Speedy J, Hoad V, Masser B. Offering new and returned donors the option to give plasma: implications for donor retention and donor adverse events. Vox Sang. 2021;116:273–80.
3. Burkhardt T, Dimanski B, Karl R, Sievert U, Karl A, Hübler C, et al. Donor vigilance data of a blood transfusion service: a multicenter analysis. Transfus Apher Sci. 2015;53:180–4.
4. Young P, Crowder L, Steele W, Irving D, Pink J, Kutner JM, et al. Frequency of rare, serious donor reactions: international perspective. Transfusion. 2021;61:1780–8.
5. Newman B. Venipuncture nerve injuries after whole-blood donation. Transfusion. 2001;41:571–2.
6. Thijsen A, Masser B. Vasovagal reactions in blood donors: risks, prevention and management. Transfus Med. 2019;29:13–22.
7. Grindon AJ. Adverse reactions to whole blood donation and plasmapheresis. Crit Rev Clin Lab Sci. 1982;17:51–75.
8. European Directorate for the Quality of Medicines & HealthCare. The guide to the preparation, use and quality assurance of blood components. 20th ed. Strasbourg: Council of Europe; 2020.
9. Schreiber GB, Becker M, Fransen M, Hershman J, Lenart J, Song G, et al. Plasmavigilance—adverse events among US source plasma donors. Transfusion. 2021;61:2941–57.
10. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224–32.
11. Pink J, Bell B, Kotsiou G, Wright S, Thyer J. Safe and sustainable plasmapheresis. ISBT Sci Ser. 2017;12:471–82.
12. Cepeda-Lopez AC, Zimmermann MB, Wussler S, Melse-Boonstra A, Naef N, Mueller SM, et al. Greater blood volume and Hb mass in obese women quantified by the carbon monoxide-rebreathing method affects interpretation of iron biomarkers and iron requirements. Int J Obes (Lond). 2019;43:999–1008.
13. Hartmann J, Ragusa MJ, Popovsky MA, Leitman SF. Source plasma collection in the United States: toward a more personalized approach. Am J Haematol. 2020;95:E139–42.
14. Schiller AM, Howard JT, Convertino VA. The physiology of blood loss and shock: new insights from a human laboratory model of hemorrhage. Exp Biol Med. 2017;242:874–83.
15. Karger R, Halbe M, Dinges G, Wulf H, Kretschmer V. Blood volume regulation in donors undergoing intermittent-flow plasmapheresis involving a high extracorporeal blood volume. Transfusion. 2006;46:1609–15.
16. Thijsen A, Masser B, Davison TE, van Dongen A, Williams LA. Beyond fear: a longitudinal investigation of emotions and risk of a vasovagal reaction in first-time whole-blood donors. Transfusion. 2023;63:163–70.
17. Wang C, Chen L, Sun C, Zhang Y, Cao C, Ma Y, et al. Prevention of blood donation-related vasovagal response by applied muscle tension: a meta-analysis. J Int Med Res. 2022;50:3000605221121958.
18. Vassallo RR, Bravo MD, Kamel H. Improved donor safety in high-volume apheresis collections. Transfusion. 2017;57:319–24.
19. Lewin A, Deschênes J, Rabusseau I, Thibeault C, Renaud C, Germain M. Pre-donation water and salty snacks to prevent vasovagal reactions among blood donors. Transfusion. 2023;63:156–62.
20. Bell AM, Nolen JD, Knudson CM, Raife TJ. Severe citrate toxicity complicating volunteer apheresis platelet donation. J Clin Apher. 2007;22:15–6.
21. Evers J, Taborski U. Distribution of citrate and citrate infusion rate during donor plasmaphereses. J Clin Apher. 2016;31:59–62.
22. Bialkowski W, Bruhn R, Edgren G, Papanek P. Citrate anticoagulation: are blood donors donating bone? J Clin Apher. 2016;31:459–63.
23. Amrein K, Katschnig C, Sipurzynski S, Stojakovic T, Lanzer G, Stach E, et al. Apheresis affects bone and mineral metabolism. Bone. 2010;46:789–95.
24. Bialkowski W, Blank RD, Zheng C, Gottschall JL, Papanek PE. Impact of frequent apheresis blood donation on bone density: a prospective,

longitudinal, randomized, controlled trial. Bone Rep. 2019;10:100188.
25. Grau K, Vasan SK, Rostgaard K, Bialkowski W, Norda R, Hjalgrim H, et al. No association between frequent apheresis donation and risk of fractures: a retrospective cohort analysis from Sweden. Transfusion. 2017;57:390–6.
26. Burkhardt T, Rothe R, Moog R. Immunoglobulin G levels during collection of large volume plasma for fractionation. Transfus Apher Sci. 2017;56:417–20.
27. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol. 2019;10:33.
28. Friedman BA, Schork MA, Mocniak JL, Oberman HA. Short-term and long-term effects of plasmapheresis on serum proteins and immunoglobulins. Transfusion. 1975;15:467–72.
29. Wasi S, Santowski T, Murray SA, Perrault RA, Gill P. The Canadian red cross plasmapheresis donor safety program: changes in plasma proteins after long-term plasmapheresis. Vox Sang. 1991;60:82–7.
30. Ciszewski TS, Ralston S, Acteson D, Wasi S, Strong SJ. Protein levels and plasmapheresis intensity. Transfus Med. 1993;3:59–65.
31. Riggert J, Hagchenas D, Seyfert UT. Determination of IgG subclasses 1-4 in plasmapheresis donors. Vox Sang. 1999;77:107–8.
32. Jansson U. Collection of plasma considering the calculated blood volume of the individual donor. Effects for donors, plasma collection, collection routines and economy. Report to National Board of Health and Welfare, Sweden. 2013.
33. Schulzki T, Seidel K, Storch H, Karges H, Kiessig S, Schneider S, et al. A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA). Vox Sang. 2006;91:162–73.
34. Moog R, Laitinen T, Taborski U. Safety of plasmapheresis in donors with low IgG levels: results of a prospective, controlled multicentre study. Transfus Med Hemother. 2022;49:271–9.
35. Taborski U, Laitinen T. Donor safety in an individualized plasmapheresis program—results of an interim analysis. Transfus Apher Sci. 2022;61:103446.
36. Burgin M, Hopkins G, Moore B, Nasser J, Richardson A, Minchinton R. Serum IgG and IgM levels in new and regular long-term plasmapheresis donors. Med Lab Sci. 1992;49:265–70.
37. Pfeiffer H, Hechler J, Zimmermann R, Hackstein H, Achenbach S. Iron store of repeat plasma and platelet apheresis donors. Clin Lab. 2021;67:387–95.
38. Bier-Ulrich AM, Haubelt H, Anders C, Nagel D, Schneider S, Siegler KE, et al. The impact of intensive serial plasmapheresis and iron supplementation on iron metabolism and Hb concentration in menstruating women: a prospective randomized placebo-controlled double-blind study. Transfusion. 2003;43:405–10.
39. Salvin HE, Pasricha S-R, Marks DC, Speedy J. Iron deficiency in blood donors: a national cross-sectional study. Transfusion. 2014;54:2434–44.
40. Schreiber GB, Brinser R, Rosa-Bray M, Yu ZF, Simon T. Frequent source plasma donors are not at risk of iron depletion: the ferritin levels in plasma donor (FLIPD) study. Transfusion. 2018;58:951–9.
41. Fischer T, Surikova I, Heesen E, Wilms G, Laitinen T, Taborski U. Loss of red cell mass in a plasmapheresis machine: effect of rinsing the disposable tubing with normal saline and reinfusion. Transfus Apher Sci. 2013;49:80–3.
42. International Society of Blood Transfusion and International Haemovigilance Network. Standard for Surveillance of Complications Related to Blood Donation. Amsterdam: ISBT; 2014.
43. Rapido F. The potential adverse effects of haemolysis. Blood Transfus. 2017;15:218–21.
44. Wiersum-Osselton JC, Politis C, Richardson C, Goto N, Grouzi E, Marano G, et al. Complications of blood donation reported to haemovigilance systems: analysis of eleven years of international surveillance. Vox Sang. 2021;116:628–36.
45. Toung Thomas JK, Rossberg Mark I, Hutchins GM. Volume of air in a lethal venous air embolism. Anesthesiology. 2001;94:360–1.
46. Ende N, Ziskind J. Air embolism in blood donors. JAMA. 1950;143:1483–5.
47. Edgren G, Reilly M, Hjalgrim H, Tran TN, Rostgaard K, Adami J, et al. Donation frequency, iron loss, and risk of cancer among blood donors. J Natl Cancer Inst. 2008;100:572–9.
48. Palmer DS, Scalia V, O'Toole J, Welch C, Yi Q, Goldman M. Incidence of gammopathies in long-term plasmapheresis donors at Canadian Blood Services. Transfusion. 2015;55:1347–54.
49. Dolovich J, Sagona M, Pearson F, Buccholz D, Hiner E, Marshall C. Sensitization of repeat plasmapheresis donors to ethylene oxide gas. Transfusion. 1987;27:90–3.
50. Leurent G, Bedossa M, Camus C, Behar N, Mabo P. Can plasma donation induce coronary-artery thrombosis. J Blood Disord Transfus. 2010;1:103.
51. Shams P, Tipoo FA. Lateral ST-elevation myocardial infarction after donation of COVID-19 convalescent plasma in a naïve donor. BMJ Case Rep. 2021;14:e242542.
52. Evers J, Taborski U. Anticoagulation, bleeding, and clotting at donor plasmapheresis. J Clin Apher. 2018;33:538–40.
53. Rosa-Bray M, Wisdom C, Marier JF, Mouksassi MS, Wada S. The effect of plasmapheresis on blood pressure in voluntary plasma donors. Vox Sang. 2015;108:11–7.
54. Rosa-Bray M, Wisdom C, Wada S, Johnson BR, Grifols-Roura V, Grifols-Lucas V. Prospective multicentre study of the effect of voluntary plasmapheresis on plasma cholesterol levels in donors. Vox Sang. 2013;105:108–15.
55. Atsma F, Veldhuizen I, de Vegt F, Doggen C, de Kort W. Cardiovascular and demographic characteristics in whole blood and plasma donors: results from the Donor InSight study. Transfusion. 2011;51:412–20.
56. Bolan CD, Greer SE, Cecco SA, Oblitas JM, Rehak NN, Leitman SF. Comprehensive analysis of citrate effects during plateletpheresis in normal donors. Transfusion. 2001;41:1165–71.
57. Boot CL, Luken JS, van den Burg PJ, de Kort WL, Koopman MM, Vrielink H, et al. Bone density in apheresis donors and whole blood donors. Vox Sang. 2015;109:410–3.
58. European Directorate for the Quality of Medicines & HealthCare and European Union. EDQM & EU Commission plasma supply management symposium recommendations to stakeholders. Strasbourg: EDQM and CoE; 2019. [cited 2023 June 12]. Available from: https://www.avis.it/application/files/7616/0093/4859/transfusion_edqm_eu_commission_plasma_supply_management_symposium_recommendations_to_stakeholders.pdf

How to cite this article: Hoad VC, Castrén J, Norda R, Pink J. A donor safety evidence literature review of the short- and long-term effects of plasmapheresis. Vox Sang. 2024;119:94–101.

Received: 11 June 2023 | Revised: 6 August 2023 | Accepted: 9 August 2023

DOI: 10.1111/vox.13516

REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries

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Funding information
The authors received no specific funding for this work.

Abstract

Industrial plasma fractionation, a complex and highly regulated technology, remains largely inaccessible to many low- and middle-income countries (LMICs). This, combined with the limited availability and high cost of plasma-derived medicinal products (PDMPs), creates deficiency of access to adequate treatment for patients in resource-limited countries, and leads to their suffering. Meanwhile, an increasing number of LMICs produce surplus plasma, as a by-product of red blood cell preparation from whole blood, that is discarded because of the lack of suitability for fractionation. This article reviews pragmatic technological options for processing plasma collected from LMICs into therapies and supports a realistic stepwise approach aligned with recent World Health Organization guidance and initiatives launched by the Working Party for Global Blood Safety of the International Society of Blood Transfusion. When industrial options based on contract or toll plasma fractionation programme and, even more, domestic fractionation facilities require larger volumes of quality plasma than is produced, alternative methods should be considered. In-bag minipool or small-scale production procedures implementable in blood establishments or national service centres are the only realistic options available to gradually reduce plasma wastage, provide safer treatments for patients currently treated with non-pathogen-reduced blood products and concurrently improve Good Manufacturing Practice (GMP) levels with minimum capital investment. As a next step, when the available volume of quality-assured plasma reaches the necessary thresholds, LMICs could consider engaging with an established fractionator in a fractionation agreement or a contract in support of a domestic fractionation facility to improve the domestic PDMP supply and patients' treatment.

Keywords

contract/toll plasma fractionation, haemophilia care, immunoglobulin concentrates, LMICs, pathogen-reduced cryoprecipitate, primary immunodeficiency, safe plasma proteins

Highlights

- Access to essential plasma-derived medicinal products (PDMPs) is inadequate in most low- and middle-income countries.
- Technologies exist for local preparation of safe plasma proteins as alternative or supplemental products to PDMPs to replace immunoglobulins and certain clotting factors.

- A stepwise practical approach can improve patient access to safe plasma proteins through local production while supporting advancement to contract or domestic fractionation of domestic plasma where feasible.

INTRODUCTION

Plasma-derived medicinal products (PDMPs) are crucial therapeutic proteins used in human medicine to treat conditions such as bleeding or immunological disorders and other diseases caused by congenital or acquired plasma protein deficiencies [1–3]. Several PDMPs feature on the World Health Organization (WHO) model lists of essential medicines for adults and for children [4]. While recombinant technologies are used to produce some plasma proteins, industrial fractionation of human plasma remains the primary method for obtaining many protein-based therapies, importantly including polyvalent immunoglobulins. Leading plasma fractionators, located in high-income countries (HICs), primarily focus on meeting the clinical demands for PDMPs within HICs, where their costs can be afforded. Consequently, the volume of plasma processed by established fractionators is driven by the needs of HICs, neglecting the needs of low- and middle-income countries (LMICs) and resulting in an imbalance in the availability of PDMPs between HICs and LMICs.

Over the years, the plasma fractionation industry has become a highly regulated, specialized and complex bioprocessing industry, producing a wide range of therapeutic plasma proteins with high quality and safety standards [1, 2]. Increasing demand for PDMPs in HICs has led the fractionation industry to expand capacity (nearly 60 million litres globally, over 80% obtained by plasmapheresis) and process larger plasma pools (5000 L or more at the stage of plasma pooling). This expansion aimed to boost productivity, increase availability and reduce production costs. However, despite these efforts, HICs still occasionally experience PDMP shortages, which can worsen during health or military crises [5, 6]. This situation has rekindled the view, including in LMICs, that plasma is a strategic national resource that should be managed responsibly to provide patient access to treatments [3, 7].

The persistent lack of access to PDMPs in many LMICs, which has been a reality for decades, affects most notably patients with bleeding disorders [8–10] or primary immunodeficiencies [11]. This shortage of safe PDMPs and appropriate treatment options leads to preventable patient suffering and mortality including risks of serious infections from exposure to non-pathogen-reduced blood or plasma, all resulting in substantial societal costs [9]. Patients' organizations, international as well as regional, play a crucial role in alerting governments to the urgent need to improve the supply of PDMPs in LMICs. Undoubtedly, humanitarian aid programmes, coordinated by patient organizations such as the World Federation of Haemophilia, are invaluable in meeting patients' needs [10], but they are insufficient at the moment and will not sustainably ensure domestic independence, even partial, in product supply for the long term. This situation underscores the rationale for using available recovered plasma in LMICs, produced as a side-product of red blood cell concentrates, as a source of PDMPs [12–14]. Shortages of PDMPs in LMICs occur in a context where the countries are producing increasing volumes of plasma domestically in their efforts to meet clinical needs for red blood cell concentrates. However, over the years, the growing sophistication and regulation of the plasma fractionation industry in HICs [1, 15, 16] have widened the regulatory, quality assurance and technological gap between HICs and LMICs. This gap, within the broader context of the global plasma product market, makes it increasingly challenging for most LMICs to fractionate this plasma domestically or to implement a contract or toll plasma fractionation programme [14].

To improve access to PDMPs in LMICs, WHO published a 'Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma' [12] within the scope of the 'Action framework to advance universal access to safe, effective and quality assured blood products' [17]. Additionally, the Working Party for Global Blood Safety (GBS) of the International Society of Blood Transfusion (ISBT) has provided educational forums [13, 18, 19] and has contributed to the creation of an International Coalition for Safe Plasma Proteins (ICSPP), which 'In cooperation with the WHO will facilitate in-country projects on stepwise enhancement of the quality, safety and volume of domestic plasma; local small-scale preparation of virus-safe clotting factors and immunoglobulins; and progress toward industrial plasma fractionation' [20].

The present paper provides further explanations on what we consider realistic stepwise options that could be made available to LMICs for the preparation of safe plasma proteins from domestic plasma.

REASONS FOR THE WASTAGE OF PLASMA IN LMICs

Every year, several million litres of plasma that could be used for fractionation, if of sufficient quality, are wasted in LMICs [21] for various reasons including the following:

Lack of component preparation and insufficient plasma quality

Several technical reasons explain why plasma is either not produced or is wasted:

1. The need for red blood cell replacement drives blood collection. However, many countries continue to transfuse whole blood [22] to patients in need of only red blood cells, while it could be separated into components of red blood cell concentrates, platelet concentrates and plasma. This practice of not separating whole blood is linked to a variety of issues. For instance, a lack of proper education and training in blood separation techniques can lead to a persistence

in the use of whole blood. Financial constraints can restrict access to necessary equipment and facilities, which slows down the adoption of blood separation procedures. Clinical practices may lead to continued use of whole blood over blood components to prioritize immediate patient needs. Lastly, infrastructure challenges can limit the ability of blood establishments to store and manage separated blood components, leading to favouring simpler storage and handling of whole blood. To date, the use of whole blood remains prevalent in several low-income countries although a continuous trend towards its separation into components is seen [22].

2. Many LMICs collecting a high proportion of low-volume whole-blood donations (200–300 mL), based on average body weight considerations of the donors, as opposed to the larger 450–500 mL volumes typically collected in HICs. While this does not inherently preclude plasma fractionation, it creates an additional technical challenge, requiring some adjustments to the typical processing of fractionation especially for the steps of plasma bag opening, thawing and large-scale cryoprecipitation.
3. The lack of a nationally coordinated blood system typically dominated by hospital-based collections. This results in fragmentation with numerous small blood collection sites positioned across a country and non-harmonized production and testing practices of the collected blood.
4. The absence of inspection and licensing of the blood establishments by national regulatory authorities, which is due to a lack of appropriate legislation, inadequate investment in the regulatory authority or a regulatory environment not involved with oversight of blood transfusion.
5. The production methods of plasma failing to meet the quality and safety requirements for fractionation due to a state of non-compliance with Good Manufacturing Practice (GMP) for the production of plasma for fractionation and manufacture of PDMPs. The non-compliance encompasses a variety of factors, for example, less stringent blood donor screening as well as testing procedures that are insufficient to control the prevalence of transfusion transmissible infectious diseases in the donor population; deficient traceability systems; lack of validation of production and testing facilities; inadequate collection, freezing and storage practices that cannot ensure proper cold chain; and insufficient manpower.

Overcoming such challenges in making sure that plasma meets GMP requirements for fractionation is a complex and time-consuming task that requires both national and international efforts, including capacity-building in blood establishments, improvements in healthcare infrastructure, changes in regulatory oversight and a national coordinated and sufficiently funded domestic blood system.

Insufficient volume and national infrastructure

Additional factors need to be considered when explaining why plasma from LMICs may still go unused even when GMP requirements are met in the most advanced blood establishments. One key factor is the increase in the plasma volume requirements due to the expanded capacity of the plasma fractionation industry in HICs. A few decades ago, a contract or toll plasma fractionation programme could be successfully established based on yearly sustainable volumes of 5000–10,000 L. However, today, established fractionators tend to require volumes approaching or exceeding 50,000 L on a yearly basis. Additionally, the volume of quality plasma considered necessary to justify the construction of a domestic plasma fractionation facility is roughly 300,000 L annually. Such a situation can affect the capacity of LMICs to use domestic plasma for PDMP manufacture when the yearly volume does not reach approximately 50,000 L. Moreover, a structured national programme is needed to ensure that plasma collected at multiple sites is properly frozen, stored and shipped with maintenance of product integrity and continuity of the cold chain [12, 13, 21, 23].

STEPWISE TECHNICAL OPTIONS FOR PROVIDING ACCESS TO SAFE PLASMA PROTEINS FROM DOMESTIC PLASMA IN LMICs

Pragmatic solutions, tailored to the developmental state of the blood transfusion system and the volume of available plasma, should be implemented [12, 13]. When plasma meets GMP requirements for further manufacture, these technical solutions can help avoid wastage, regardless of the available volume. This stepwise approach allows for the processing of plasma and increases access to safe plasma protein therapies. Over time, it can help to gradually meet patients' needs in safe plasma therapies in LMICs (Figure 1).

Pathogen-reduction treatments of single units of plasma and cryoprecipitate

Several photochemical technologies, including psoralen/UVA, riboflavin/UVB and methylene blue/visible light illumination, have been validated and licensed in various countries for the pathogen reduction treatment of individual plasma units for transfusion [24]. This pathogen-reduced material represents a safer alternative to untreated plasma for clinical indications where its use is justified, such as volume replacement associated with bleeding complications. Additionally, the cryoprecipitation of pathogen-reduced plasma can produce virally inactivated cryoprecipitate and cryoprecipitate-poor plasma as a first step for availability of plasma proteins, when logistically feasible. Pathogen-reduced cryoprecipitate (Cryo-PR) can be used in the treatment of various bleeding disorders including deficiencies in factor VIII, fibrinogen and von Willebrand factor [25], while, in principle, Cryo-PR-poor plasma may be used to substitute for local use of its non-pathogen-reduced counterpart.

Minipool and small-scale GMP processing of virally inactivated plasma protein fractions

In recent years, the feasibility of performing a minipool solvent/detergent (S/D)-filtration treatment on a low-volume (i.e., concentrated)

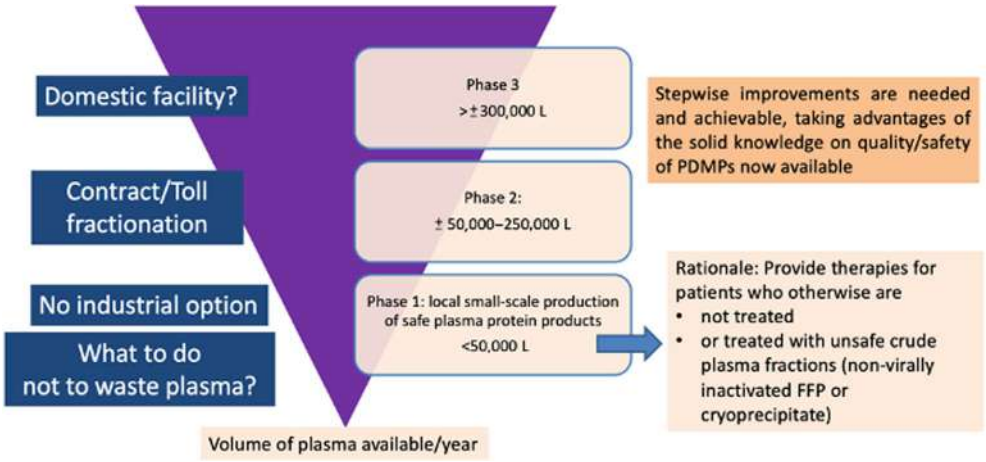

FIGURE 1 Illustration of the stepwise approach for production of safe therapeutic plasma proteins by implementing different technical solutions based on the volume of plasma available domestically. FFP, fresh frozen plasma; PDMPs, plasma-derived medicinal products.

cryoprecipitate using a bag system has been demonstrated by El-Ekiaby et al. at the Shabrawishi Hospital Blood Centre in Egypt [26]. This process, applied to a pool of 30–35 cryoprecipitates, includes an S/D virus inactivation treatment, oil extraction to remove a large proportion of the S/D agents, depth-charcoal filtration to polish S/D agent removal and 0.2-µm filtration to ensure bacterial sterility and removal of cell debris. Each batch contains approximately 3500 IU of factor VIII and von Willebrand factor ristocetin cofactor (vWF:rCo) activity and over 5000 mg of clottable fibrinogen. The final product is then dispensed into a series of bags and stored frozen until use. Quality control tests are performed on each batch, allowing each individual bag of cryoprecipitate to be labelled with precise potency for coagulation factor VIII, von Willebrand factor and fibrinogen. It contains a mean of 10.5 IU/mL of factor VIII, >10 IU/mL of vWF:rCo activity and 17 mg/mL of clottable fibrinogen [27] as well as factor XIII. Therefore, a 50-mL unit of the final product contains approximately 525 IU of FVIII:C, at least 500 IU of vWF:rCo activity and roughly 850 mg of clottable fibrinogen. As such, compared to untreated cryoprecipitate, this option is safety-assured against blood-borne enveloped viruses (including human immunodeficiency virus, hepatitis B virus and hepatitis C virus) and provides a higher concentration of coagulation factors, no or low levels of anti-A and anti-B isoagglutinin (due to the near-complete removal of plasma during cryoprecipitation), bacterial sterility, precise dosage, absence of blood cell debris and improved treatment consistency. This virally inactivated and filtered cryoprecipitate can be used in the acute treatment of bleeding in haemophilia A, von Willebrand disease, congenital fibrinogen deficiency as well as acquired fibrinogen deficiency from massive bleeding (e.g., post-partum haemorrhage and major trauma) and factor XIII deficiency, replacing untreated cryoprecipitate and serving as an alternative or supplementary product when PDMPs are not available or supplies are insufficient. This represents a significant step forward in the virus safety of cryoprecipitate-based therapy. Use of such locally prepared minipool S/D-filtration treatment of cryoprecipitate in Egypt since 2013 has resulted in the treatment of more than 2000 patients with haemophilia A who received 32 million units of coagulation factor VIII [28]. Production of freeze-dried and heat-treated cryoprecipitate has been developed and is still used in Thailand [29]. Since the end of 2022, the ICSPP has started to support a pilot project on cryoprecipitate, pathogen-reduced with S/D at the National Blood Transfusion Center in Dakar, Senegal, to field-test organization and management, technology implementation and validation, clinical efficacy and patient safety as well as sustainability of local preparation using a pathogen-reduction step. Recently, WHO has included Cryo-PR on the Model List of Essential Medicines (EML) for adults and for children, thereby recognizing its role in the acute treatment of patients with congenital (or acquired) deficiency in fibrinogen, factor VIII, von Willebrand factor or factor XIII, when coagulation factor concentrate (CFC) or analogous recombinant products are not available or affordable [4, 30].

The same group in Egypt has validated an in-bag caprylic acid purification and virus inactivation process to produce immunoglobulins from whole plasma or cryo-poor plasma. This process involves in-bag fractionation of plasma or cryoprecipitate-poor plasma with 5% caprylic acid, which precipitates non-immunoglobulin proteins, followed by centrifugation, dialysis to remove caprylic acid, concentration to ∼50 mg/mL, depth filtration and bacterial filtration [31]. Several batches of purified immunoglobulins can be mixed to increase the batch size and therefore the number of donors contributing to the final pool and the diversity of antibody specificities to neutralize a wide range of pathogens. Such pooling also contributes to the batch-to-batch consistency. This preparation has been successfully evaluated in children with immune thrombocytopaenia [32]. It should be noted that caprylic acid fractionation has been in use for many years for producing anti-venom immunoglobulins from the plasma of immunized horses in some LMICs [33]. A group from DOW University in Karachi, Pakistan, has also recently prepared clinical-grade anti-SARS-CoV-2 immunoglobulins from 4 to 8 L of human plasma using a similar technology [34]. This immunoglobulin underwent clinical evaluations in COVID-19 patients where it was found to be well tolerated [35]. This achievement demonstrates the feasibility for preparation of both normal and hyperimmune immunoglobulins, especially those that are on

the WHO EML for adults and children and are in short supply or unavailable in LMICs [4].

These relatively simple technical developments have numerous benefits. They can be implemented on small yearly plasma volumes within small facilities with minimal capital investment. They provide access to vital plasma proteins until PDMPs, which should always be regarded as the medically preferred therapeutic option, are available in sufficient quantity and affordable to all. Additionally, their preparation and use contribute to learning about GMP plasma collection and processing, reducing plasma wastage and promoting sustainability of blood establishments. Furthermore, these developments foster 'South-to-South' knowledge-sharing across blood establishments and regulators, facilitating the identification of context-specific solutions to improve access to plasma therapies. It is crucial, however, that such developments are overseen by trained local regulators to ensure the implementation of GMP at all stages of production.

Regarding cost consideration, several studies indicate that cryoprecipitate and Cryo-PR may be less expensive to provide than CFCs. It was stated in the recent ISBT application to incorporate Cryo-PR in the WHO EML [36] that 'the relative cost of non-Cryo-PR versus clotting factor concentrates has been examined in the context of comparative efficacy studies. For example, in studies comparing cryoprecipitate to commercial concentrates of fibrinogen, fibrinogen concentrates were found to cost two to four times that of cryoprecipitate per gram of fibrinogen [37, 38]'. In addition, 'data on the comparative cost of Cryo-PR versus plasma derived and recombinant CFC are limited, but some settings demonstrate significant savings [28]. In Egypt, the cost per unit of factor VIII from the minipool S/D-treated Cryo-PR was estimated in 2018 to be 0.07 USD compared with 0.14 USD for commercial factor VIII concentrates, whereas the average cost per unit of factor VIII for all types of commercial clotting factor concentrates was higher at 0.21 USD [28]. The current cost per international unit of factor VIII for the S/D-F cryoprecipitate in Egypt is between 0.16 and 0.086 USD based on the yield per processed pool of 30–35 cryoprecipitates. The same unit cost applies to von Willebrand factor (ristocetin cofactor activity) in this production system, and the cost per gram of fibrinogen is 24–29 USD [36]. In Thailand, the current cost of heat-treated freeze-dried cryoprecipitate (HTFDC) containing >200 IU FVIII:C per vial is approximately 21.47 USD (800 Baht), representing <0.107 USD per unit of factor VIII. The cost per gram of fibrinogen for HTFDC in Thailand is <51.12 USD [36]. In comparison, the cost per IU of factor VIII of an imported commercial clotting factor concentrate is typically more than twice the unit price for locally prepared Cryo-PR products made in Egypt and Thailand' [36]. The cost of commercial factor VIII concentrates in a selection of countries was found to range from 0.27 USD in South Africa to 2.53 USD in the United States and between 0.63 and 1.09 USD in other countries [39]. The possibility of applying a pathogen reduction treatment to a minipool of cryoprecipitate, instead of single units, contributes substantially to cost reduction. Differences in the unit costs of labour and materials may also contribute to this disparity.

Although these data suggest a cost benefit of cryoprecipitate and Cryo-PR in resource-constrained settings, they should not be preferred to CFCs within the scope of a stepwise improvement to access safe plasma proteins. Therefore, facilitating their preparation and use should not replace national progress towards assuring the availability of CFCs and other plasma protein products, as described below.

Industrial-scale fractionation

Industrial-scale plasma fractionation can be envisaged either through contract arrangements whereby domestic plasma is fractionated by a foreign fractionator (typically for a fee or 'toll'), or with the construction and operation of a domestic facility.

Contract/toll plasma fractionation

For LMICs with well-developed blood transfusion systems and the capacity to generate around 50,000 L of quality plasma annually, it becomes feasible to consider a contract/toll plasma fractionation programme with a reputable, licensed fractionator [12, 13, 40]. This decision requires careful selection of the plasma fractionator, considering its capacity to meet the country's clinical needs in terms of product specifications, guaranteed yield, product range, and more. Entering such an agreement requires harmonized quality procedures at a national level, including donor screening, donation testing and handling of plasma. These procedures must align with the requirements of the regulator overseeing the plasma fractionation activities and the fractionator's specifications, and be confirmed by audits carried out by the fractionator. Both blood establishments and fractionators should be inspected by regulatory authorities or audited by skilled, experienced experts (if inspections are not feasible), and the resulting PDMPs should obtain a formal marketing authorization. Contract/toll plasma fractionation offers a practical way to produce vital PDMPs from domestic plasma, reducing wastage and ensuring a more stable PDMP supply that can potentially complement direct imports. This approach avoids plasma wastage, improves the sustainability of blood establishments and provides a crucial learning phase in plasma processing. It requires minimal capital investment, apart from adapted facilities for plasma freezing and storage and their monitoring. It also serves as a training opportunity for domestic operators on plasma fractionation technologies before any potential technology transfer.

Domestic fractionation facility

Embarking on the construction of a domestic plasma fractionation plant is challenging and needs a careful feasibility study, considering the volume of plasma available at domestic or regional levels, as well as capital investment, skilled and experienced staff availability, manpower training and technological requirements. As mentioned above, it is estimated that the procurement of a consistent minimum annual volume of approximately 300,000 L of quality plasma should be assured [12, 13]. Although implementation of plasma fractionation technologies developed locally cannot be excluded (e.g., as a scale-up phase of a

small-pool pilot programme), it is considered that a secure, possibly complementary approach, lies in a technology transfer agreement signed with an established fractionator. The transition to domestic fractionation is simpler when the technology transfer is provided by a previously contracted foreign fractionator and the products provided through contract/toll fractionation have previously been validated. Such a plasma fractionator should provide all the necessary detailed technical documentation supporting the implementation of the manufacturing process of a selected range of PDMPs needed locally. Examples of documentation include standard operating procedures (SOPs), manufacturing protocols, quality control procedures, equipment and software manuals, validation procedures and regulatory filings. Furthermore, the provider of technology should offer training programmes to ensure the recipient's manpower is capable to operate the plasma fractionation processes and the associated utilities. This includes technical training on equipment operation, maintenance, and troubleshooting, as well as on the manufacturing process, quality control and compliance with GMP. There is also a need, during and after the technology transfer, for technical support to troubleshoot any issues that may arise. This encompasses guidance on process optimization, adjustments or improvements. The technology provider should assist in the validation of the new processes, including process validation, analytical method validation and cleaning validation, to ensure that they meet regulatory requirements, and should support implementation and maintenance of a robust quality assurance system, as well as adherence to GMP standards. Even after the technology transfer process is complete, the technology provider should be in a position to offer continued support to ensure the successful implementation and operation of the technology. Last but not least, it is crucial that the recipient of the technology should be capable of recruiting and retaining the specialized skilled manpower required to operate the new facility. The whole programme should have the full support of the government, which should be committed to its success and provide the expert regulatory oversight and skilled expertise to ensure GMP compliance [12]. A fiscal model for sustainability is also crucial, often requiring some level of governmental support.

OVERALL CONSIDERATIONS

It should be kept in perspective that such a stepwise approach encompasses not only the technical solutions described above but also essential considerations related to human factors. The first step is capacity-building for government regulators, blood establishment operators and healthcare providers to strengthen the entire blood system. Forging partnerships with more advanced blood establishments, abroad or domestically, can prove beneficial for LMICs seeking to improve quality plasma collection and access to plasma protein therapies. In particular, externally supported education and training programmes can play a crucial role in enhancing the skills and knowledge of the professionals involved in blood collection, processing and distribution as well as the use of plasma-derived products. International collaboration is especially helpful at this stage to help achieve recognized international standards for plasma quality and safety. Once the quality and available volume of plasma meet standards for fractionation, further steps can be taken to progress towards fractionation of domestic plasma. Collaborating with experienced centres and industry suppliers will allow knowledge sharing, technology transfer and best practices implementation, leading to more efficient and effective plasma processing, as supported by WHO [13, 21]. Understanding organizational restructuring requirements and implementing quality management systems are pivotal steps in building a robust and sustainable plasma supply chain [13, 21]. Emphasizing these aspects ensures that all stages of plasma processing adhere to international standards and GMP, thereby optimizing the safety and quality of therapeutic plasma proteins [23, 41, 42]. Cultural considerations also play a substantial role for fruitful collaboration and communication within the blood and plasma community to facilitate optimal collaboration between different stakeholders involved, and a harmonized approach to providing safe plasma protein therapies.

All these actions and coordination should aim at prioritizing patient safety and quality of care by emphasizing the value of safe plasma protein therapies. When plasma meets GMP requirements for further manufacture, these technical solutions, coupled with the proposed technical approaches described here, can collectively help avoid wastage of plasma, regardless of the available volume. This comprehensive and stepwise approach will allow the processing of plasma in a manner that optimizes resources and maximizes access to safe plasma protein therapies. Over time, this approach will facilitate a gradual and sustainable expansion in meeting patients' needs for safe plasma therapies in LMICs, as depicted in Figure 1.

CONCLUSION

Rapid developments are taking place in the biotechnology and gene therapy industry to enhance the efficiency of treatment of patients with genetic haematological diseases. Still, there is a continuous reliance on PDMPs to treat life-threatening conditions affecting, in particular, patients with bleeding or immunological disorders or others suffering from acquired or congenital deficiencies in plasma proteins. To date, many patients in LMICs affected with plasma protein deficiencies suffer from lack of treatment or are treated with crude blood fractions that expose them to the risk of transfusion-transmitted infections. Patient treatment in LMICs for these conditions has improved over the last few decades, but only marginally compared to the needs. Nonetheless, the blood transfusion systems in LMICs are also improving thanks to efforts coordinated by WHO and ISBT, among others, as illustrated by the steady increase in blood collections from voluntary non-remunerated blood donors, the higher proportion of blood separated into components and an increasing volume of recovered plasma available at the domestic level. This situation provides a window of opportunity for implementing tailor-made new pragmatic stepwise improvements in the access to safe plasma proteins, as highlighted in recent WHO Guidance [12]. The stepwise approach proposes to initiate improvements in the safety of patient treatment starting with local

preparation of pathogen-reduced units of plasma, cryoprecipitate and cryoprecipitate-poor plasma, followed by minipool or small-pool manufacture of virally inactivated cryoprecipitate and immunoglobulins, contract/toll fractionation of domestic plasma and, when practical and feasible, domestic fractionation. Such a stepwise approach is warranted and can be made possible thanks to the substantial knowledge gained over the last decades on the crucial factors contributing to the quality and safety of plasma protein fractions. All along this stepwise approach for the benefit of patients, engagement with international organizations or coalitions is critical to provide suitable guidance. Furthermore, it is critically important that regulatory authorities play a critical role in ensuring the implementation of GMP at all stages of such stepwise development including harmonization of standards across domestic blood establishments that provide plasma for fractionation.

ACKNOWLEDGEMENTS

All authors are members of the working party for Global Blood Safety of the International Society of Blood Transfusion, and members of the Steering Committee of the International Coalition for Safe Plasma Proteins.

T.B. wrote the first version of the manuscript. All authors provided comments and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Burnouf T. Modern plasma fractionation. Transfus Med Rev. 2007; 21:101–17.
2. Burnouf T. An overview of plasma fractionation. Ann Blood. 2018;3:33.
3. Strengers PF. Challenges for plasma-derived medicinal products. Transfus Med Hemother. 2023;50:116–22.
4. WHO Model List of Essential Medicines - 23rd list. 2023 Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02. Accessed 5 Aug 2023.
5. Covington ML, Voma C, Stowell SR. Shortage of plasma-derived products: a looming crisis? Blood. 2022;139:3222–5.
6. 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.
7. Strengers PF, Klein HG. Plasma is a strategic resource. Transfusion. 2016;56:3133–7.
8. Ghosh K, Ghosh K. Overcoming the challenges of treating hemophilia in resource-limited nations: a focus on medication access and adherence. Expert Rev Hematol. 2021;14:721–30.
9. Faber JC, Burnouf T. Bitter progress in the treatment of haemophilia A in low-income countries. Lancet Haematol. 2018;5:e239.
10. Pierce GF, Adediran M, Diop S, Dunn AL, El Ekiaby M, Kaczmarek R, et al. Achieving access to haemophilia care in low-income and lower-middle-income countries: expanded Humanitarian Aid Program of the World Federation of Hemophilia after 5 years. Lancet Haematol. 2022;9:e689–97.
11. Prevot J, Jolles S. Global immunoglobulin supply: steaming towards the iceberg? Curr Opin Allergy Clin Immunol. 2020;20:557–64.
12. WHO. Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. 2021 [cited 2021 Dec 24]. Available from: https://apps.who.int/iris/handle/10665/340171. Accessed 2 Aug 2023.
13. Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries: Local Production and Pathways to Fractionation. 2021 Available from: https://www.isbtweb.org/isbt-working-parties/global-blood-safety/resources/pdmpworkshop.html. Accessed 2 Aug 2023.
14. Burnouf T, Faber JC, Radosevic M, Goubran H, Seghatchian J. Plasma fractionation in countries with limited infrastructure and low-/medium income: how to move forward? Transfus Apher Sci. 2020; 59:102715.
15. Weinstein M. Regulation of plasma for fractionation in the United States. Ann Blood. 2018;3:1–15.
16. Rossi F. The organization of transfusion and fractionation in France and its regulation. Ann Blood. 2018;3:3.
17. WHO Action framework to advance universal access to safe, effective and quality assured blood products. Available from: https://www.who.int/publications/i/item/action-framework-to-advance-uas-bloodprods-978-92-4-000038-4. Accessed 2 Aug 2023.
18. Burnouf T, Epstein J, Faber JC, Smid M. Stepwise access to safe plasma proteins in resource-constrained countries: local production and pathways to fractionation-report of an International Society of Blood Transfusion Workshop. Vox Sang. 2022;117:789–95.
19. Burnouf T, Epstein J, Faber JC, Tayou Tagny C, Somuah D, Smid WM. Rationale for supporting stepwise access to safe plasma proteins through local production in low- and middle-income countries: a commentary of an international workshop. Biologicals. 2022;79:27–30.
20. Launch of the International Coalition for Safe Plasma Proteins (ICSPP). Available from: https://www.isbtweb.org/resource/launch-of-the-international-coalition-for-safe-plasma-proteins-icspp.html. Accessed 21 May 2023.
21. World Health Organization. Improving access to safe blood products through local production and technology transfer in blood establishments. 2015 Available from: https://www.who.int/publications/i/item/9789241564892. Accessed 2 Aug 2023.
22. World Health Organization. Global status report on blood safety and availability. 2021 Available from: https://m.nearbyme.io/search/?search_term=World%20Health%20Organization.%20Global%20status%20report%20on%20blood%20safety%20and%20availability%202021&brand=gc1. Accessed 2 Aug 2023.
23. WHO recommendations for the production, control and regulation of human plasma for fractionation, Annex 4, TRS No 941. https://www.who.int/publications/m/item/annex4-ecbs-human-plasma-fractionation 2005.
24. Cicchetti A, Berrino A, Casini M, Codella P, Facco G, Fiore A, et al. Health technology assessment of pathogen reduction technologies applied to plasma for clinical use. Blood Transfus. 2016;14:287–386.
25. Thomas KA, Shea SM, Spinella PC. Effects of pathogen reduction technology and storage duration on the ability of cryoprecipitate to rescue induced coagulopathies in vitro. Transfusion. 2021;61: 1943–54.
26. El-Ekiaby M, Sayed MA, Caron C, Burnouf S, El-Sharkawy N, Goubran H, et al. Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system. Transfus Med. 2010;20:48–61.
27. El-Ekiaby M, Goubran HA, Radosevich M, Abd-Allah A, El-Ekiaby A, Burnouf T. Pharmacokinetic study of minipooled solvent/detergent-filtered cryoprecipitate factor VIII. Haemophilia. 2011;17:e884–8.
28. El Ekiaby M, Burnouf T, Goubran H, Radosevich M, El Ekiaby A. Role of the mini-pool cryoprecipitate technology for cost-saving and

guarantee of local factor VIII, von Willebrand factor and fibrinogen product supply: Egypt experience. Ann Blood. 2018;3:22.
29. Nuchprayoon I, Sahasittiwat S, Kittikalayawong A, Chantanakajornfung A. Lyophilized cryoprecipitate for children with hemophilia A. J Med Assoc Thail. 2002;85:S293–7.
30. World Health Organization. The selection and use of essential medicines 2023: executive summary of the report of the 24th WHO expert committee on selection and use of essential medicines, 24–28 April 2023. Available from: https://apps.who.int/iris/handle/10665/371291. Accessed 4 Aug 2023.
31. El-Ekiaby M, Vargas M, Sayed M, Gorgy G, Goubran H, Mirjana R, et al. Minipool caprylic acid fractionation of plasma using disposable equipment: a practical method to enhance immunoglobulin supply in developing countries. PLoS Negl Trop Dis. 2015;9:e0003501.
32. Elalfy M, Reda M, Elghamry I, Elalfy O, Meabed M, el-Ekiaby N, et al. A randomized multicenter study: safety and efficacy of mini-pool intravenous immunoglobulin versus standard immunoglobulin in children aged 1-18 years with immune thrombocytopenia. Transfusion. 2017;57:3019–25.
33. Rojas G, Jimenez JM, Gutierrez JM. Caprylic acid fractionation of hyperimmune horse plasma: description of a simple procedure for antivenom production. Toxicon. 1994;32:351–63.
34. Ali S, Uddin SM, Ali A, Anjum F, Ali R, Shalim E, et al. Production of hyperimmune anti-SARS-CoV-2 intravenous immunoglobulin from pooled COVID-19 convalescent plasma. Immunotherapy. 2021;13:397–407.
35. Ali S, Uddin SM, Shalim E, Sayeed MA, Anjum F, Saleem F, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: a phase I/II randomized control trial. EClinicalMedicine. 2021;36:100926.
36. Application Submitted by the International Society of Blood Transfusion (ISBT) for Inclusion on the WHO EML and EMLc. Available from: https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a11_cryoprecipitate-pr.pdf?sfvrsn=87f1db91_3. Accessed 5 Aug 2023.
37. Okerberg CK, Williams LA 3rd, Kilgore ML, Kim CH, Marques MB, Schwartz J, et al. Cryoprecipitate AHF vs. fibrinogen concentrates for fibrinogen replacement in acquired bleeding patients – an economic evaluation. Vox Sang. 2016;111:292–8.
38. Novak A, Stanworth SJ, Curry N. Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage – how do they compare? Expert Rev Hematol. 2018;11:351–60.
39. Average prices of factor VIII in selected countries in 2017 (in U.S. dollars). Available from: https://www.statista.com/statistics/1089192/price-of-factor-viii-by-country/. Accessed 4 Aug 2023.
40. Farrugia A, Scaramuccia D. The dynamics of contract plasma fractionation. Biologicals. 2017;46:159–67.
41. WHO guidelines on good manufacturing practices for blood establishments, Annex 4, TRS No 961. Available from https://www.who.int/publications/m/item/gmp-for-blood-establishments-annex-4-trs-no-961. Accessed 4 Aug 2023.
42. Farrugia A, Evers T, Falcou PF, Burnouf T, Amorim L, Thomas S. Plasma fractionation issues. Biologicals. 2009;37:88–93.

How to cite this article: Burnouf T, Epstein J, Faber J-C, Smid WM, on behalf of the Working Party for Global Blood Safety of the International Society of Blood Transfusion. Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries. Vox Sang. 2024;119:102–9.

Received: 18 May 2023 | Revised: 5 September 2023 | Accepted: 17 September 2023

DOI: 10.1111/vox.13540

COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Europe needs 2 million extra donors of blood and plasma: How to find them?

BACKGROUND

In the summer of 2022, the European Commission published the Proposed Regulation on Substances of Human Origin (SoHO) [1] to update and replace the European Union (EU) Blood Directive [2] and the Tissues and Cells Directive [3]. The Regulation aims to protect donors and to ensure the safety and quality of blood, tissues and cells and to introduce measures to prevent shortages of these components produced from this precious material. With this Proposed Regulation, the European Commission renews its commitment to the principle of voluntary and unpaid donations. This principle prevents exploitation of donors—by risking their own health—without discouraging donations.

On 18 July 2023, the ENVI Committee of the European Parliament voted on its amendments on the Draft Report by MEP Nathalie Colin-Oesterlé on the SoHO Regulation in the EU, with 59 votes in favour, 4 against and 4 abstentions [4]. The Report is currently scheduled to be voted by the Parliament in its plenary session on 11 September. Once adopted, it will constitute the Parliament's negotiating position for the trialogue talks with the Council. With regard to the discussion on voluntary and unpaid donations, the ENVI Committee has sharpened its position. MEPs insisted that EU countries could allow compensation or reimbursement for losses or expenses related to their donations, whereby MEPs have asserted that compensation should not be used as an incentive to recruit donors, nor should it lead to the exploitation of vulnerable people. They also wanted strict rules on advertising around SoHO donations, which should prohibit any references to financial rewards. Based on transparent criteria, Member States shall establish the conditions for such forms of compensation or reimbursement in national legislation, ensuring that they are financially neutral and consistent with the standards laid down in Article 54 of the new Regulation and in accordance with the principle of voluntary and unpaid donation.

In this article, we calculate that Europe needs at least 2 million extra blood and plasma donors, who are willing to donate their blood and/or plasma several times a year. With these 2 million extra donors, Europe can continue to adhere to the principle of a blood transfusion system with voluntary non-remunerated (unpaid) donors (VNRDs) and be relatively self-sufficient. With these extra donors, Europe shall become less dependent on plasma derived from donors from other parts of the world, in particular from the United States.

Furthermore, we explore the possibilities of a closer collaboration between Blood Collection Services and patient and donor organizations. New ways of communication are needed to motivate EU citizens on the importance of donating their 'red' blood and/or 'yellow' plasma. Also, stronger cooperation between the private and the public sector regarding the fractionation of the collected plasma needs to be considered. The support of individual EU Member States is not sufficient to reach this goal. Only a combined action plan of all EU Member States together with the European Commission can lead to success.

This article reflects the perspective of representatives from the international donor community and from the patient community. We feel a joint responsibility to make a proposal that addresses the demand for plasma-derived medicinal products (PDMPs) for patient groups suffering from mainly rare diseases and that stimulates the donation of blood and plasma without underlying financial incentives.

INTRODUCTION

The EU SoHO Proposal includes an extensive evaluation period of the existing Directives for blood, tissues and cells based on consultations with EU Member States and relevant stakeholders. It also considers the recent COVID-19 pandemic, which has shown Europe's overdependence on non-EU ('third') countries for a variety of medical supplies (masks, swabs and protective clothing) and raw materials to produce medicines. In relation to plasma, Europe is dependent on ~40% or 4–5 million litres of American plasma from paid donors [5]. This dependency has grown during the last decades despite the 1985-formulated European principles of self-sufficiency and VNRD. We make a strong plea for strategic autonomy of Europe for plasma from VNRDs in line with the new EU proposal on SoHOs. Case studies in countries such as Italy, Belgium and Denmark have shown that sustainable supply of blood products is realistic with only VNRDs [6].

To reach this goal, Europe should expand its pool of blood and plasma donors and adjust the conceptualization of blood transfusion as a combination of 'red' blood (blood components such as red cells, platelets and plasma for transfusion) and 'yellow' blood plasma (plasma for fractionation needed to produce PDMPs such as albumin, immunoglobulins, clotting factors and serine protease inhibitors). In

BOX 1 Blood and plasma

In the past century, the products of human blood were traced and isolated. Nowadays, most people are familiar with the possibility to donate blood. In a Blood Collection Service, a blood donor donates a maximum of 500 mL of whole blood at a time. This takes 30–45 min. After donation, the blood is separated into blood cells and plasma which can be used as plasma for transfusion or as plasma for manufacturing (recovered plasma).

Plasma can also be donated using plasmapheresis. Whole blood of the plasma donor enters the plasmapheresis machine where plasma (source plasma) is separated from blood cells which are returned in the circulatory system of the donor. A plasma donation of 650–850 mL takes just over an hour.

From source plasma and recovered plasma, PDMPs can be made with a long shelf-life. Examples are coagulation factors for haemophilia, albumin to treat burn wounds and liver problems and immunoglobulins for all kinds of immunological diseases.

Plasma can be donated more often than blood. Most European countries rely on voluntary non-remunerated blood and plasmapheresis donors. Plasmapheresis donors are paid for their donations in four countries in Europe (Austria, Germany, Czech Republic and Hungary) and in the United States, Ukraine, China and others.

The European Directorate for the Quality of Medicine (EDQM) recommends that a plasma donor may give 25 L of plasma per year, which corresponds to 33 donations per year. In the United States, a plasma donor can donate plasma 104 times per year, that is, twice weekly, and three times more than what the EDQM recommends.

Box 1, we have explained the main developments in whole-blood and plasma collections in the previous decades.

The demand for red blood and yellow plasma

In recent years, the demand for red blood and yellow plasma in Europe has evolved in two different directions. The demand for red blood has decreased because of improved blood products and developments in patient blood management strategies, including cell-saving techniques during surgery and non-invasive surgical procedures. The demand for the yellow PDMPs has increased by ~8%–9% per year [7]. The increasing demand for and use of immunoglobulins is the main cause of the worldwide plasma shortage in both private and public sectors. This is especially detrimental for patient groups who depend on immunoglobulins for very different indications such as primary and

BOX 2 Number of donors needed and how to accommodate them

Currently, Europe has 15 million donors and 1400 Blood Collection Services, where 20 million units of whole blood are collected. Each year, EU patients are treated with 25 million blood transfusions to treat anaemia and during surgery or trauma care. The number of EU citizens who receive PDMPs is unknown.

At present, the EU has a shortage of almost 3.8 million litres of plasma for manufacturing. In 2025, Europe will need almost 8 million litres of plasma to reduce dependence on plasma from the United States.

With an extra need for 8 million litres of plasma, we propose that the collection of European source plasma should increase as follows:

The calculation is conservative and global.

One million whole blood donations of 500 mL each give 250,000 L of recovered plasma.

One million plasma donations of 750 mL each give 750,000 L of source plasma.

Whole-blood donations can be made up to four times a year, and plasma donations can be made up to a maximum of 33 per year.

We calculate for whole-blood donors an average frequency of two donations per year and for plasma donors an average frequency of five donations per year.

One million extra whole-blood donors, who give 250 mL recovered plasma and who donate twice a year, would generate 500,000 litres of recovered plasma.

One million extra plasma donors, who give 750 mL source plasma and who donate five times a year, would deliver 3,750,000 litres of source plasma.

An ethical issue remains that with this amount of recovered plasma, there will be an excess of red cells and platelets for which there is no need in Europe. The recommended Action Plan should also address this issue.

So, around 2 million extra whole-blood and plasma donors can solve the actual shortage of around 4 million litres of plasma in the EU. Another 2 million extra donors of whole blood and plasma can prevent the expected shortage in 2025.

The combined Blood Collection Services in the EU should plan how to accommodate 2–4 million extra donors in their systems, given production efficiencies and scales of operation. These are quite different for whole-blood donors and plasma donors.

A balanced mix of whole-blood donations and plasma donations is the preferred mode of action to keep existing donors and to attract new donors. For Blood Collection Services, it is preferable to have both types of donors in the same donor base.

The advantage of low-frequency donations is the reduced individual donor burden, the increased donor health protection, the higher diversity of antibodies in a larger donor base and an increase of the total donor pool.

The capacity per plasmapheresis centre is on average at least 20,000 L/year. To collect almost 4 million litres extra, some 200 extra plasmapheresis centres are needed with 15 or more beds. [Correction added on 31 October 2023, after first online publication: The amount of recovered plasma was corrected throughout in Box 2.]

secondary immune deficiencies and immunosuppressive problems or rare auto-immune and inflammatory diseases in the field of immunology, haematology, neurology and dermatology. In most EU countries, there is a shortage of immunoglobulin products. The long-standing, but still unresolved discussion among medical professionals about the indications for immunoglobulin use is unlikely to provide an answer to those patients, and their families, who are strongly dependent on these products [8].

There is an estimated 38% deficit of plasma in Europe, which is equivalent to 4–8 million litres of blood plasma [9]. This implies that around 2–4 million extra plasma donations are needed from donors who donate their whole blood at least twice a year or their plasma five times per year. Around 8 million extra donations can be obtained from these donors. Another 2 million extra donors of whole blood and plasma can prevent a further shortage of plasma in 2025, given the projected growth of PDMPs [9]. In a population of 447 million citizens in Europe, there are over 165 million eligible donors. This means that it must be possible to recruit 2–4 million extra donors.

For a calculation of these figures, see Box 2.

The paid versus unpaid (voluntary) discussion

The new EU SoHO Regulation and especially the voting on the Amendments in the ENVI Committee once again stressed the principle of VNRDs.

For more than 50 years, a debate has been going on about whether or not donors should be paid for their donation of blood and plasma. The ethical discussion on paid and unpaid donations was already raised in 1970 with the publication of the book *The gift-relationship: from human blood to social policy* by Richard Titmuss [10]. Titmuss is one of the founding fathers of the idea of the Welfare State and voiced his philosophy of altruism in social and health policy. Titmuss compared the British system of blood donations with systems in other countries and especially with the American one. In Britain, the system relies on VNRDs, while in the United States the plasma supply was and still is largely in the hands of for-profit enterprises. Already in September 1966, Titmuss had written about 'the hazards of blood commercialization to health, in particular patients' with the greater risks of contracting serum hepatitis and other blood-borne diseases because the health of paid donors was less reliable than that of volunteers' [11]. He intended to signal the dangers of the increasing commercialization of society. The US Food and Drug Administration (FDA) came out with a regulation in 1977 which required that each container of blood and blood components should bear the label statement 'Paid Donor' or 'Volunteer Donor'. This regulation was at that time based on the argument that blood from a paid donor was more likely to induce hepatitis in recipients than blood from a volunteer donor. This FDA labelling regulation is still in place [12].

A second important book was written by the Dutch journalist Piet J. Hagen, which was published in 1982 titled *Blood: gift or merchandise* [13]. The basic question Hagen wanted to answer was 'How (can) a sufficient and high-quality blood supply [...] be organized in a responsible way and at reasonable costs'. His answer is not one-on-one, unlike Richard Titmuss's. Hagen is more realistic and states that if 'under the altruistic system in a certain country the needs of patients cannot be met adequately, one has to reconsider one's position'.

After Hagen's book was published in 1982, the paid–unpaid discussion got a new dimension with the occurrence of thousands and thousands of HIV as well as HCV infections in the international haemophilia community. Countries with a dominant market share of clotting factor products manufactured from plasma from paid donors had a much higher share of these infections than those countries—especially in Europe—that used mainly haemophilia products prepared from plasma from VNRDs, such as Belgium, The Netherlands and the Scandinavian countries [14]. These transmissions of blood-borne infections caused enormous loss and grief in the haemophilia community. Still today, people suffer from the long-term effects of these viral infections, and in the United Kingdom the Infected Blood Inquiry shows how the UK Government nowadays has to deal with compensations issues [15].

A more recent overview on the discussion on paid versus unpaid donations was published in 2020 by the Fundacio Victor Grifols i Lucas with the title 'Ethics and plasma donation: an overview' [16]. In this overview, the final conclusion is that 'it is questionable as to whether plasma self-sufficiency is attainable in an individual country or region, at least in the short to medium term, and particularly if based exclusively on unpaid donations. The reality is that most countries have to purchase plasma products from companies that manufacture them using plasma from individuals who are remunerated for their donation, as the plasma obtained from each country's altruistic donors is not remotely sufficient to meet demand for these products'. In this overview, ethical considerations are pragmatically coupled with supply and demand issues, whereas the original altruistic approach by Richard Titmuss was coupled with social and health policies. The pragmatic approach in Grifols's overview is rather comparable with Piet J. Hagen's view.

Although the United States is the main supplier of plasma from paid donors, and despite that FDA permits a high frequency of plasma donation up to 104 times per year, there are also in that country opponents of the paid plasma donation system. In his book *What money can't buy: the moral limits of markets*, Michael J. Sandel returns to Titmuss's basic assumptions that 'Markets are crowding out non-market norms' and that 'Commodification of blood offers a good illustration of the two objections to markets identified earlier—fairness

and corruption' [17]. In *Blood Money: the story of life, death and profit inside America's Blood Industry* by Kathleen McLaughlin, she describes how Americans and their families with two or three jobs still live in a difficult financial situation and where payment for plasma donations is needed to survive [18]. In this regard, it is significant how the author warns that—even after what happened in the 1980s and 1990s with contaminated plasma—once again 'We've built an entire segment of global medicine upon the certainty that some number of American simply can't live on a regular income alone. They need money to supplement their wages and make their lives easier. And we don't exactly know if or how this frequent extraction of blood proteins might harm their bodies in the long turn'. In *Poverty by America*, Matthew Desmond describes that the United States, the richest country of the world, has more poverty than any other advanced democracy [19]. And that US policies privilege the affluent more than the poor. In that book, he also mentions paid plasma donation as a way to get income, but that in a particular case it does not work as 'She tried donating plasma, but her veins were too small'. Sandel and Desmond are in the paid–unpaid discussion not in favour of the ethical–market arguments for paid donations but favour the ethical–societal arguments for more solidarity and equity.

On 18 July 2023, the ENVI Committee of the EU Parliament confirmed that blood donation in Europe is based on the principle of voluntary and unpaid donation and that compensation, even in countries where it is permitted, should not be used as an incentive to recruit donors or lead to the exploitation of vulnerable people. They also wanted strict rules on advertising around SoHO donations, which should prohibit any references to financial rewards. This is in sharp contrast with daily practice in the United States nowadays, where websites of plasma collection centres already at entrance mention that you can earn up to $6000 per year [20].

As authors of this article, we still and without hesitation are in favour of VNRDs—Alice because she has been a plasma donor since the age of 18 and has first-hand experience of the value of systems based on the ethical value of voluntary, unpaid donation and the essential role that donor organizations can play in creating a community of regular, motivated donors. The promotion of these values in all countries of the world is indeed one of the main objectives of the International Federation of Blood Donor Organizations (IFBDO/FIODS), of which she is a member of the Executive Council and head of the European Continental Committee [21].

Cees is in favour of VNRDs because he had already warned in 1979 about the risks of the paid donor system and because he is a long-term survivor of HIV and HCV, which he got being a haemophiliac [22]. He believes strongly that we have a moral legacy towards all who suffered from these blood-related viral infections to strive for a safe and healthy environment for donors as well as recipients of blood and PDMPs.

A series of proposed actions

We propose a series of actions that the EU Member States and relevant stakeholders (blood collections services, donor organizations, patient groups, EU Commission, EU Member States, public health authorities, sector associations, etc.) can adopt to realize the requested increase of blood and plasma donations and group and number them 1 to 10 according to the levels of responsibility. At the moment, the organization and responsibility for collecting blood and plasma in the EU Member States varies widely, so the need for a strong EU coordination effort is crucial. Once the new SoHO regulation is adopted, it seems logical that the new SoHO Coordination Board at the EU level together with the new SoHO National Authorities in the EU Member States should further explore what actions are needed in the different EU Member States but with the final aim to reach EU self-sufficiency.

EU Member States

1. EU Member States should encourage a joint effort by public health authorities, Blood Collection Services and patient and donor organizations to attract more donors of blood and plasma. The proposed SoHO Regulation focuses on donor protection, and whole-blood and plasma donors are equally committed, so the new rules should not introduce changes to treatment of donors based on the type of donation. A balanced mix of whole-blood and plasma donors is required to keep existing donors and to attract new donors.

EU blood collection services

2. The public European Blood Collection Services should collectively formulate a policy to increase the number of donors in different EU countries. The balance between whole-blood and plasmapheresis donations should be made clear to the individual EU Member States. A first step towards such a policy is the recently started SUPPLY project led by the European Blood Alliance (EBA) [23].
3. In addition to the above actions, a programme is required to collect more blood and plasma in each Member State. Such a programme should cover a period of at least 5–10 years to meet the currently expected demand for PDMPs and especially immunoglobulins.
4. A structured communication and a social marketing strategy needs to be developed to attract new donors, considering national differences in donor attitudes. These strategies should be based on the donation of red blood and yellow plasma, as both are equally important parts of the contribution that each citizen can make to the health system. We realize that one of the most strategic challenges is the necessary cultural change (points 5 and 6). Strategies are also needed to ensure that all EU Member States and societal groups contribute equally to the donation of blood or plasma. The other question is who shall be responsible for such a communication strategy and where are the finances to be found. Communication needs to be sustainable and not a one-time issue. To that end, it seems a good idea the proposed establishment—within the new legislation—of a European day dedicated to essential SoHO donations [24].

5. Blood and plasma donation must be easy. This means that Blood Collection Services should be open for donations after working hours. Employers should facilitate their workers to donate blood or plasma during working hours. However, donations should be voluntary and pressure from management or peer group must be avoided.

Civil society and companies

6. Organizations in both the public and private sector should take the lead in organizing special programmes for their employees to donate blood or plasma collectively. The same is true for minority groups, who often are willing to donate if that can be organized in close cooperation with their peer group.

Donor and patient organizations

7. Patient and donor organizations should collectively develop campaigns to inform EU citizens why blood and blood plasma donations are needed and that regularly donating blood and plasma is safe, and show which patient groups profit from their donations. If such organizations are lacking or are inactive in some countries, they can be supported by the organizations from other countries or their European support groups.
8. All over Europe, Blood Collection Services should cooperate with donor and patient organizations to attract more donors and keep them motivated to stay as donors. Such communities can indeed play a strategic, complementary and ever more effective role not only in recruiting and retaining donors but also in terms of donor education and— more in general—in developing a shared European culture of anonymous, unpaid and regular blood/plasma donation.

European Commission

9. As much as permissible according to EU financial rules, the European Commission should finance the expansion of Blood Collection Services and the necessary extra equipment to collect more blood plasma where needed. The experiences gained during the collection of convalescent plasma during the COVID-19 pandemic can be used.

Public–private partnerships

10. The collected blood plasma could be made available by the public sector to the private sector for fractionation (possibly in a sort of 'outward' or 'counter' processing regime), as in the last decades in Europe most public fractionation centers have disappeared or have not the scale to process this extra plasma. If it is possible according to EU regulations, legislation should be developed to ensure that plasma collected in Europe is used for the benefit of European patients. Efforts to increase plasma collection in Europe will be undermined if the plasma is funnelled to a global market.

Limitations of this article

We have calculated that the EU needs at least 2 million extra donors of blood and plasma. Of course, this calculation has its limitations. There are no accurate or actual data of demand and supply of blood components and PDMPs as far as we know on which we can make a more accurate analysis. Or data are lagging behind as with the data collected by the EDQM, which goes back to 2017–2019 before the COVID-19 pandemic [25]. Data on PDMPs are more in the private domain. Information is also missing on plasma collected in the four EU countries with paid donations; nor is information available whether this collected plasma is returning also to these countries once processed to PDMPs.

Collecting more accurate data in the future on the collection and use of blood and blood components and PDMPs is one of the challenges for the to-be-established single SoHO National Authority in the EU Member States and the SoHO Coordination Board at the EU level.

Another limitation of this article is the reality level of the proposed EU SoHO Regulation. It is quite an ideal for the EU to become less dependent on US plasma in a situation where this has not proven to become a reality in the past 50 years. Or even worse, the EU has in these 50 years become more and more dependent on the use of US plasma from paid donations. But the COVID-19 pandemic and the possibility that the former US President Donald Trump wanted to make use of the 'US Defense Act' to limit the export of US plasma to non-US countries made EU policy makers once more realize their strategic dependence on the United States for PDMPs. So, there is a huge challenge for the EU ahead to realize this concept of independence from US plasma and to replace it by enough plasma from NRVD donations from EU blood and plasma donors. The issue is also complicated because the EU continues with a regulatory situation where blood and blood components are in the jurisdiction of the new SoHO regulation whereas the PDMPs are part of the EU Pharmaceutical Legislation.

In the end, however, one of the main messages we would like to convey is that to claim that it is necessary to pay—for the achievement of self-sufficiency in blood and PDMPs at the European level—for the donation of blood or plasma constitutes a short-sighted way of dealing with the challenge of our independence from supplies coming from the United States. And the reason is that, on one hand, we know that our donors are ready to donate plasma if they are well informed and if they have the opportunity to make this act a positive experience, in public and well-organized collection centres. On the other hand, relying on public collection systems that operate on the basis of a counter-processing regime represents the most appropriate way to protect our community as a whole, which keeps both those who donate and those who need blood-derived medicines safe from exploitation and market fluctuations. Europe is showing its

engagement in this regard, and we count on our contribution as donors and patients to help achieve our common goals.

SUMMARY

With the almost unanimously adopted amendments in the ENVI Committee of the European Parliament of the new EU SoHO Regulation, the challenge is how the EU can become less dependent on US plasma. Currently, the EU is almost 40% dependent on PDMPs from paid donations. The ENVI Committee has sharpened the rules for donation and insisted that EU countries could allow compensation or reimbursement for losses or expenses related to their donations. Compensation should not be used as an incentive to recruit donors, nor should it lead to the exploitation of vulnerable people. They also want strict rules on advertising around SoHO donations, which should prohibit any references to financial rewards.

To become independent of the United States for plasma donations implies a big challenge for the EU. In this article, we have formulated a number of actions for all stakeholders to reach this goal; we have calculated that Europe needs at least 2 million extra blood and plasma donors who are willing to donate their blood and/or their plasma several times a year. Furthermore, we explored the possibilities of a closer cooperation between Blood Collection Services and patient and donor organizations. Finally, only a combined action plan of all EU Member States together with the European Commission can lead to a lesser or no degree of dependence on US plasma from paid donations.

ACKNOWLEDGEMENTS

We are grateful to Dr. Paul Strengers (consultant) for his notes on a previous version of this article and his assistance with the calculation in Box 2 and Dr. Annemarie de Knecht-van Eekelen (medical historian) for the editing of this manuscript.

C.S. wrote the first draft of the manuscript and A.S. reviewed and finalized the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Ref. 9. These data were derived from the following resources available in the public domain: Ref. 9. There are no data in the publication.

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REFERENCES

1. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on Standards of Quality and Safety for Substances of Human Origin Intended for Human Application and Repealing Directives 2002/98/EC and 2004/23/EC. Published 14 July 2022. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52022PC0338. Last accessed 3 Sep 2023.
2. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 Setting Standards of Quality and Safety for the Collection, Testing, Processing, Storage and Distribution of Human Blood and Blood Components and Amending Directive 2001/83/EC. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2002/98/ec-european-parliament-council-27-january-2003-setting-standards-quality-safety-collection-testing_en.pdf. Last accessed 3 Sep 2023.
3. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF#:~:text=This%20Directive%20lays%20down%20standards,of%20protection%20of%20human%20health. Last accessed 3 Sep 2023.
4. European Parliament 2019–2024. Committee on the Environment, Public Health and Food Safety, 2022/0216 (COD). Draft report Nathalie Colin-Oesterlé (PE738.661v01-00) Amendments 118-327.
5. The Brussels Times. EU Looks to Reduce Dependency on the US for Human Plasma Needs. March 7, 2023. Available from: https://www.brusselstimes.com/396659/eu-looks-to-reduce-dependency-on-the-us-for-human-plasma-needs. Last accessed 3 Sep 2023.
6. Vandekerckhove P. How Europe Can Ensure Sustainable Supply of Blood Components on a Voluntary Non-Remunerated Basis. European Parliament. 25 January 2023. Available from: https://europeanbloodalliance.eu/wp-content/uploads/2023/01/EBAevent_Sustainable-supply-of-blood-components-on-a-VNRD-basis_Philippe Vandekerckhove.pdf. Last accessed 3 Sep 2023.
7. Strengers P. Challenges for plasma-derived medicinal products. Transfus Med Hemother. 2023;50:116–22.
8. Brand A, De Angelis V, Vuk T, Garraud O, Lozano M, Politis D, et al. Review of indications for immunoglobulin (IG) use: narrowing the gap between supply and demand. Transfus Clin Biol. 2021;28:96–122.
9. Hotchko M. Plasma Flows on a Global Level Why It Travels So Far. PPTA Presentation "Introduction to the Global Journey of Plasma". January 2021. Available from: https://marketingresearchbureau.com/wp-content/uploads/2021/09/Hotchko-MRB-website-presentation.pdf. Last accessed 3 Sep 2023.
10. Titmuss RM. The gift relationship: from human blood to social policy. London: Allen and Unwin; 1970.
11. Fontaine P. Blood, politics, and social science: Richard Titmuss and the Institute of Economic Affairs, 1957-1973. Isis. 2002;93:401–34.
12. Compliance Policy Guide CPG Sec. 230.150: Blood Donor Classification Statement, Paid or Volunteer Donor Guidance for FDA Staff. 2019.
13. Hagen PJ. Blood: gift or merchandise. New York: Alan R. Liss Inc.; 1982.

14. Smit C, Rosendaal FR, Varekamp I, Brocker-Vriends A, van Dijck H, Suurmeijer TP, et al. Physical condition, longevity and social performance of Dutch Haemophiliacs 1972-1985. BMJ. 1989;298:235–8.
15. Available from: www.infectedbloodinquiry.org.uk. Last accessed 3 Sep 2023.
16. Victor Grifols i Lucas Foundation. Ethics and plasma donation: an overview. Barcelona: Victor Grifols i Lucas Foundation; 2020.
17. Sandel MJ. What money can't buy: the moral limits of markets. London: Penguin Books; 2013.
18. McLaughlin K. Blood money: the story of life, death, poverty inside's America's blood industry. New York: Atria/One Signal Publishers; 2023.
19. Desmond M. Poverty, by America. New York: Crown Publishing Group; 2023.
20. Available from: www.lifeplasma.com. Last accessed 3 Sep 2023.
21. Available from: www.fiods-ifbdo.org. Last accessed 3 Sep 2023.
22. Smit C. Surviving hemophilia, a roadtrip through the world of healthcare. Utrecht: Eburon Academic Publishers; 2020.
23. Supply Project Kick-Off: EBA Leads EU Project to Strengthen Voluntary Non-Remunerated Plasma Collection Capacity in Europe. Available from: https://europeanbloodalliance.eu/supply-project-kick-off/. Last accessed 3 Sep 2023.
24. European Parliament document no. 2022/0216 (COD) from 18 January 2023, DRAFT REPORT on the proposal for a regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC (COM(2022)0338 – C9-0226/2022 – 2022/0216(COD)) Committee on the Environment, Public Health and Food Safety. Rapporteur: Nathalie Colin-Oesterlé. p. 55: Amendment Article 62a. Development of a strategy for the promotion of European SoHO supply self-sufficiency. Available from: https://www.europarl.europa.eu/doceo/document/ENVI-PR-738661_EN.pdf. Last accessed 3 Sep 2023.
25. The collection, testing and use of blood and blood components in Europe. EDQM. 2017, 2018 and 2019 report. 2022.

How to cite this article: Simonetti A, Smit C. Europe needs 2 million extra donors of blood and plasma: How to find them? Vox Sang. 2024;119:121–7.

Received: 25 July 2023 | Revised: 13 September 2023 | Accepted: 17 September 2023

DOI: 10.1111/vox.13544

REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Safety and protection of plasma donors: A scoping review and evidence gap map

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Funding information
EU4Health Programme by the European Union, Grant/Award Number: 101056988; Foundation for Scientific Research of the Belgian Red Cross

Abstract

Background and Objectives: As part of a large-scale project to safely increase plasma collection in Europe, the current scoping review identifies the existing evidence (gaps) on adverse events (AEs) and other health effects in plasmapheresis donors, as well as factors that may be associated with such events/effects.

Materials and Methods: We searched six databases and three registries. Study characteristics (publication type, language, study design, population, outcomes, associated factors, time of assessment, duration of follow-up, number and frequency of donations, convalescent plasma [y/n], setting and location) were synthesized narratively and in an interactive evidence gap map (EGM).

Results: Ninety-four research articles and five registrations were identified. Around 90% were observational studies (57 controlled and 33 uncontrolled), and most of them were performed in Europe (55%) or the United States (20%). Factors studied in association with donor health included donor characteristics (e.g., sex, age) ($n = 27$), cumulative number of donations ($n = 21$), donation frequency ($n = 11$), plasma collection device or programme ($n = 11$), donor status (first time vs. repeat) ($n = 10$), donation volume per session ($n = 8$), time in donation programme ($n = 3$), preventive measures ($n = 2$) or other ($n = 9$).

Conclusion: The current scoping review provides an accessible tool for researchers and policymakers to identify the available evidence (gaps) concerning plasmapheresis donation safety. Controlled prospective studies with long-term donor follow-up are scarce. Furthermore, additional experimental studies comparing the health effects of different donation frequencies are required to inform a safe upper limit for donation frequency.

Keywords

adverse events, health effects, plasma donor, plasmapheresis, safety

Highlights

- We systematically identified, categorized and described 94 research articles and 5 registrations, focusing on adverse events and/or other health effects in plasmapheresis donors.

- To increase plasma collections in Europe safely, there is a need for studies investigating the health effects of frequent and long-term donation, as well as the effectiveness of interventions to prevent the impact on the donor.
- The current scoping review aims to aid researchers and policymakers in efficiently identifying the available evidence and existing research gaps concerning plasmapheresis donation safety.

INTRODUCTION

Plasma-derived medicinal products (PDMPs) are essential for the prophylaxis and treatment of several disorders. The vast majority of plasma used for the manufacturing of PDMPs stems from source plasma from plasmapheresis donations. During this procedure, plasma is retained, whereas blood cells are returned to the donor [1].

The production of PDMPs heavily relies on plasma that is collected outside of Europe, with the United States providing the largest source of human plasma globally [1, 2]. Such dependency entails a considerable risk of shortages, particularly during health crises such as COVID-19. A scarcity of source plasma, and thus of PDMPs, would threaten the supply of essential pharmacological treatments. In addition, safety regulations regarding plasma (donation), such as donor reimbursement and maximum donation frequency, differ between Europe and United States. Thus, plasma collection in the European Union should be expanded to ensure a stable and adequate supply of PDMPs. However, evidence-based guidelines on increasing plasma collection while maintaining plasma and donor safety are currently lacking.

With the ultimate aim of preparing recommendations for blood establishments, competent authorities and medical societies for safely increasing plasma collection, the European Blood Alliance (EBA) initiated the 'SUPPLY' project (Strengthening voluntary non-remunerated plasma collection capacity in Europe) [3]. Situated within the SUPPLY project, the current scoping review aimed to systematically identify and map the available evidence (gaps) regarding adverse events (AEs) and other health effects in plasmapheresis donors. In addition, factors that have been studied in association with AEs or health effects are discussed, with a particular focus on donor status (first-time vs. repeat donation), cumulative number of donations, donation frequency and preventive measures.

METHODS

This scoping review is reported according to the 'PRISMA Extension for Scoping Reviews' guideline (Data S1).

Preregistered study protocol

The preregistered study protocol (https://osf.io/hqj6z) and an overview of deviations (https://osf.io/8zx62) from the protocol were published on the Open Science Framework (OSF).

Eligibility criteria

Population

Include: adults who underwent plasma withdrawal via plasmapheresis.

Exclude: adults donating whole blood or platelets; a mixed donor population (whole blood, plasmapheresis and/or plateletpheresis) without separate data for plasma donors; patient populations who underwent plasmapheresis (therapeutic plasma exchange) and/or received PDMPs.

Concept and context

Include: safety of plasma donation(s) in adults, regardless of the setting and geographical location of data collection.

Exclude: donor recruitment or retention, effects of plasma processing and fractionation, plasma safety for the recipient and supply of plasma(-derivates).

Outcomes

Include: (1) AEs, defined and categorized according to the 'Standard for Surveillance of Complications Related to Blood Donation' [4] with two additional categories: 'generic' (i.e., study mentioning the measurement of 'AEs' as such, without further specification or classification) and 'other' for AEs not covered by the existing categories; and (2) other health effects, including physiological parameters (e.g., blood pressure, heart rate) and parameters measured in blood or plasma (e.g., the concentration of blood cells, proteins, electrolytes).

Exclude: health-related outcomes that cannot clearly be linked to plasma donation (including self-reported general health status, measurements in the plasma product after donation without analysis of a possible link with donor/collection characteristics or when the product of plasma donation underwent processing steps before analysis).

Study design

Include: systematic reviews, (non-)randomized controlled trials, (un-)controlled observational studies and narrative reviews

(not included in data charting table but used as a source of potentially relevant studies).

Exclude: animal, ex vivo or in vitro studies.

Publication type

Include: registrations, study protocols and peer-reviewed articles regardless of publication status, language and date.

Exclude: conference abstracts, book chapters, editorials, dissertations and letters to the editor.

Search strategy and study selection process

We searched for eligible studies on 10 October 2022 using the six databases, three registries and search strings listed in Data S2. References were screened in duplicate (N.S. and H.V.R.) using EndNote X9. Disagreements were resolved by discussion between the reviewers and, if necessary, by consulting the expert panel (K.v.d.H., C.E., S.M., P.T., V.C.). A PRISMA flow chart was created using Shiny app [5].

Data charting, synthesis and presentation

Study characteristics (publication type and language, study design, population, outcomes, associated factors, time of assessment, duration of follow-up, number and frequency of donations within the study period, convalescent plasma [y/n], study setting and location) were charted in duplicate. The categories and variables for which data were sought were continuously adapted during the review process, as we followed an exploratory approach [6]. Extracting study results, judging the quality of evidence and answering specific research questions were outside the scope of this review [7] and were performed in a separate systematic review project [8]. Extracted information, available at https://osf.io/h8js5, was synthesized narratively using frequency counting per conceptual category and an evidence gap map (EGM; https://cebap.org/storage/cebap/schroyens-2023-egm.html) was created using EPPI-Mapper [9].

RESULTS

Search results

Figure 1 illustrates the review process. Two full texts could not be retrieved [10, 11]. To avoid duplication of studies, the protocol [12] and two of the registrations [13, 14] of studies that are described by identified research articles [15, 16] are not included in our summary. The remaining 94 research articles and 5 registrations are described below. References of all included studies are available in Data S3 and the EGM (https://cebap.org/storage/cebap/schroyens-2023-egm.html).

Characteristics of included studies

Data charting table and EGM

A detailed overview of study characteristics is available on OSF (https://osf.io/h8js5). Based on this overview, a more comprehensive and interactive EGM (https://cebap.org/storage/cebap/schroyens-2023-egm.html) was created (see also Figures 2–4).

Population

Most studies (68 out of 99) exclusively included plasmapheresis donors, whereas others included an additional, separately analysed group of blood donors, plateletpheresis or other types of apheresis donors (red or white blood cells) (see EGM with population filter). Five studies included convalescent plasma donors.

Publication date, location and language

Research articles were published between 1956 and October 2022 and registrations between 2016 and 2022. Around 55% of the studies were performed in Europe (25 in Germany, 6 in Croatia, 5 in Italy, 3 in France, 3 in Poland, 2 in Denmark, 2 in Norway, 2 in United Kingdom, 1 in Russia, Slovakia, Sweden, Switzerland, the Netherlands and Ukraine each), followed by North America (21 in the United States, 6 in Canada, 2 in Cuba), 5 in Asia (2 in Japan, 1 in China, India and Iran each) and 4 in Australia. Two research articles contained data from different countries, including Australia, Brazil, the Netherlands, Wales, the United States, and Singapore or Europe. Registrations were from Australia ($n = 2$), Czech Republic, the United States or Norway. Eighteen studies were not in English.

Study design

Most published studies ($n = 88$) had an observational design, of which 56 were controlled studies (including 41 cohorts [26 retrospective, 8 prospective and 7 unclear], 13 were controlled before and after, 1 case–control and 1 cross-sectional study) and 32 were uncontrolled, monitoring a group of donors before and after donation(s) ($n = 19$) or only after donation(s) ($n = 13$). Thirteen studies had a controlled experimental design (i.e., [non-]randomized controlled trials), comparing plasmapheresis donors to a no-donation control group [17, 18], or blood donors [15, 19]; or investigating the effect of iron supplementation [20], saline infusion [21–23], apheresis device or programme [16, 24, 25], donation volume [26] or donation frequency [27]. Of note, research

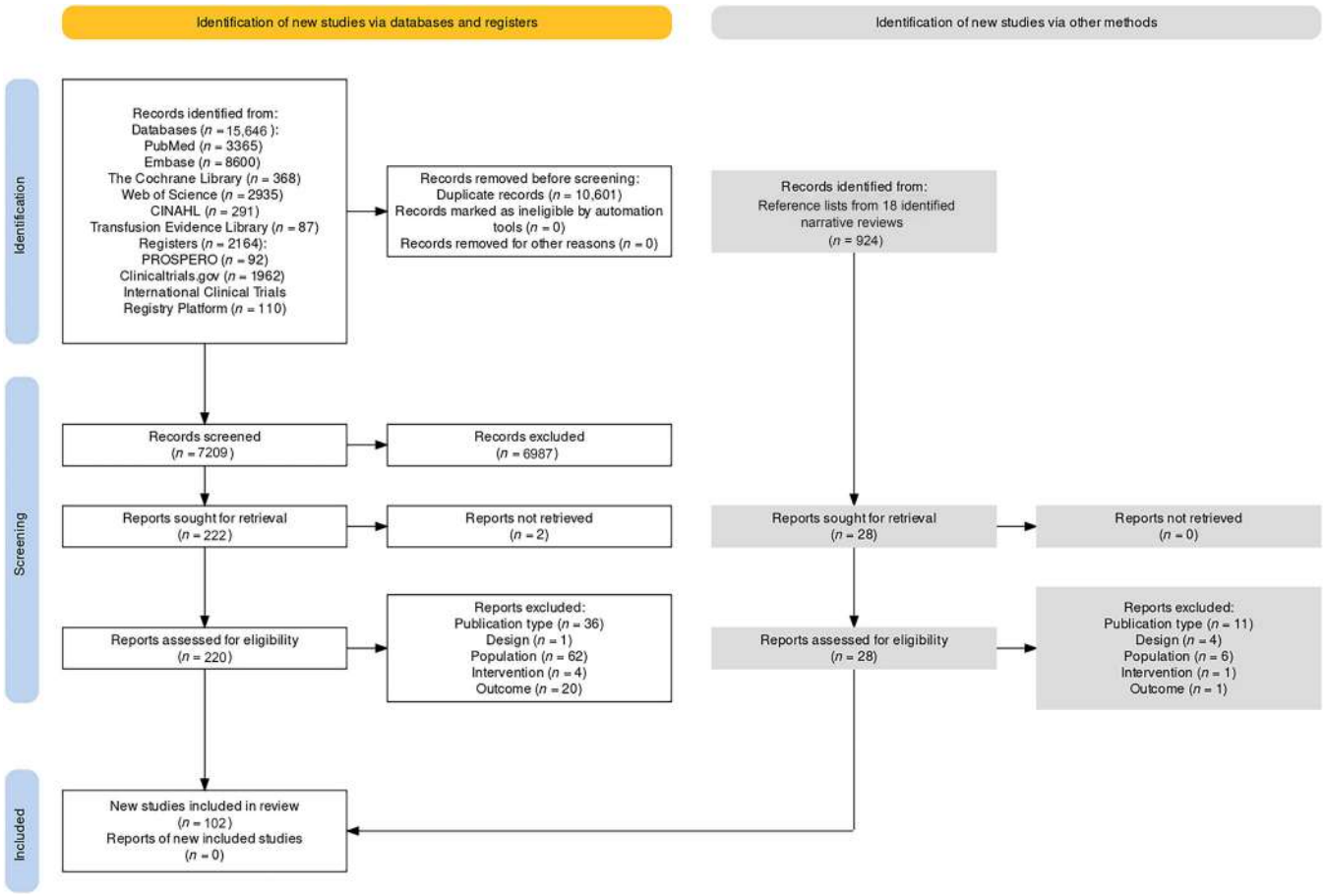

FIGURE 1 PRISMA flow diagram. Apart from 97 records identified via database and registry searches, 5 research articles were found via the reference lists of 18 narrative reviews (see https://osf.io/8zx62 for references). Overall, 102 records were obtained, including 94 research articles, 1 study protocol and 7 registrations.

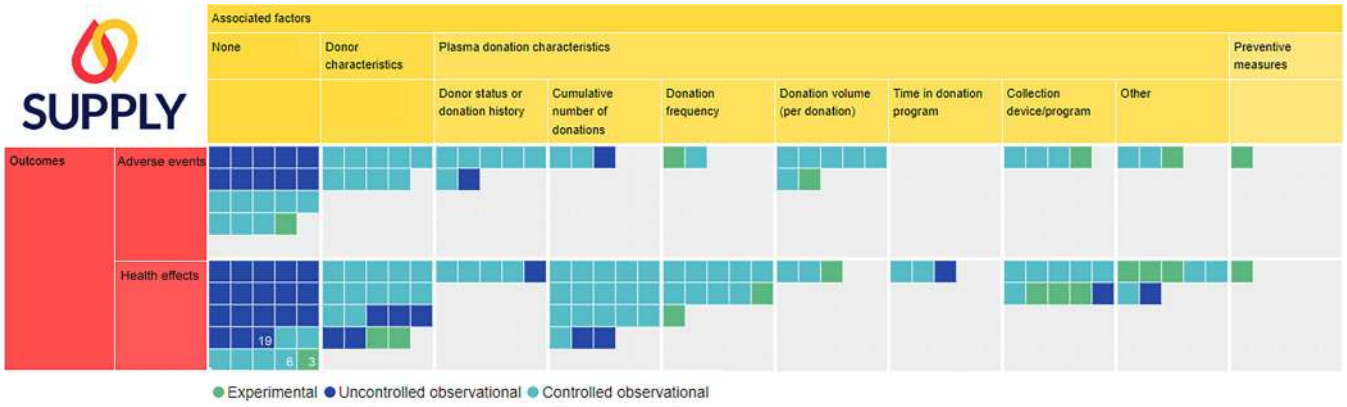

FIGURE 2 Evidence gap map, with rows representing outcomes and columns containing factors that have been studied in association with those outcomes. Squares represent studies, subdivided according to study design. An interactive version of the map is available online (https://cebap.org/storage/cebap/schroyens-2023-egm.html), in which descriptions of categories can be obtained by hovering over the column/row headers, lists of studies within each category can be obtained by clicking on the map and studies can be filtered based on study design, publication type, publication date, location, publication language, follow-up period, population and whether or not convalescent plasma was donated. Generated using v.2.2.4 of EPPI-Mapper powered by EPPI Reviewer and created by the Digital Solution Foundry team.

articles, using two different study designs depending on the factor or outcome under study, were counted twice here and in the EGM [23, 28–33].

Registrations were classified as controlled experimental ($n = 3$), controlled observational ($n = 1$) or uncontrolled observational ($n = 1$).

FIGURE 3 Evidence gap map with adverse events. An interactive version of the map is available at https://cebap.org/storage/cebap/schroyens-2023-egm.html. CV, cardiovascular event.

FIGURE 4 Evidence gap map with health effects. An interactive version of the map is available at https://cebap.org/storage/cebap/schroyens-2023-egm.html.

Reported outcomes

Thirty-five research articles and three registrations mentioned AE assessment, while 74 research articles and 3 registrations mentioned the investigation of other health effects in plasmapheresis donors (Figure 2).

Adverse events

Of the 35 articles, over 40% mentioned the measurement of AEs without specifying the type of events, adopted surveillance tool or categorization (classified as 'generic' in the EGM at https://cebap.org/storage/cebap/schroyens-2023-egm.html) (Figure 3). Assessed AEs included vasovagal reactions ($n = 17$), complications with local symptoms (directly caused by needle insertion) ($n = 14$), apheresis-related events ($n = 14$), allergic reactions ($n = 11$), major cardiovascular events ($n = 11$) or other ($n = 14$; including fractures, non-localized infections or AEs classified as 'other' according to the adopted vigilance scheme). The 'Standard for Surveillance of Complications Related to Blood Donation' [4] was the most commonly used tool [34–40].

About half of the articles ($n = 18$) had only assessed AE frequency, whereas the other half ($n = 17$) investigated plasmapheresis-related factors that may be associated with the occurrence of AEs (in order of frequency):

1. donor characteristics (age, sex, body weight and body mass index; or pre-donation values of blood pressure, pulse and blood volume; or IgG, total protein, haemoglobin [Hb] and haematocrit [Hct] levels);
2. donor status (first time vs. repeat);
3. donation volume per session;
4. plasma collection device or programme;
5. cumulative number of donations;
6. donation frequency;
7. or other factors (extracorporeal blood volume [41], geographical region of plasma collection [37] or donation with or without saline infusion [21]).

Three registrations aim to assess the effect of donation frequency [42], applied muscle tension [43] (registration withdrawn) or did not include any plasmapheresis-related factors [44].

Health effects

Of 73 studies assessing health effects, the majority investigated protein depletion (total protein, albumin and/or IgG levels) ($n = 40$) and/or haematological parameters (full blood count, Hct, Hb, lymphocyte, platelet, red blood cell, reticulocyte, schizocyte and/or white blood cell counts) ($n = 37$) (Figure 4). Others included coagulation-related outcomes ($n = 24$), physiological parameters ($n = 13$), iron metabolism ($n = 12$), other proteins/electrolytes measured in blood/plasma ($n = 45$; a list of which is available on our OSF page [45] at https://osf.io/5nz3v) and/or products used during plasmapheresis (citrate, mono(2-ethylhexyl) phthalate, di(2-ethylhexyl) phthalate [DEHP]) or synthetics ($n = 9$).

Twenty-eight studies had only measured health effects, whereas most studies investigated plasmapheresis-related factors that may be associated with the occurrence of health effects, including (in order of frequency):

1. donor characteristics (age, sex, body weight and body mass index; or pre-donation values of blood pressure, pulse and blood volume; or IgG, total protein, Hb and Hct levels);
2. cumulative number of donations;
3. donation frequency;
4. plasma collection device or programme;
5. donor status (first time vs. repeat);
6. donation volume per session;
7. time in donation programme;
8. iron supplementation as a preventive measure;
9. or other factors (saline infusion [22, 23], compensated, paid or unpaid donors [46], source plasma versus RhIg plasma [47] and the anticoagulant used [48]).

Three identified registrations mentioned the following factors: collection device and left versus right antecubital donation [49], cumulative number of donations (i.e., 4 vs. 8 cycles) or donation frequency.

Factors associated with AEs and/or health effects

The effectiveness of preventive measures, donor status (first-time vs. repeat), cumulative number of donations and donation frequency in relation to donor health were a priori identified as SUPPLY project objectives [3] and are elaborated below.

The effects of preventive measures on donor safety/health

A randomized controlled trial (RCT) assessed the effect of daily iron supplementation (vs. placebo) on haematological parameters, iron metabolism, protein depletion, alanine aminotransferase and viral markers in menstruating women who donated plasma at 1-week intervals over 24 weeks [20]. An RCT registration on the effect of applied muscle tension on AE rates has been withdrawn [43].

Donor safety/health in first-time versus repeat plasmapheresis donors

Ten observational studies assessed AEs or health effects in first-time and repeat plasmapheresis donors separately. Half of these studies were published recently (after 2020). Assessed AEs included 'all AEs' (generic), vasovagal reactions, local symptoms, apheresis-related

complications, allergic reactions, major cardiovascular events and other types. Health-related outcomes included total protein, albumin, IgG and other Ig levels, monoclonal gammopathies or other gamma globulin abnormalities, or DEHP (plasticizer) in donor plasma or blood.

The association between cumulative number of donations and donor safety and/or health

Twenty observational studies investigated the association between the cumulative number of plasmaphereses (i.e., multiple donations) and donor safety and/or health. No experimental studies were identified.

Three studies reported on AEs, including 'all AEs' (see 'generic' in EGM), vasovagal reactions or (osteoporotic) fractures. In addition, 18 studies assessed health markers measured in donor blood or plasma, including—in order of frequency—total protein levels, albumin, IgG levels, coagulation tests, haematological parameters, iron metabolism or 'other'. One study addressed physiological parameters.

Finally, a case series registration aims to investigate the indicators of biological age after four versus eight plasmaphereses.

The association between donation frequency and donor safety and/or health

Studies are described below if (1) they specified the time interval between subsequent donations or the number of donations per given time unit (e.g., weekly donation, bi-weekly donation, three donations every 2 weeks) and (2) if the donation frequency was constant/unchanged during the study period. For example, studies providing the number of donations per year are not included under this category if it was unclear whether the donation frequency remained constant throughout the year.

Ten studies, including one experimental study and nine controlled observational studies, investigated the association between frequency of plasmaphereses and donor safety and/or health. The most recent article dates from 2015, and 70% were published before 2000. Five studies took place within the same research group in Croatia.

One study assessed AEs (see 'generic' in EGM), whereas all 10 studies assessed the impact on donor health, including—in order of frequency—total protein, IgG levels, albumin, haematological parameters, coagulation tests or other health markers measured in donor blood or plasma. One study included physiological parameters.

Finally, an RCT registration aims to investigate the effect of donation frequency on total protein, IgG levels, other plasma proteins and psychological distress.

Long-term (≥1 week) follow-up of plasmapheresis donors

Thirty-eight studies (including three registrations) had a follow-up period (i.e., time between the first donation and last donor assessment) of 1 week or longer. Studies are not included in the overview below if they assessed the effect of multiple donations without specifying (or allowing calculation of) the follow-up period [23].

Follow-up after a single donation ($n = 6$)

Five studies (and one registration [44]) investigated the effect of a single donation on AEs or health effects and included a follow-up period of 1 week [19, 44, 50], 3 weeks [51], 1 month after the donation [35] or unspecified (presumably longer than 1 week) [38].

Follow-up during or after multiple donations ($n = 32$)

Thirty-two studies monitored donors (before and) after or during a specified period in which multiple donations were given. Studies are subdivided according to study design and listed in the order of increasing follow-up period.

Controlled experimental studies (n = *6)*

Three controlled experimental studies (and one registration [42]) examined the effect of iron supplementation [20], donation frequency [27, 42] or collection programme [16] on donor health with a follow-up period of 1–6 months. Finally, two studies had a longer follow-up period (6–12 months), comparing whole blood donations, plasma donations and observation only [15], or different donation volumes [26].

Controlled observational studies (n = *16)*

Three studies assessed donors who frequently donated for 1–6 months, monitoring AEs and haematological parameters after 10 weekly donations [33], serum protein levels before and after 5 monthly donations [52], or blood pressure during 4 months (prospective study) [53]. Five retrospective studies investigated donors who frequently underwent plasmapheresis for 1 year, focusing on either iron metabolism [54–57], haematological parameters [57, 58] or other proteins [57]. Eight papers reported a study period of more than 1 year and up to 23 years, looking at a wide variety of outcomes and including four prospective studies [32, 59–61], three retrospective cohorts [62–64] and one cohort with unclear classification [31].

Uncontrolled observational studies (n = *10)*

Three uncontrolled before-and-after studies assessed health effects with a study period of 1–6 months [33, 65, 66]. Two case series, one of which is a registration [67], mentioned a 6-to-12-month follow-up for health effects [68]. Finally, we identified five studies with a follow-up period of over 1 year: one before-and-after study assessing AEs [69] and four case series looking at other health effects [32, 70–72].

DISCUSSION

The current scoping review mapped 94 research articles and 5 registrations focusing on AEs and/or other health effects in plasmapheresis donors, most of which were performed in Europe (55%) or the United States (20%). The majority of studies ($n = 91$, including 2 registrations) employed an observational design (57 controlled and 33 uncontrolled, monitoring a group of donors [before and] after donation(s)). Only 16 studies (including 3 registrations) had an experimental design. Given that we did not identify any systematic review (registration), our ongoing systematic review on donation frequency [8] that was performed in the follow-up of the current scoping review is presumably the first one to focus on the impact of plasmapheresis on donor health.

In the framework of developing safety guidelines for plasmapheresis donors while increasing plasma collection within Europe, it is of paramount importance to consider the effect of frequent and long-term plasmapheresis donation. Although we identified 10 studies investigating the association between donation frequency and donor health, there was only one experimental study [27]. In addition, studies are relatively old (70% were published before 2000 and the most recent one dates from 2015), and five studies are from the same research group. More than 30 studies analysed donors during or after a specified period (1 month–23 years) in which multiple donations were given. However, 10 of these studies did not include a control group, limiting the certainty of their conclusions. Among the controlled studies, the majority were observational ($n = 16$) and retrospective ($n = 11$). Such retrospective studies are subject to bias, given that long-term donors are self-selected to withstand the donation frequency under evaluation. Additional well-designed observational studies are needed to investigate the long-term impact of plasmapheresis donation on donor health.

Studies on preventive interventions against AEs or other health effects are scarce, given that there is only one such study reporting on the effect of iron supplementation. The effectiveness of identified interventions in blood donors (e.g., to reduce vasovagal reactions [73]) needs to be validated in plasmapheresis donors.

The strength of the current scoping review includes its rigorous and systematic methodology, as reflected by the independent screening and extraction conducted by two reviewers. This review covers a broad research area, encompassing all studies that recorded AEs and other health-related outcomes in plasmapheresis donors. In addition to a detailed table (https://osf.io/h8js5) with study characteristics, a comprehensive, accessible and interactive visual overview is provided in the form of an EGM (https://cebap.org/storage/cebap/schroyens-2023-egm.html).

On the other hand, the first limitation of this scoping review is the arbitrary and ambiguous nature of the developed factor/outcome categories, even though these categories were developed in consultation with content experts (S.M., K.v.d.H., C.E., P.T., V.C.). To ensure transparency, descriptions and examples of these categories can be obtained by hovering over their labels in the data charting table (https://osf.io/h8js5) and EGM. For further clarification, lists of all encountered factors (https://osf.io/uv6fe) and health effects (https://osf.io/5nz3v) are available on our OSF page, with each of the factors/outcomes listed under their relevant category. Second, it should be noted that scoping reviews typically do not involve extracting study results and judging the quality of studies, and therefore do not contribute to the development of practical recommendations regarding donor safety. Rather, the scoping review provides an overview of the available evidence and evidence gaps for researchers, blood banks, plasma industry representatives and policymakers.

To conclude, based on the evidence (gaps) identified in the current scoping review, we propose the following research recommendations. First, additional experimental studies are required to investigate the impact of various donation frequencies on donor health, such as the registered study by Strand et al. [42]. The results of these studies will help establish a safe upper limit for plasma donation frequency. Second, to obtain conclusive evidence regarding the health effects of frequent and long-term donation, more controlled prospective studies are warranted. Ideally, these studies would monitor drop-out rates and reasons, as well as the long-term health of those who have dropped out; and incorporate intention-to-treat analyses to mitigate potential bias arising from the healthy donor effect [74]. Finally, considering the incomplete reporting on AEs in several identified studies, we recommend that future studies specify the exact timing of outcome measurement and describe the adopted surveillance tools or AEs that are being monitored.

ACKNOWLEDGEMENTS

We acknowledge the following members of SUPPLY Work Package 5 to provide input throughout the different steps in conducting this scoping review: Thomas Burkhardt (German Red Cross, Germany), Elodie Pouchol (Établissement Français du Sang, France), Pascale Richard (Établissement Français du Sang, France), Marloes Spekman (Sanquin, The Netherlands) and Torsten Tonn (German Red Cross, Germany). This work was funded by the EU4Health Programme by the European Union (101056988) and the Foundation for Scientific Research of the Belgian Red Cross. The content of this manuscript represents the views of the authors only and is their sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the European Health and Digital Executive Agency (HaDEA) or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

K.v.d.H., V.C., C.E., P.T. conceptualized, validated the research and acquired funding, N.S., T.D. and H.V.R. performed the research, N.S. wrote the original draft of the manuscript, T.D., E.D.B., S.M., K.v.d.H., V.C., C.E., P.T. and H.V.R. reviewed and edited the manuscript; E.D.B. and H.V.R. supervised and H.V.R. coordinated the project.

CONFLICT OF INTEREST STATEMENT

H.V.R., N.S., V.C., E.D.B. and T.D. are employed by Belgian Red Cross–Flanders, responsible and reimbursed for supplying adequate quantities of safe blood products to hospitals in Flanders and Brussels. P.T. is employed by the Etablissement Français du Sang, the French

transfusion public service in charge of blood, plasma and platelet collection in France. K.v.d.H. is employed by Sanquin, responsible for safe blood supply in the Netherlands. The authors have disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/kbv6z/.

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REFERENCES

1. 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.
2. European Blood Alliance Strengthening Plasma Collection in Europe. Available from: https://europeanbloodalliance.eu/strengthening-plasma-collection-in-europe/. Last accessed 15 Sep 2022.
3. SUPPLY. SUPPLY Project: Strengthening Voluntary Non-Remunerated Plasma Collection Capacity in Europe. Available from: https://supply-project.eu/. Last accessed 10 Jul 2023.
4. Goldman M, Land K, Robillard P, Wiersum-Osselton J. Development of standard definitions for surveillance of complications related to blood donation. Vox Sang. 2016;110:185–8.
5. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and open synthesis. Campbell Syst Rev. 2022;18:e1230.
6. Campbell F, Tricco AC, Munn Z, Pollock D, Saran A, Sutton A, et al. Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different – the "Big Picture" review family. Syst Rev. 2023;12:45.
7. Munn Z, Pollock D, Khalil H, Alexander L, McLnerney P, Godfrey CM, et al. What are scoping reviews? Providing a formal definition of scoping reviews as a type of evidence synthesis. JBI Evid Synth. 2022;20:950–2.
8. Van Remoortel H, D'aes T, Schroyens N, De Buck E, van den Hurk K, Erikstrup C, et al. The Impact of Frequent Plasmapheresis on Adverse Events, Cardiovascular Health, and Protein Levels in Plasma Donors: A Systematic Review of Controlled Experimental and Observational Studies. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=405419. Last accessed 25 Jul 2023.
9. EPPI-Reviewer. EPPI-Mapper. Available from: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3790. Last accessed 25 Jul 2023.
10. Wang XB, Chen KV. Monitoring of plasma protein contents of plasma donors at various ages and frequencies of donation. Chin J Biol. 2014;27:1433–4.
11. Pistotnik M, Grgicevic D, Flego DG. Effects of plasmapheresis on the blood donors. Changes caused by long-term plasmapheresis in normal donors. Bilt Hematol Transfuz. 1975;3:31–6.
12. Silver G, Krastev Y, Forbes MK, Hamdorf B, Lewis B, Tisbury M, et al. Study protocol for a randomised controlled trial examining the effect of blood and plasma donation on serum perfluoroalkyl and polyfluoroalkyl substance (PFAS) levels in firefighters. BMJ Open. 2021;11:e044833.
13. Gasiorowski R. A Study Examining the Effect of Blood and Plasma Donation on Serum Per- and Poly-Fluoroalkyl Substances (PFAS) Levels in Metropolitan Fire Brigade Staff. Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376871&showOriginal=true&isReview=true. Last accessed 25 Jul 2023.
14. Leitman SF. IMPACT (Improving Plasma Collection) Clinical Trial. Available from: https://ClinicalTrials.gov/show/NCT04320823. Last accessed 25 Jul 2023.
15. Gasiorowski R, Forbes MK, Silver G, Krastev Y, Hamdorf B, Lewis B, et al. Effect of plasma and blood donations on levels of perfluoroalkyl and polyfluoroalkyl substances in firefighters in Australia: a randomized clinical trial. JAMA Netw Open. 2022;5:e226257.
16. Hartmann J, Ragusa MJ, Burchardt ER, Manukyan Z, Popovsky MA, Leitman SF. Personalized collection of plasma from healthy donors: a randomized controlled trial of a novel technology-enabled nomogram. Transfusion. 2021;61:1789–98.
17. Karger R, Halbe M, Dinges G, Wulf H, Kretschmer V. Blood volume regulation in donors undergoing intermittent-flow plasmapheresis involving a high extracorporeal blood volume. Transfusion. 2006;46:1609–15.
18. Karger R, Halbe M, Giffhorn-Katz S, Katz N, Kretschmer V. Atrial natriuretic peptide serum concentration decreases in donors undergoing discontinuous plasmapheresis involving a large extracorporeal blood volume. Transfusion. 2007;47:1717–24.
19. Hill DW, Vingren JL, Burdette SD. Effect of plasma donation and blood donation on aerobic and anaerobic responses in exhaustive, severe-intensity exercise. Appl Physiol Nutr Metab. 2013;38:551–7.
20. Bier-Ulrich AM, Haubelt H, Anders C, Nagel D, Schneider S, Siegler KE, et al. The impact of intensive serial plasmapheresis and iron supplementation on iron metabolism and Hb concentration in menstruating women: a prospective randomized placebo-controlled double-blind study. Transfusion. 2003;43:405–10.
21. Buzza M, Marks DC, Capper H, Cassin E, Badcock CA, Reid S, et al. A prospective trial assessing the safety and efficacy of collecting up to 840 mL of plasma in conjunction with saline infusion during plasmapheresis. Transfusion. 2012;52:1806–13.
22. Evers J, Ehren N, Engelen T, Hansen M, Luethje K, Taborski U. Course of hemoglobin and hematocrit during and after preparatory plasmaphereses without and with infusion of NaCl 0.9% 500 ml. Transfus Med Hemother. 2014;41:114–6.
23. Fischer T, Surikova I, Heesen E, Wilms G, Laitinen T, Taborski U. Loss of red cell mass in a plasmapheresis machine: effect of rinsing the disposable tubing with normal saline and reinfusion. Transfus Apher Sci. 2013;49:80–3.
24. Feuring M, Gutfleisch A, Ganschow A, Richter E, Eichler H, Dempfle CE, et al. Impact of plasmapheresis on platelet hemostatic capacity in healthy voluntary blood donors detected by the platelet function analyzer PFA-100. Platelets. 2001;12:236–40.
25. de Back DZ, Nezjad SG, Beuger BM, Veldhuis M, Clifford E, Ait Ichou F, et al. Apheresis causes complement deposition on red blood cells (RBCs) and RBC antigen alterations, possibly inducing enhanced clearance. Transfusion. 2018;58:2627–34.
26. Smálik S, Beranová G, Filová J. Effect of long-term plasmapheresis on the donors blood picture. Bratisl Lek Listy. 1972;58:545–57.
27. Ciszewski TS, Ralston S, Acteson D, Wasi S, Strong SJ. Protein levels and plasmapheresis intensity. Transfus Med. 1993;3:59–65.
28. Evers J, Schreiber GB, Taborski U. Report on 50 cases of severe acute hypotension at donor plasmaphereses: treatment and course. Int J Artif Organs. 2017;40:230–3.
29. Neumeyer HF, Quentin SH, Wieding JU. Comparative analysis of various plasmapheresis methods – modern procedures of mechanical plasma collection compared with each other and with manual bag centrifugation procedures. Beitr Infusionsther. 1993;29:163–89.
30. Rosa-Bray M, Wisdom C, Wada S, Johnson BR, Grifols-Roura V, Grifols-Lucas V. Prospective multicentre study of the effect of

voluntary plasmapheresis on plasma cholesterol levels in donors. Vox Sang. 2013;105:108–15.
31. Salvaggio J, Arquembourg P, Bickers J, Bice D. The effect of prolonged plasmapheresis on immunoglobulins, other serum proteins, delayed hypersensitivity and phytohemagglutinin-induced lymphocyte transformation. Int Arch Allergy Appl Immunol. 1971;41:883–94.
32. Taborski U, Laitinen T. Donor safety in an individualized plasmapheresis program – results of an interim analysis. Transfus Apher Sci. 2022;61:103446.
33. Ullrich H, Wiebecke D, Keller F. Side effects and risk factors of various plasma donation methods. Beitr Infusionsther. 1991;28:77–81.
34. Cho JH, Rajbhandary S, van Buren NL, Fung MK, Al-Ghafry M, Fridey JL, et al. The safety of COVID-19 convalescent plasma donation: a multi-institutional donor hemovigilance study. Transfusion. 2021;61:2668–76.
35. He R, Lin H, Xie S, Lv Q, Kong Y, Li L, et al. Donor tolerability of convalescent plasma donation. J Clin Apher. 2021;36:429–36.
36. Heuft HG, Fischer E, Weingand T, Burkhardt T, Leitner G, Baume H, et al. Donor safety in haemapheresis: development of an internet-based registry for comprehensive assessment of adverse events from healthy donors. Transfus Med Hemother. 2017;44:188–200.
37. Mikkelsen C, Paarup HM, Bruun MT, Pedersen LO, Hasslund S, Larsen R, et al. The new donor vigilance system in Denmark reveals regional differences in adverse reactions supposedly caused by variation in the registration. Vox Sang. 2022;117:321–7.
38. Orru S, Poetzsch K, Hoffelner M, Heiden M, Funk MB, Keller-Stanislawski B, et al. Blood donation-related adverse reactions: results of an online survey among donors in Germany (2018). Transfus Med Hemother. 2021;48:272–83.
39. Thijsen A, Davison TE, Speedy J, Hoad V, Masser B. Offering new and returned donors the option to give plasma: implications for donor retention and donor adverse events. Vox Sang. 2021;116:273–80.
40. Young P, Crowder L, Steele W, Irving D, Pink J, Kutner JM, et al. Frequency of rare, serious donor reactions: international perspective. Transfusion. 2021;61:1780–8.
41. Karger R, Slonka J, Junck H, Kretschmer V. Extracorporeal blood volume of donors during automated intermittent-flow plasmapheresis and its relevance to the prevention of circulatory reactions. Transfusion. 2003;43:1096–106.
42. Strand TA, Haugen M, Magnussen K. The Effect of Donation Frequency on Donor Health in Blood Donors Donating Plasma by Plasmapheresis. Available from: https://ClinicalTrials.gov/show/NCT05179200. Last accessed 25 Jul 2023.
43. Knight E. IMPLEMENT Study – Reducing Vasovagal Syncope and Presyncope Symptoms in Plasma Donors Using Applied Muscle Tension. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12620000652976. Last accessed 25 Jul 2023.
44. Bell B, Knight E. A Trial to Investigate the Different Experiences of First Time Blood Donors Over 30 Years of Age Who Donate Whole Blood or Who Donate Plasma by Apheresis. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12616001307493. Last accessed 25 Jul 2023.
45. Schroyens N, D'aes T, Van Remoortel H. Safety and Protection of Plasma Donors: A Scoping Review. Available from: https://osf.io/kbv6z/. Last accessed 25 Jul 2023.
46. Laub R, Baurin S, Timmerman D, Branckaert T, Strengers P. Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sang. 2010;99:220–31.
47. Lewis SL, Kutvirt SG, Bonner PN, Simon TL. Plasma proteins and lymphocyte phenotypes in long-term plasma donors. Transfusion. 1994;34:578–85.
48. Rock G, McCombie N, Tittley P. A new technique for the collection of plasma: machine plasmapheresis. Transfusion. 1981;21:241–6.
49. Mack SM. Clinical Evaluation of the CM-1500 During Apheresis Blood Donation. Available from: https://clinicaltrials.gov/show/NCT05012462. Last accessed 25 Jul 2023.
50. Ikeda H, Tomono T, Sakai E, Endo N, Yokoyama S, Ogawa M, et al. An extensive study of donor plasmapheresis using a membrane method by the special study group of the Japanese Red Cross Society. Prog Clin Biol Res. 1990;337:503–6.
51. Matthes G, Pawlow I, Ziemer S. Age-dependent regeneration of plasma proteins after donor plasmapheresis. Beitr Infusionsther. 1992;19:29–31.
52. Burgin M, Hopkins G, Moore B, Nasser J, Richardson A, Minchinton R. Serum IgG and IgM levels in new and regular long-term plasmapheresis donors. Med Lab Sci. 1992;49:265–70.
53. Rosa-Bray M, Wisdom C, Marier JF, Mouksassi MS, Wada S. The effect of plasmapheresis on blood pressure in voluntary plasma donors. Vox Sang. 2015;108:11–7.
54. Schreiber GB, Brinser R, Rosa-Bray M, Yu ZF, Simon T. Frequent source plasma donors are not at risk of iron depletion: the Ferritin Levels in Plasma Donor (FLIPD) study. Transfusion. 2018;58:951–9.
55. Martlew VJ, Waters HM, Howarth JE. The impact of apheresis on iron stores. Transfus Sci. 1988;9:343–6.
56. Sánchez Frenes P, Valdés YN, Sayas MBB, Bouza MJS. Prospective study during a year of the iron concentration in plasma donors. Rev Cuba Hematol Inmunol Hemoter. 2017;33:65–74.
57. Tran-Mi B, Storch H, Seidel K, Schulzki T, Haubelt H, Anders C, et al. The impact of different intensities of regular donor plasmapheresis on humoral and cellular immunity, red cell and iron metabolism, and cardiovascular risk markers. Vox Sang. 2004;86:189–97.
58. Sánchez Frenes P, Pérez Ulloa LE, Sánchez Bouza MJ, González Álvarez M, Cuellar Contreras Y, García TD. Assessment of haemoglobin concentration in regular plasma donors. Rev Cuba Hematol Inmunol Hemoter. 2015;31:150–9.
59. Friedman BA, Schork MA, Mocniak JL, Oberman HA. Short-term and long-term effects of plasmapheresis on serum proteins and immunoglobulins. Transfusion. 1975;15:467–72.
60. Smolens J, Stokes J Jr, Vogt AB. Human plasmapheresis and its effect on antibodies. J Immunol. 1957;79:434–9.
61. Schulzki T, Seidel K, Storch H, Karges H, Kiessig S, Schneider S, et al. A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA). Vox Sang. 2006;91:162–73.
62. Grau K, Vasan SK, Rostgaard K, Bialkowski W, Norda R, Hjalgrim H, et al. No association between frequent apheresis donation and risk of fractures: a retrospective cohort analysis from Sweden. Transfusion. 2017;57:390–6.
63. Grgicevic D, Pistotnik M, Pende B. Observation of the changes of plasma proteins after long term plasmapheresis. Dev Biol Stand. 1980;48:279–86.
64. Rosiek A, Rzymkiewicz L, Owczarska K, Łętowska M. Consequences of long-term plasma, platelet and whole blood donating. Acta Haematol Pol. 2006;37:75–84.
65. Abe U, Sakamoto H, Kiyokawa H. Effects of plasmapheresis on female blood donors. Rinsho Ketsueki. 1985;26:1855–9.
66. Kliman A, Carbone PP, Gaydos LA, Freireich EJ. Effects of intensive plasmapheresis on normal blood donors. Blood. 1964;23:647–56.
67. Borsky P. Effects of Plasmapheresis on Aging Biomarkers. Available from: https://ClinicalTrials.gov/show/NCT05004220. Last accessed 25 Jul 2023.
68. Smolens J, Stokes J Jr, McGee E, Hunter V. Feasibility and safety of frequent plasmapheresis of the same human donors. Proc Soc Exp Biol Med. 1956;91:611–4.
69. Bechtloff S, Tran-My B, Haubelt H, Stelzer G, Anders C, Hellstern P. A prospective trial on the safety of long-term intensive plasmapheresis in donors. Vox Sang. 2005;88:189–95.
70. Iavorskyĭ VV. Effect of frequency donations of plasma standard dose on immune reactivity of regular donors. Klin Khir. 2013;8:65–8.

71. Palmer DS, Scalia V, O'Toole J, Welch C, Yi Q, Goldman M. Incidence of gammopathies in long-term plasmapheresis donors at Canadian Blood Services. Transfusion. 2015;55:1347–54.
72. Shanbrom E, Lundak R, Walford RL. Long-term plasmapheresis: effects on specific plasma proteins. Transfusion. 1972;12:162–7.
73. Fisher SA, Allen D, Doree C, Naylor J, Di Angelantonio E, Roberts DJ. Interventions to reduce vasovagal reactions in blood donors: a systematic review and meta-analysis. Transfus Med. 2016;26:15–33.
74. Brodersen T, Rostgaard K, Lau CJ, Juel K, Erikstrup C, Nielsen KR, et al. The healthy donor effect and survey participation, becoming a donor and donor career. Transfusion. 2023;63:143–55.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schroyens N, D'aes T, De Buck E, Mikkelsen S, Tiberghien P, van den Hurk K, et al. Safety and protection of plasma donors: A scoping review and evidence gap map. Vox Sang. 2024;119:110–20.

Received: 10 September 2023 | Revised: 2 November 2023 | Accepted: 2 November 2023

DOI: 10.1111/vox.13566

COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Safeguarding plasma for fractionation: How can we deal with operational challenges in European Union countries

The World Health Organization (WHO) and stakeholder organizations in the blood transfusion chain have identified global shortages of plasma for fractionation (PfF) and an increasing demand for immune globulines (IgG) products, combined with decreasing supply of recovered plasma, in high-income countries [1–4]. In the European Union (EU), the volume of PfF collected does not match the needs of patients for plasma-derived medicinal products (PDMPs). EU countries depend for about one-third of PfF on plasma collected in plasmapheresis centres in the United States [2–4]. Many EU countries, including Denmark, have self-sufficiency targets for PfF, but all now rely on the global PDMP market. European countries, where 27% of IgG products are used, collect about 15% of the PfF globally. Globally, about 65% of plasma for PDMP production originates from commercial plasma apheresis centres in the United States, which makes the EU strategically dependent on that country [2]. This EU dependence on PfF import also has a negative impact on global availability, especially worsening patient outcomes in low- and medium-income countries [5].

In recent years, discussions have shifted from self-sufficiency to strategic independence [3, 6]. Complicating this is the fact that collection of PfF is regulated by the EU blood directives, which are applicable to all collections of blood products for humans whatever the intended use, while production and sale of PDMPs are regulated by EU pharmaceutical legislation [7, 8]. To achieve strategic independence, the European Blood Alliance (EBA) and partner stakeholders in the EU co-funded the 'Supply' project to make the case for an increase of PfF supply by strengthening the public sector [9].

Blood establishments (BEs) in the EU are public or semi-public organizations collecting blood from voluntary non-remunerated donors (VNRDs). Self-sufficiency for labile blood products is the rule, which, however, is achieved only in a few countries for PfF.

Now the question is: how can BEs in the EU succeed in providing blood products from VNRDs matching patient needs while many EU countries are unable to collect the volumes of PfF for the PDMP needs of patients.

In addition to incomplete and complex legislation, exemplified by a variety of regulations at the national level, different factors contribute to the ongoing PfF shortages:

1. *In most countries, a national system with a clear target for PfF is missing*. Globally, IgG is the driving force for PfF collection. The total need is the sum of PDMP needs for a pallet of clinical indications that differs between countries and changes over time [4]. The need for IgG has increased and is expected to increase further, but may level off when new alternative therapies become available [2, 4]. Triage of patients and relocation of products in case of shortages can lead to underestimating the need and consequences for patients who depend on PDMPs.
2. *Estimated PDMP need is not translated into a national PfF target and action in all EU countries*, whereas targets for blood products for BEs are defined; the accompanying resources and eventual shortages in hospitals are immediately clear. In four EU countries (Austria, Czech Republic, Germany and Hungary) with commercial plasmapheresis centers, PfF collection is significantly higher but depends on two separate systems, preventing national ownership of the collected plasma [3]. Insufficient PfF collections mean that EU relies on PDMPs from non-EU plasma available and affordable in an international competitive market environment.
3. Contrary to the situation for blood products, there is no direct feedback mechanism for PfF when collections occur in national BEs and fractionation is done by a few internationally operating fractionators. When the target is not achieved, the consequences are for the hospitals and (maybe) the fractionator, and will not directly affect the BE.
4. The blood supply system for labile products follows a clear chain from the donor to the patient. The BEs cover collection, processing, testing, release, storage and distribution of the products, while hospitals in general cover compatibility testing and clinical transfusion in patients. The actors, BEs and hospitals, have a direct relation and feedback. *The opposite is true for PfF, where at each part of the logistic chain, actors operate separately*. The first part, from donor to storage by the BEs (including plasma collection centres), is separated from purchasing PfF, quality review, batch fractionation processing, PDMP production and sale to (hospital) pharmacies by fractionators. Delivery and infusion in patients constitute the third part. The independent operations of multiple actors for each part result in a complex and fluid system lacking direct feedback. For example, in a tender system, PfF collectors can over time work with more fractionators.
5. *Impact of specific occurrences of transmissible diseases on PfF supply in the EU*. Mad Cow Disease and its variant Creutzfeldt–Jacob Disease in humans led to a ban of plasma from the United Kingdom for years. At that time, this immediately deepened the

reliance on US PfF and PDMPs, especially because the US Food and Drug Administration also banned non-US PfF. Recently, the United Kingdom, based on a risk analysis, decided to lift the ban on UK plasma for the production of certain PDMPs. Similarly, other countries (Ireland, the United States, Australia) have lifted geographical donation rules for donors who had resided in the United Kingdom [10]. Furthermore, during the COVID-19 pandemic, the risks of shortages when relying on one foreign country increased and lower volumes collected during lock-down could lead to shortages even with a delay of more than 1 year [11]. On a positive note, during the pandemic, BEs succeeded in collecting COVID-19 convalescent plasma for transfusion as well as for fractionation at very short notice. For example, Sanquin in the Netherlands collected 30,000 donations in the second half of 2020 from voluntary donors, the vast majority of them being new.

6. Recovered plasma volume decreases as a result of lower use of red blood cell concentrates by patients, which leads to an increasing need for source plasma.

In summary, BEs (including plasmapheresis centres) collect PfF under EU blood directives and supply the collected PfF to internationally operating fractionators for PDMP production, regulated by the European Medical Agency. Hospital pharmacists procure PDMPs from fractionators. This results in a complex logistic framework with changing relations and, in general, lacking direct feedback.

In a desired situation, the supply of blood products should be embedded in centrally coordinated systems based on clear EU directives, translated into national laws and regulations with clear responsibilities for BEs and the competent authority. The preference in the EU is collection from VNRDs by public organizations for ethical and safety reasons, which is in line with WHO guidance [1]. At present, PfF in the EU consists of a combination of recovered and sourced by (semi-) public BEs and source plasma in commercial apheresis centres in four EU countries.

To increase PfF collection in the EU to the level that matches the PDMP need of patients nationally, a (semi-) public BE and VNRD is preferred. Strengthening of the public system for PfF collection program needs to also include the development of optimal tendering models for fractionation, as advocated by EBA, representing (semi-public BEs and others. This requires EU countries to develop national plasma systems with a legal and regulatory basis, clearly defined responsibilities of the stakeholders, a yearly collection plan and sufficient resources (supply) and tender models for PfF in alignment with the national PDMP need as well as the required fractionation capacity. Existing national differences demand a stepwise approach, preferably starting in countries with a high PfF deficit. The existing escape route by relying on PDMPs produced from non-EU plasma and, in case of shortages, the triage of patients and relocation of products may seem manageable, but, unfortunately, this is not true for the patients depending on these products.

ACKNOWLEDGEMENTS

W.M.S. wrote the first version of the manuscript, and D.C.T.-T. provided comments. Both authors agreed on the final manuscript.

FUNDING INFORMATION

The authors received no specific funding for this work

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The commentary is based on information from public available documents listed in the references of the paper.

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REFERENCES

1. WHO. Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: WHO; 2021.
2. Prevot J, Jolles S. Global immunoglobulin supply: steaming towards the iceberg? Curr Opin Allergy Clin Immunol. 2020;20:557–64.
3. Domanović D, von Bonsdorff L, Tiberghien P, Strengers P, Hotchko M, O'Leary P, et al. Plasma collection and supply in Europe: Proceedings of an International Plasma and Fractionation Association and European Blood Alliance symposium. Vox Sang. 2023;118:798–806.
4. Strengers PFW. Challenges for plasma-derived medicinal products. Transfus Med Hemother. 2023;50:116–22.
5. Burnouf T, Epstein J, Faber JC, Smid WM. Stepwise access to safe plasma proteins in resource-constrained countries: local production and pathways to fractionation—report of an International Society of Blood Transfusion Workshop. Vox Sang. 2022;117:789–95.
6. Strengers PF, Klein HG. Plasma is a strategic resource. Transfusion. 2016;56:3133–7.
7. European Commission. Commission staff working document—Evaluation of the Union legislation on blood, tissues and cells. 2019. Available from: https://health.ec.europa.eu/system/files/2019-10/swd_2019_376_en_0.pdf. Last accessed 10 Sep 2023.
8. European Commission. Stakeholder workshop with Blood Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718) 4 May 2021. 2021. Available from: https://health.ec.europa.eu/system/files/2021-08/ev_20210504_mi_en_0.pdf. Last accessed 10 Sep 2023.

9. Link Supply project website (4-9-2023). Available from: https://supply-project.eu. Last accessed 7 Sep 2023.
10. Thomas S, Roberts B, Domanović D, Kramer K, Klochkov D, Sivasubramaniyam S, et al. Safety profile of plasma for fractionation donated in the United Kingdom, with respect to variant Creutzfeldt-Jakob disease. Vox Sang. 2023;118:345–53.
11. Covington ML, Voma C, Stowell SR. Shortage of plasma-derived products: a looming crisis? Blood. 2022;26:3222–5.

How to cite this article: Smid WM, Thijssen-Timmer DC. Safeguarding plasma for fractionation: How can we deal with operational challenges in European Union countries. Vox Sang. 2024;119:128–30.

Received: 6 October 2023 | Revised: 26 December 2023 | Accepted: 27 December 2023

DOI: 10.1111/vox.13588

COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

The availability of plasma donors and plasma: A sociologist's perspective

SOCIETAL AND SCIENTIFIC BACKGROUND

Plasma donations are essential for producing plasma-derived medicinal products (PDMPs) to treat chronic diseases or critical conditions of patients [1]. As such, plasma is an important resource and brings health value to patients. Currently, about 35%–40% of the European plasma need is collected abroad, mostly in the USA from paid donors [2]. Due to current and emerging social, geopolitical, or economic challenges, plasma, regarded as an important raw material and 'strategic resource' is at risk of supply interruption [1–3], leading to a lack of essential products for European patients. Importantly, plasma is not a commodity; it is given by human donors. Donating blood (products) has often been referred to as 'gift of life' [4–6]. Blood for transfusion and plasma for PDMP production are not available without donors. In Europe alone, millions of patients are annually treated with blood products from voluntary donors. In most European countries, high-quality and well-functioning health care systems guarantee access to health care, and usually sufficient and suitable blood products are available. However, donor numbers have been decreasing while the demand for specific blood products, that is, plasma is ever increasing [2, 7]. Declining donor numbers together with the danger of supply interruption through political turmoil and a complex market of pharmaceutical products increase the risk of regional PDMP shortages. Many countries aim to achieve strategic independence in terms of PDMP availability. Therefore, a balanced and sufficient supply, based on large enough donor pools, better-regulated PDMP procurement, international collaborations and donations based on health solidarity is crucial [2, 8].

A LIFE COURSE APPROACH TO DONOR RESEARCH

Enough plasma donations by voluntary donors are one step towards achieving sufficient supply. To understand, explain and influence donation, studies have proposed different groups of determinants [9], including demographic characteristics [10], biological make-up, psychological mechanisms, such as reciprocity and reputation [11], and social network characteristics [12, 13]. Yet, previous research remained fragmented across disciplines and current theories fail to capture the complexity and dynamics of changing motivations and life course circumstances that determine donation [14, 15]. I suggest a life course approach to donor behaviour. The life course approach is a well-established framework in sociology for studying behaviour [16]. It examines individual determinants, links life stages over time and, importantly, examines behaviour within social networks and cultural contexts. Several reviews have indicated the lack of research into the topic of contextual and social network influences on donation behaviour. Especially when it comes to encouraging donations, institutional and sociocultural context are paramount [10, 17]. Cultural contexts set social norms for societies, that is, informal rules that guide and/or constrain social behaviours and determine how acceptable a given behaviour is viewed by members of a society or group [18] while institutions (i.e. plasma collection establishments) can direct specific policies to encouraging donation, such as recruitment messages and various forms of incentives, including, for example, time off work or financial incentives [19]. In 2000, Kieran Healy, in his seminal paper [20] on the role of the institutional context of blood establishments for donor motivation and donation rates, found interesting differences between Red Cross, hospital and state blood banks. He argued that collection regimes produce their own donor populations by their different structural and institutional opportunities and barriers. Although this paper mainly analysed whole blood donations, a similar reasoning can be applied to the structural and institutional opportunities and barriers for plasma donation. In Europe, such structural and institutional factors include, among others, different market situations, for example, monopolies compared to fragmented markets and not-for profit compared to for-profit collectors. Different markets are closely linked to specific incentive structures to motivate, recruit and retain plasma donations [21]. Taken together, this means that in addition to individual determinants, such as altruistic values and intentions, donation behaviour should be understood within the social and cultural contexts where it occurs, including incentive structures, social norms, market settings and (inter)national policymaking.

INCENTIVES

Incentives aim to motivate individuals to behave in a certain way and are generally considered effective tools for encouraging

behaviour [19]. Beneficial health behaviours, such vaccination or screening attendance, have been shown to be positively impacted by (monetary) incentives, especially for the short term [22]. However, the surprisingly inconsistent effects of (monetary) incentives on giving behaviour, for example, tax breaks for charity donations and rewards for blood donors remain puzzling [19]. This raises the question for European policymakers if and how incentives can be used to increase plasma donation. Incentives can come either as monetary or non-monetary. Monetary incentives take the form of direct cash payment, vouchers, travel compensations or tax breaks, whereas non-monetary incentives include gifts (e.g., mugs and towels), on-site refreshments, time off work or health checks [19, 21, 23]. To shed light on the diverse landscape of incentives and their potential effect on recruiting and retaining donors across different cultural, structural and institutional contexts, we recently conducted two studies [19, 21]. We first took stock of incentives across several hundred organizations in 26, mainly European, countries and found a large variety of incentive strategies for recruiting and rewarding plasma donors in Europe [21]. While snacks and health checks are commonly provided by nearly all countries, loyalty programmes, small gifts, coupons, lotteries, travel compensations and time off work expand the incentive portfolio. Only in seven countries, with commercial plasma collectors, donors are provided with financial incentives ranging from the equivalent of 10 to 35 Euros [2, 21].

Second, in an effort to explain inconsistencies in the effects of incentives, we proposed that social norms about blood donation, that is, how acceptable the general public regards incentives for blood (product) donation. We examined the donation behaviour of 26,000 individuals from 28 European countries and found that social norms can indeed predict how incentives, either in the form of financial payments or time off work, relate to individual-level blood donation behaviour [19]. Non-monetary incentives as time off work are associated with higher levels of donation if they align with existing social norms of acceptance. Hence, humans may not be universally persuaded by incentives to donate, but the effectiveness of incentives depends on social norms in the given cultural and institutional context. Taken together, different incentives have different effects in different contexts [19]. This illustrates the diversity of donors, institutions, regulators and states, indicating the importance of accounting for sociocultural and institutional embedding of donors and not thinking of balancing supply and demand from an economic perspective only.

ETHICAL CONSIDERATIONS AND FINAL REMARKS

The ethical question of whether it is desirable to offer incentives for what we often consider an act of altruism and solidarity has repeatedly been raised [24–27], with arguments against donor compensation showing limited basis in scientific evidence [26, 28]. Monetary incentives for blood donors may crowd out altruistic motivations, exploit vulnerable donors [2] and jeopardize blood safety [29] because they might decrease donor compliance with eligibility criteria that determine whether the donation is safe for donor and patient. However, improved testing for infectious disease markers has developed and improved such that infections in transfusion recipients, while not absent, have been minimized. For PDMPs, many pathogen-reduction steps during manufacture have increased safety considerably [30]. At the same time, there is increasing worry that too frequent plasma donation takes a toll on donor health [31–33], especially in the context of paid donors with a call for high-quality and systematic evidence based on international criteria [33]. The recent debate, for example, around European policymaking about the new regulation on substances of human origin is clear on endorsing the importance of donor safety, the principle of voluntary non-remunerated donations, but allows donor appropriate compensation and reimbursement of donors in line with national legislations. Yet, 'appropriate' donor compensation and reimbursement remain a controversial issue. Would it be bad to incentivize donors in controlled, responsible and socially accepted ways when that means that we can beat scarcity of source plasma for life-saving therapies while still protecting donor health and integrity? What kind of empirical evidence do we need to inform our policy decisions? What should the balance be among individual autonomy, effort compensation, availability of plasma but dependence on imported resources from paid donors, risk of exploitation and commodification of substances of human origin? These considerations and previously presented empirical results are complex. Therefore, I suggest an ongoing open dialogue between different scientific disciplines, policymakers, potential donors and all other stakeholders about their responsibilities towards a safe and sufficient plasma supply. Such a dialogue also includes educational efforts and creating awareness about the importance of plasma donation and associated different and sometimes conflicting interests. Future research should attend to the socially embedded nature of altruistic and self-interested action. Importantly, we also need a better understanding of the role of professionals, institutions, companies, and countries and how they may redirect their strategies of recruitment, compliance and retention. In combination, an open debate with the general public, including (potential) donors, patients and professionals and scientific rigour in research can help to shed light on existing empirical inconsistencies and sentiments around the provision of incentives for frequent plasma donors and ultimately lead to a better understanding of donor behaviour, more plasma, a better supply and demand balance, and global health solidarity.

CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

FUNDING INFORMATION

This work was supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 802227).

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REFERENCES

1. Strengers PFW, Klein HG. Plasma is a strategic resource. Transfusion. 2016;56:3133–7.
2. Strengers PFW. Challenges for plasma-derived medicinal products. Transfus Med Hemother. 2023;50:116–22.
3. Domanović D, von Bonsdorff L, Tiberghien P, Strengers P, Hotchko M, O'Leary P, et al. Plasma collection and supply in Europe: proceedings of an International Plasma and Fractionation Association and European Blood Alliance symposium. Vox Sang. 2023;118:798–806.
4. Healy KJ. Last best gifts. Altruism and the market for human blood and organs. Chicago: University of Chicago Press; 2006.
5. Parsons T, Fox RC, Lidz VM. The "gift of life" and its reciprocation. Soc Res. 1972;39:367–415.
6. Titmuss RM. The gift relationship: from human blood to social policy. London: Allen and Unwin; 1970.
7. Merz EM, van der Meer P. An introduction to the special issue Blood Donor Research. ISBT Sci Ser. 2018;13:373–4.
8. Rivera J, Lozano M. Plasmapheresis and plasma donation: challenges in the blood/plasma supply chain. Plasmatology. 2022;16:1–9.
9. Berger M, Easterbrook A, Holloway K, Devine D, Bansback N. What influences decisions to donate plasma? A rapid review of the literature. Vox Sang. 2023;118:817–24.
10. Piersma TG, Klinkenberg EF, Bekkers R, De Kort W, Merz EM. Individual, contextual and network characteristics of donors and non-donors: a systematic review of recent literature. Blood Transfus. 2017;15:382–97.
11. Ferguson E. Mechanism of altruism approach to blood donor recruitment and retention: a review and future directions. Transfus Med. 2015;25:211–26.
12. Schröder JM, Merz EM, Suanet B, Wiepking P. The social contagion of prosocial behaviour: how neighbourhood blood donations influence individual donation behaviour. Health Place. 2023;83:103072.
13. Schröder JM, Merz EM, Suanet B, Wiepking P. Did you donate? Talking about donations predicts compliance with solicitations for donations. PLoS One. 2023;18:e0281214.
14. Merz EM. Giving – in your (blood) group? Inaugural lecture 15-09-2022. Amsterdam: Vrije Universiteit; 2022.
15. Penner LA, Dovidio JF, Piliavin JA, Schroeder DA. Prosocial behavior: multilevel perspectives. Annu Rev Psychol. 2005;56:365–92.
16. Elder GH Jr. Time, human agency, and social change: perspectives on the life course. Soc Psych Quart. 1994;57:4–15.
17. Masser BM, Ferguson E, Merz E-M, Williams LA. Beyond description—the predictive role of affect, memory, and context on the decision to donate or not donate blood. Transfus Med Hemother. 2020;47:175–85.
18. Bicchieri C. The Grammar of Society: the nature and dynamics of social norms. Cambridge: Cambridge University Press; 2005.
19. Graf C, Suanet B, Wiepking P, Merz EM. Social norms offer explanation for inconsistent effects of incentives on prosocial behavior. J Econ Behav Organ. 2023;211:429–41.
20. Healy K. Embedded altruism: blood collection regimes and the European Union's donor population. Am J Sociol. 2000;105:1633–57.
21. Koch E, Leiße A, Veseli B, et al. (working paper). Incentives for plasma donation in Europe. University of Hamburg: Report for project SUPPLY Strengthening voluntary non-remunerated plasma collection capacity in Europe.
22. Giles EL, Robalino S, McColl E, Sniehotta FF, Adams J. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. PLoS One. 2014;9:e90347.
23. Zeller MP, Ellingham D, Devine D, Lozano M, Lewis P, Zhiburt E, et al. Vox Sanguinis International Forum on donor incentives: summary. Vox Sang. 2020;115:339–44.
24. Folléa G, De SE, Wit J. Renewed considerations on ethical values for blood and plasma donations and donors. Blood Transfus. 2014;12:s387–8.
25. Petrini C. Production of plasma-derived medicinal products: ethical implications for blood donation and donors. Blood Transfus. 2014;12:s389–s394.
26. Farrugia A, Penrod J, Bult JM. Payment, compensation, and replacement—the ethics and motivation of blood and plasma donation. Vox Sang. 2010;99:202–11.
27. Farrugia A, Penrod J, Bult JM. The ethics of paid plasma donation: a plea for patient centeredness. HEC Forum. 2015;27:417–29.
28. Lacetera N, Macis M, Slonim R. Economic rewards to motivate blood donations. Science. 2013;340:927–8.
29. Kalibatas V, Kalibatiene L. Reducing the risk of transfusion-transmitted-infectious disease markers in blood and blood component donations: movement from remunerated to voluntary, non-remunerated donations in Lithuania from 2013 to 2020. PLoS One. 2022;17:e0277650.
30. Sayers M. Paid donors: a contradiction in terms and contraindicated in practice. Transfusion. 2020;2020:S138–41.
31. Li H, Condon F, Kessler D, Nandi V, Rebosa M, Westerman M, et al. Evidence of relative iron deficiency in platelet- and plasma-pheresis donors correlates with donation frequency. J Clin Apher. 2016;31:551–8.
32. Mortier A, Khoudary J, van Dooslaer de Ten Ryen S, Lannoy C, Benoit N, Antoine N, et al. Effects of plasmapheresis frequency on health status and exercise performance in men: a randomized controlled trial. Vox Sang. 2024;119:134–43.
33. van Remoortel H, van den Hurk K, Compernolle V, O'Leary P, Tiberghien P, Erikstrup C. Very-high frequency plasmapheresis and donor health–absence of evidence is not equal to evidence of absence. Transfusion. 2023;63:2358–61.

How to cite this article: Merz E-M. The availability of plasma donors and plasma: A sociologist's perspective. Vox Sang. 2024;119:131–3.

Received: 11 July 2023 | Revised: 3 November 2023 | Accepted: 7 November 2023

DOI: 10.1111/vox.13569

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Effects of plasmapheresis frequency on health status and exercise performance in men: A randomized controlled trial

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Funding information
Science Foundation of the Belgian Red Cross Flanders

Abstract

Background and Objectives: Most research studies on the effects of repeated plasma donation are observational with different study limitations, resulting in high uncertainty on the link between repeated plasma donation and health consequences. Here, we prospectively investigated the safety of intensive or less intensive plasma donation protocols.

Materials and Methods: Sixty-three male subjects participated in this randomized controlled trial and were divided into low-frequency (LF, once/month, $n = 16$), high-frequency (HF, three times/month, $n = 16$), very high-frequency (VHF, two times/week, $n = 16$) and a placebo (P, once/month, $n = 15$) groups. Biochemical, haematological, clinical, physiological and exercise-related data were collected before (D0), after 1½ months (D42) and after 3 months (D84) of donation.

Results: In VHF, red blood cells, haemoglobin and haematocrit levels decreased while reticulocyte levels increased from D0 to D84. In both HF and VHF, plasma ferritin levels were lower at D42 and D84 compared to D0. In VHF, plasma levels of albumin, immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) dropped from D0 to D42 and remained lower at D84 than at D0. In HF, plasma IgG, IgA and IgM were lower at D42, and IgG and IgM were lower at D84, compared to D0. Few adverse events were reported in HF and VHF. Repeated plasma donation had no effect on blood pressure, body composition or exercise performance.

Conclusion: VHF plasmapheresis may result in a large reduction in ferritin and IgG levels. HF and VHF plasmapheresis may result in little to no difference in other biochemical, haematological, clinical, physiological and exercise-related parameters.

Keywords

albumin, donor selection, immunoglobulin, maximum oxygen consumption, maximum power output

Highlights

- This is the first randomized controlled trial prospectively investigating the effects of repeated plasma donation on a whole range of health consequences, namely biochemical and haematological parameters, blood pressure, body composition, adverse events and exercise performance.
- Haematological and biochemical parameters were severely impacted when plasmapheresis was repeated twice a week, mildly impacted with a frequency of three times per month and not impacted with a frequency of once a month. Markers for exercise performance were not altered over a 3-month period in any of the donation groups.
- Immunoglobulin G (IgG) levels dropped below the lower limit of normal (6 g/L) in the majority of donors donating twice per week. Before inducing very intensive donation regimens, the health effect of inducing hypo-IgG in donors should be investigated.

INTRODUCTION

More and more inflammatory, neurological, haematological and immunological diseases can be effectively treated with human plasma-derived products [1]. As such, the demand for plasma as the starting material for the manufacture of intravenous immunoglobulin and other plasma derivatives is growing significantly and is expected to continue to increase [2]. Future demand for intravenous immunoglobulin in developed countries is largely being driven by populations that are increasing in age and weight as well as the emergence of new indications. To increase the amount of collected plasma, one can expand the existing donor base, collect higher volumes per donation or stimulate donors to donate more frequently.

Plasma donors in the United States may donate twice within 7 days as long as the interval between donations is at least 2 days [3]. A prospective cohort study in Germany switched 3783 donors from a moderate to an intensive plasmapheresis program (maximum 60 donations annually and at least 72 h between two donations) over a 3-year period and concluded that, despite a 12.4% drop-out rate due to immunoglobulin G (IgG) levels, long-term intensive donor plasmapheresis is safe [4]. However, only very few studies have prospectively looked at the effect of repeated intensive plasma donation; either a control group was lacking [4, 5] or the control group was not randomized [6]. The majority of the studies were retrospective [7–12] or limited to one single donation [13–15]. We have recently found that repeated whole blood donation with a 3-month interval in between induced a drop in markers for iron status, which worsened with the number of donations [16]. The effects of repeated donations, whether whole blood or plasma, can be different from the effects measured after a single donation. It is therefore critical to test and document this repetitive effect to build trustable and valid guidelines concerning repetitive plasma donation. Up to now, each study has looked at a very limited number of outcomes separately, namely biochemical and haematological [4, 6, 8–11, 13, 14], blood pressure [5], clinical symptoms and adverse events [12, 13], bone metabolism [7] and exercise performance [15]. The aim of the present study was to collect data on (1) haematological and biochemical markers, (2) physiological and exercise-related parameters and (3) adverse events to get a comprehensive picture of the safety of intensive or less intensive plasma donation protocols over a 3-month period.

MATERIALS AND METHODS

Subjects

Potential study participants were either new plasmapheresis donors or previous donors who had not donated for at least 2 weeks. Eligible study participants were randomly assigned, via a computer-generated randomization table, into a placebo group (P), a low-frequency group (LF, one plasma donation per month), a high-frequency group (HF, three plasma donations per month) and a very high-frequency group (VHF, two plasma donations per week) to participate in this longitudinal study. The donation frequency regimen in the VHF group (two times/week) represents the current plasma donation regulation in countries such as Austria, Germany, Hungary, the United States, and Canada, whereas most other countries have a minimum donation interval of 14 days [17]. The P group donated at the same frequency as LF (once/month). All participants were blinded to the group selection.

Inclusion criteria were as follows: male, age 18–50 years, body mass index (BMI) 20–28 kg/m^2, and no contraindication to perform maximum-intensity exercise assessed by the physical activity readiness questionnaire. During the whole duration of the study, subjects were asked to maintain their habitual lifestyle, that is, physical activity and diet. All participants provided written informed consent after being explained about all potential risks of the study and the right to withdraw from it at any time. This study was conducted at UCLouvain, Belgium, from March 2022 to December 2022, and was approved by the Ethics Committee of UCLouvain (2020/04NOV/541). The investigation was performed according to the principles outlined in the Declaration of Helsinki. The study (RK2020) was registered at clinicaltrials.gov and received the identifier NCT05815615. Participants and the public were not involved in the research other than by their participation in the study.

Experimental procedures

One week before the first plasma donation (D0, Visit 1), subjects reported to the exercise physiology laboratory. First, systolic and diastolic blood pressure (SBP and DBP) were measured automatically (Omron) in the supine position. Then, five blood samples were taken

from an antecubital vein from the non-dominant arm: three 4-mL EDTA tubes, one 8-mL clot activator tube and one 4-mL sodium fluoride/potassium oxalate tube. After blood sampling, a maximum strength test of the dominant arm was performed using an electronic dynamometer (Grip-D, Takei, Japan) followed by a maximum strength test (1RM) with the dominant leg on a leg extension machine (ProDual, Body-Solid, IL, USA). After an individualized and standardized warm-up protocol, the 1RM test consisted of a maximum of five attempts interspersed by 3 min of rest. The 1RM corresponded to the highest load lifted once with a correct technique. Then, body mass and height were measured (Seca GmbH, Hamburg, Germany) and body composition (bone mineral content, fat-free mass and fat mass) was assessed by dual-energy X-ray absorptiometry scan (Discovery W, Hologic Inc., MA, USA). Finally, a progressive test on a bicycle ergometer (Cyclus 2, RBM elektronik automation GmbH, Leipzig, Germany) was performed to measure the peak oxygen consumption (VO_2 peak). The test started at 70 W, followed by incremental loads of 30 W every 2 min until exhaustion. The maximum power output (P_{max}) was calculated as the last step completed plus the last increment corrected for the sustained duration, which corresponded to the total time of the test. VO_2, carbon dioxide production (VCO_2) (Medisoft Ergocard, MGC Diagnostics Corporation, MN, USA) and the heart rate (HR) (Polar, Kempele, Finland) were continuously monitored during the test. Pulse oxygen was calculated by dividing VO_2 peak and HRmax at the end of the test. Blood lactate was measured before, during (at 190 W) and at the end of the test by taking a capillary blood sample (5 µL) from an earlobe (Lactate Pro, Arkray, Japan). The whole sampling and testing procedure was repeated 42 days (D42, Visit 2) and 84 days (D84, Visit 3) after the first plasma donation under exactly the same conditions. Adverse events, categorized according to international standards [18], were recorded in the blood information system throughout the entire experiment. Citrate reactions were not considered in our analysis because preventive calcium supplements were provided routinely to the regular donors.

Plasma donation

One week after blood sampling and exercise pre-testing (D0 or Visit 1), participants reported to the Red Cross Center in Leuven or Mechelen (Belgium). They underwent a plasma donation of maximum 650 mL (exclusive of anticoagulant) according to the Belgian Law of 01/02/2005, without exceeding 20% of total body volume during or 16% of total body volume at the end of the plasma donation (donation group), or had a similar sensation of undergoing a plasma donation (P group), by infusing NaCl 0.9% using a NexSys PCS device (Haemonetics). During each donation or simulation of donation, the punctured arm was shielded, and subjects were listening to music through a headset. According to our standard operating procedures, a rinse back with NaCl 0.9% (34 or 50 mL) was given after each cycle and at the end of the plasmapheresis procedure. In total, a volume of 30 mL of whole blood (six samples) was collected at each donation.

Blood analyses

Each tube was centrifuged for 10 min at 2000*g* at 4°C and analysed within 24 h following the blood drawing. The supernatant was collected and stored at −80°C. The following parameters were analysed in a medical analysis laboratory (LIMS MBnext Group Europe, LLN, Belgium): red blood cells, haemoglobin, haematocrit, reticulocyte, iron, ferritin, C-reactive protein (CRP), glycaemia, insulinemia, glycated haemoglobin (HbA1c), creatine kinase (CK), total cholesterol, albumin, immunoglobulin A (IgA), IgG and immunoglobulin M (IgM).

Statistical analysis

A statistical power analysis was carried out to determine the optimum number of subjects needed to find a difference in total serum protein mean of 10% [8] with a standard deviation of 8% and a power of 80% according to the calculator developed by Wang and Ji [19]. According to this analysis, a total of 64 subjects were needed to participate in the study to reach an optimum number of 16 subjects per group. Potential differences in the subjects' characteristics at baseline were analysed with one-way analysis of variance (ANOVA) (IBM SPSS Statistics, Version 28.0, Armonk, NY, USA). A mixed ANOVA model for repeated measures (SAS Statistical Software 9.4, SAS Institute, Cary, NC, USA) was used with the subjects as the random variable and groups (P and donations) and condition (time) as fixed independent variables. The *p*-values of the main effects can be found in Table S1. The model used the Kenward–Roger approximation of the degree of freedom with compound symmetry variance-covariance structure. When appropriate, contrast analyses were performed to compare means, applying a Sidak correction. Linear mixed models for repeated measures give unbiased results in the presence of missing data and take potential differences at baseline into account. Normality of residuals was tested using a *Q*–*Q* plot. The total number of adverse events and the adverse event rate (per 50 donations) were calculated. Statistical significance was set at $p < 0.05$. All values are expressed as mean ± SEM, except donation history which is reported as a median (interquartile range).

RESULTS

Subject characteristics

Seventy-two volunteers were enrolled in the study: 17 in P, 16 in LF, 20 in HF and 19 in VHF groups (Figure 1). Nine subjects (two in the P group, four in the HF group and three in the VHF group) withdrew before the end of the study due to personal reasons or impossibility to comply with the repeated appointments. At the time of withdrawal, IgG (9.9 ± 1.0 g/L), Hb (14.1 ± 0.4 g/dl) and ferritin levels (64 ± 15 µg/L) were not different in this group of nine subjects compared to the other subjects. Only one subject in the VHF group presented low IgG levels (4.9 g/L) at the time of withdrawal. As they

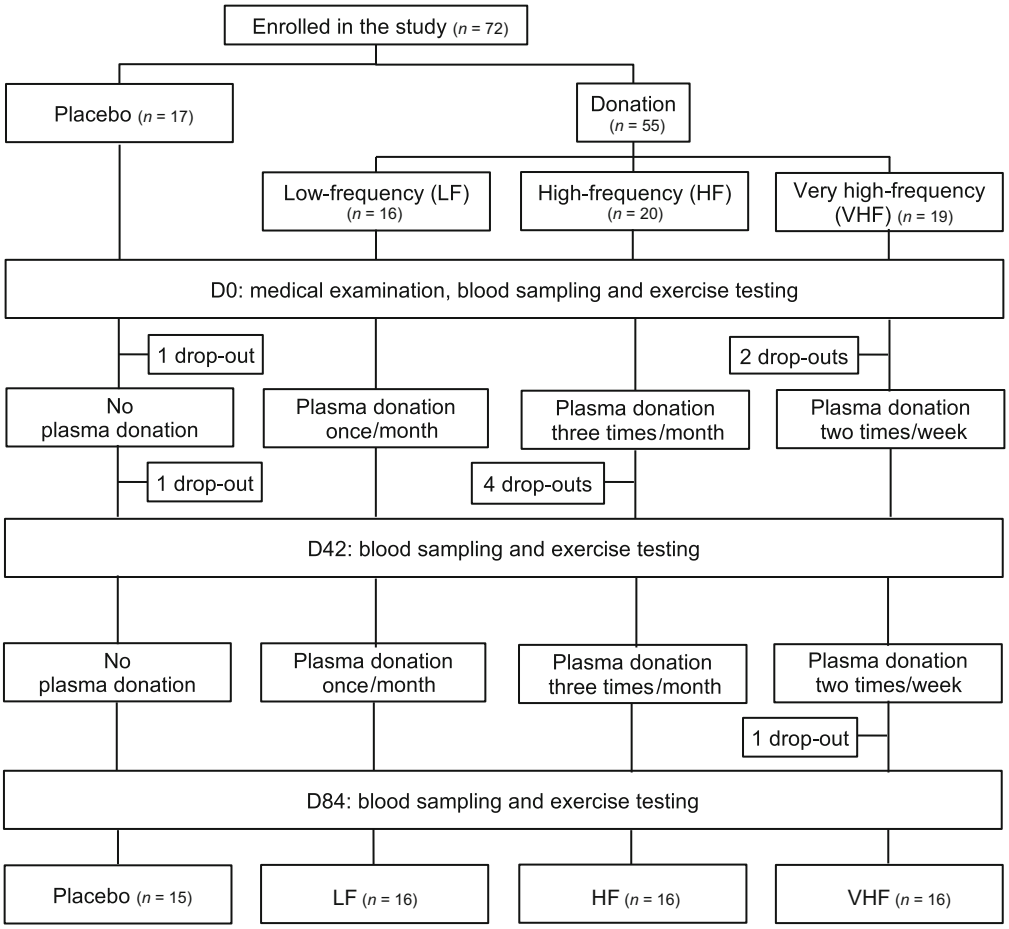

FIGURE 1 Subjects flow-chart.

were incomplete, the data of drop-outs were not included in the analyses, resulting in a total of 63 subjects: 15 in P, 16 in LF, 16 in HF and 16 in VHF groups. All participants were regular donors, except one new donor (who was allocated to the LF group). At the start of the study, the four groups were not different regarding age, BMI, the amount of physical activity per week, VO_2 peak and plasma donation history (Table S2). In addition, the recent history of whole blood donations was not different among the study groups—4 out of 16 donors in the VHF group, 3 out of 16 donors in the LF and HF groups and 3 out of 15 donors in the P donated whole blood once in the 3 months before entering the study.

Forty-nine study participants were 100% compliant with the corresponding donor regimen (5 [31%] in the VHF group, 14 [88%] in the HF group, 15 [94%] in the LF group and 15 [100%] in the P group). In the VHF group, six participants missed 1 donation, two participants missed 2–3 donations, two participants missed 5–6 donations and one participant missed 10 donations. Donors with missed donations were included in the data analysis.

VHF donation affects ferritin levels

In VHF, red blood cells ($p < 0.001$), Hb ($p < 0.001$) and haematocrit ($p = 0.003$) levels decreased, whereas reticulocyte levels ($p < 0.001$) increased from D0 to D84 (Table 1 and Figure 2a,b). In addition, reticulocyte levels were higher at D42 compared to D0 ($p < 0.001$). In both HF and VHF, plasma ferritin levels were lower at D42 ($p = 0.039$ in HF; $p = 0.001$ in VHF) and at D84 ($p = 0.008$ in HF; $p < 0.001$ in VHF) compared to D0. Except for red blood cells, all aforementioned effects of repeated plasma donation in HF and VHF were different from those of P at the same time point.

The reduced ferritin levels in the VHF (from 50.2 [D0] to 20.1 μg/L [D84], 60% reduction) were considered to be clinically meaningful. The other statistically significant differences were of no clinical importance.

VHF donation affects IgG levels

In VHF, the plasma levels of albumin (Figure 2c), IgG (Figure 2d), IgA and IgM dropped substantially from D0 to D42 ($p < 0.001$) and remained lower at D84 than at D0 ($p < 0.001$) (Table 1). Albumin and IgG levels at D42 and D84 in VHF were lower than those of P at the same time ($p < 0.01$–0.001). In HF, compared to D0, plasma IgG ($p < 0.001$), IgA ($p = 0.011$) and IgM ($p = 0.006$) were lower at D42, and IgG ($p < 0.001$) and IgM ($p < 0.001$) lower at D84. CRP, CK, SBP and DBP were unaffected by repeated plasma donation (data not shown).

TABLE 1 Effects of repeated plasma donation on haematological parameters.

		D0	D42	D84
RBC (10^6/mm^3)	P	4.8 ± 0.1	4.9 ± 0.1	5.0 ± 0.1$^{###}$
	LF	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1
	HF	4.9 ± 0.1	5.0 ± 0.1	5.0 ± 0.1
	VHF	5.0 ± 0.1	4.9 ± 0.1	4.8 ± 0.01$^{###}$
Haematocrit (%)	P	41.8 ± 0.7	42.3 ± 0.7	43.5 ± 0.7$^{###}$
	LF	42.0 ± 0.3	42.1 ± 0.3	42.0 ± 0.5
	HF	42.3 ± 0.6	42.3 ± 0.7	43.2 ± 0.5
	VHF	42.1 ± 0.4	41.8 ± 0.7	40.6 ± 0.4$^{##,§§§}$
Reticulocytes (%)	P	1.3 ± 0.1$^{£}$	1.4 ± 0.1	1.3 ± 0.1
	LF	1.3 ± 0.1$^{£}$	1.3 ± 0.1	1.3 ± 0.1
	HF	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1§
	VHF	1.3 ± 0.1$^{£}$	1.6 ± 0.1$^{###,§}$	1.6 ± 0.1$^{###,§}$
Iron (μg/dL)	P	109.3 ± 12.0	109.8 ± 12.3	122.7 ± 13.9
	LF	106.8 ± 10.2	100.3 ± 7.4	103.3 ± 7.1
	HF	83.6 ± 10.1	106.4 ± 10.6	91.3 ± 9.6§
	VHF	75.7 ± 10.0§,}$	78.8 ± 9.1§	65.0 ± 8.2§§§
Glycaemia (mg/dL)	P	92.5 ± 3.5	82.3 ± 5.3	91.4 ± 4.6
	LF	91.6 ± 4.2	91.9 ± 3.4	92.4 ± 5.6
	HF	94.9 ± 3.1	94.2 ± 4.2§	78.6 ± 3.7$^{##,§}$
	VHF	90.6 ± 2.4	82.4 ± 3.5$^{£}$	79.9 ± 3.6$^{#,§}$
Insulinemia (pmol/L)	P	73.5 ± 12.2	89.6 ± 16.4	92.6 ± 14.7
	LF	76.3 ± 17.2	83.1 ± 12.7	98.6 ± 15.0
	HF	76.8 ± 15.9	138.2 ± 31.4$^{#}$	87.0 ± 18.3
	VHF	77.5 ± 15.7	133.4 ± 47.0$^{#}$	114.9 ± 29.9
HbA1c (%)	P	5.2 ± 0.1	5.2 ± 0.1	5.2 ± 0.1
	LF	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1
	HF	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1
	VHF	5.3 ± 0.1	5.2 ± 0.1$^{#}$	5.1 ± 0.1$^{###}$
Total cholesterol (mg/dL)	P	162.7 ± 10.3	167.1 ± 8.9	175.9 ± 8.2$^{#}$
	LF	161.3 ± 7.2	167.9 ± 7.3	171.4 ± 8.9$^{#}$
	HF	160.5 ± 5.6	180.6 ± 8.2$^{###}$	175.2 ± 8.1$^{##}$
	VHF	182.9 ± 10.9	188.4 ± 12.5	189.4 ± 10.8
IgA (g/L)	P	2.2 ± 0.2	2.4 ± 0.3	2.4 ± 0.3
	LF	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2
	HF	2.2 ± 0.2	1.9 ± 0.1$^{#}$	2.1 ± 0.2
	VHF	2.5 ± 0.3	2.0 ± 0.2$^{###}$	2.1 ± 0.2$^{###}$
IgM (g/L)	P	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
	LF	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1$^{#}$
	HF	0.9 ± 0.1	0.8 ± 0.1$^{##}$	0.7 ± 0.1$^{###}$
	VHF	0.9 ± 0.1	0.6 ± 0.1$^{###}$	0.7 ± 0.1$^{###}$

Note: Values are means ± SEM. $n = 15$ in the P group, $n = 16$ in LF, HF and VHF groups.
Abbreviations: HbA1c, glycated haemoglobin; HF, high-frequency; IgA, immunoglobulin A; IgM, immunoglobulin M; LF, low-frequency; P, placebo; RBC, red blood cells; VHF, very high-frequency.
$^{#}p < 0.05$; $^{##}p < 0.01$ and $^{###}p < 0.001$ different from D0, same group. $^{§}p < 0.05$; $^{§§§}p < 0.001$ different from P, same time.

The reduced IgG levels in the VHF group (from 9.23 [D0] to 5.73 g/L [D84], 38% reduction, 9 out of 16 [56%] individuals with IgG levels <6 g/L at D84) were considered to be clinically meaningful. The other statistically significant differences were within the normal ranges and of no clinical importance.

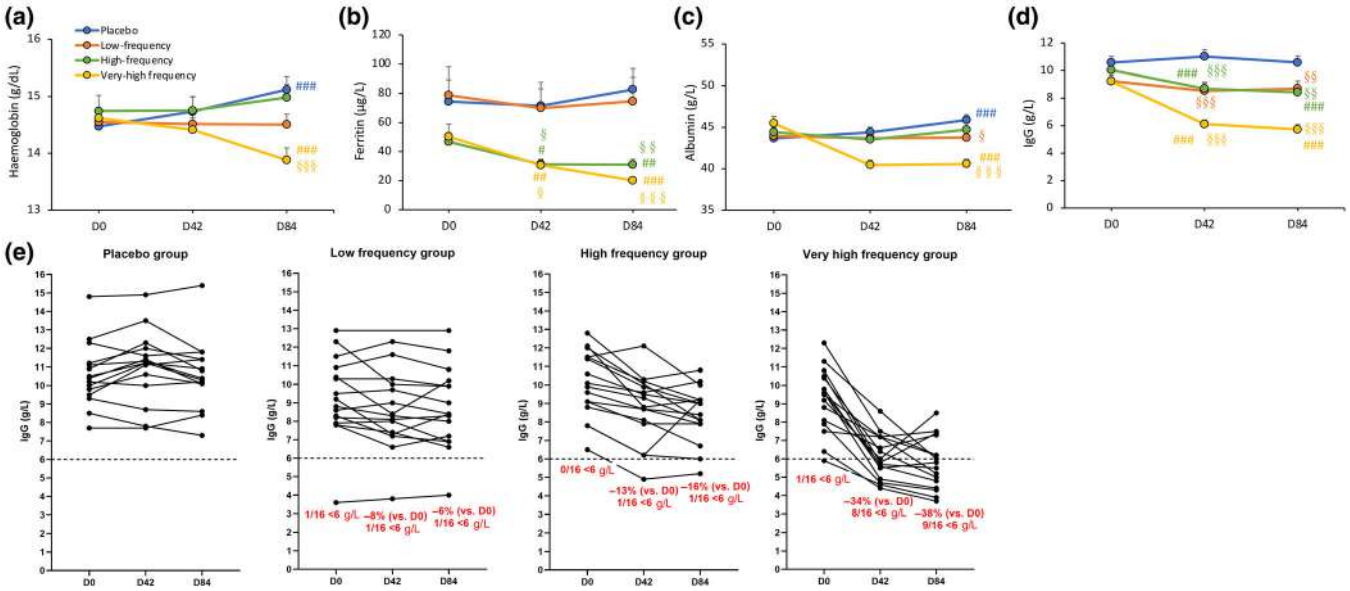

FIGURE 2 Plasma haemoglobin, ferritin, albumin and immunoglobulin levels. Evolution of plasma haemoglobin (a), ferritin (b), albumin (c), mean immunoglobulin G (IgG) (d) and individual IgG (e) levels before (D0), during (D42) and after (D84) the 3-month trial in the placebo (P) and donation groups. Data are expressed as means ± SEM. $n = 15$ in the placebo group and $n = 16$ in each of the three donation groups. $^{\#}p$ <0.05; $^{\#\#}p$ <0.01 and $^{\#\#\#}p$ <0.001 different from D0, same group. $^{\S}p$ <0.05; $^{\S\S}p$ <0.01 and $^{\S\S\S}p$ <0.001 different from P, same time.

No effect of repeated plasma donation on glycaemia, insulinemia and cholesterol levels

Glycaemia decreased from D0 to D84 in the HF ($p = 0.002$) and VHF ($p = 0.042$) groups and was lower in both at D84 compared to P (p <0.05) (Table 1). Insulinemia increased from D0 to D42 in HF ($p = 0.035$) and VHF ($p = 0.019$). In VHF, plasma HbA1c levels decreased from D0 to D42 ($p = 0.007$). Compared to D0, total cholesterol levels were higher at D42 in HF ($p < 0.001$) and at D84 in P ($p = 0.014$), LF ($p = 0.049$) and HF ($p = 0.005$). These differences were of no clinical importance.

No effect of repeated plasma donation on body composition

Fat-free mass and fat-free mass + bone mineral content were lower at D84 compared to D0 ($p = 0.040$ and $p = 0.049$, respectively) in P (Table 2). Fat mass increased from D0 to D84 in HF ($p = 0.038$) and VHF ($p = 0.041$). No effect was found for body mass, BMI or bone mineral content.

No effect of repeated plasma donation on exercise performance

The maximum power output decreased from D0 to D42 in LF ($p = 0.019$) and from D0 to D42 ($p = 0.013$) and D84 ($p = 0.012$) in VHF (Figure 3a). VO_2 peak was higher at D42 compared to D0 in HF ($p = 0.009$, Figure 3b). Pulse oxygen was higher at D42 in P ($p = 0.037$) and HF ($p = 0.006$) and higher at D84 ($p = 0.027$) in LF compared to D0 (Table 3). No effect was found for lactate at 190 W, lactate post exercise, maximum ventilation, maximum heart rate, maximum quadriceps (Figure 3c) and arm strength.

Few clinical adverse events were reported in the HF and VHF groups

The occurrence of clinical adverse events was monitored in each group during the whole experimental trial (Table S3). Five haematomas were present in HF (three events in three donors, adverse event rate: 1.08) and VHF (two events in one donor, adverse event rate: 0.28). Five vasovagal reactions were reported, one in HF (one donor, adverse event rate: 0.36) and four in VHF (three donors, adverse event rate: 0.57). Five anaemia events, defined as a Hb level below 135 g/L, were detected in four VHF donors (adverse event rate: 0.71). All anaemic participants had ferritin levels below or equal to 50 µg/L at D0. No other (major) events were reported.

DISCUSSION

For the first time, data on (1) haematological and biochemical markers, (2) physiological and exercise-related parameters and (3) adverse events were prospectively collected over 3 months to get a comprehensive picture of the health consequences of intensive or less intensive plasma donation protocols. We found that repeated plasma donation induced (1) a large reduction in ferritin and IgG levels in the

TABLE 2 Effects of repeated plasma donation on body composition.

		D0	D42	D84
Body mass (kg)	P	77.4 ± 3.8	77.7 ± 3.8	77.2 ± 3.7
	LF	78.9 ± 2.6	79.1 ± 2.7	79.5 ± 2.5
	HF	82.8 ± 2.1	83.7 ± 2.5	83.5 ± 2.5
	VHF	80.7 ± 2.9	80.2 ± 2.8	80.7 ± 3.0
BMI (kg/m^2)	P	23.6 ± 0.9	23.7 ± 0.9	23.6 ± 0.9
	LF	23.7 ± 0.6	23.6 ± 0.6	23.8 ± 0.7
	HF	24.4 ± 0.7	24.7 ± 0.8	24.7 ± 0.8
	VHF	24.0 ± 0.6	23.8 ± 0.5	24.0 ± 0.6
BMC (kg)	P	2.87 ± 0.12	2.88 ± 0.12	2.91 ± 0.12
	LF	2.97 ± 0.13	2.95 ± 0.13	2.98 ± 0.13
	HF	2.95 ± 0.06	2.95 ± 0.05	2.93 ± 0.06
	VHF	2.89 ± 0.11	2.87 ± 0.11	2.88 ± 0.11
Fat mass (kg)	P	12.7 ± 1.9	12.4 ± 1.8	13.3 ± 1.9
	LF	11.5 ± 1.1	11.5 ± 1.1	11.8 ± 1.1
	HF	14.6 ± 1.4	15.1 ± 1.5	15.4 ± 1.5$^{\#}$
	VHF	14.1 ± 1.3	13.7 ± 1.3	14.9 ± 1.4$^{\#}$
FFM (kg)	P	60.6 ± 2.3	60.9 ± 2.2	59.8 ± 2.1$^{\#}$
	LF	63.2 ± 1.7	63.2 ± 1.8	63.2 ± 1.7
	HF	63.9 ± 1.2	64.2 ± 1.2	63.6 ± 1.2
	VHF	61.8 ± 2.0	61.9 ± 1.8	61.5 ± 1.9
FFM + BMC (kg)	P	63.5 ± 2.4	63.8 ± 2.3	62.7 ± 2.2$^{\#}$
	LF	66.1 ± 1.8	66.1 ± 1.9	66.2 ± 1.7
	HF	66.8 ± 1.2	67.2 ± 1.2	66.6 ± 1.2
	VHF	64.7 ± 2.1	64.8 ± 1.9	64.3 ± 1.9
% Fat	P	15.9 ± 1.6	15.5 ± 1.6	16.8 ± 1.6
	LF	14.6 ± 1.0	14.5 ± 1.0	14.9 ± 1.0
	HF	17.5 ± 1.3	17.9 ± 1.4	18.3 ± 1.4
	VHF	17.7 ± 1.2	17.1 ± 1.2	18.4 ± 1.2

Note: Values are means ± SEM. $n = 15$ in the P group, $n = 16$ in LF, HF and VHF groups.
Abbreviations: BMC, bone mineral content; BMI, body mass index; FFM, fat-free mass; HF, high-frequency; LF, low-frequency; P, placebo; VHF, very high-frequency.
$^{\#}p$ <0.05 versus D0, same group.

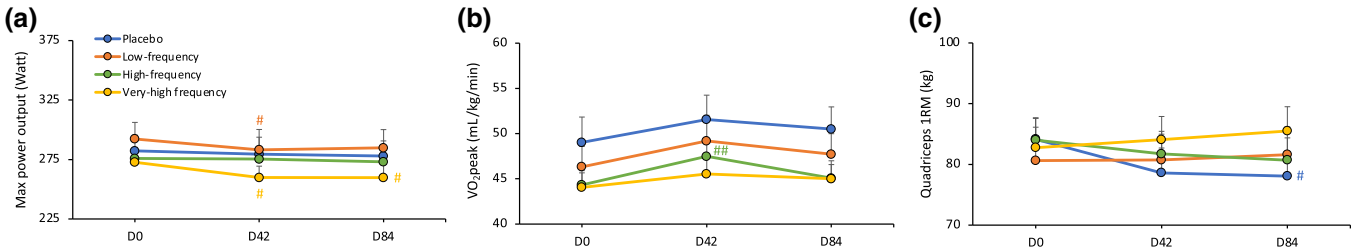

FIGURE 3 Markers for endurance and strength performance. Evolution of the maximum power output (a), peak oxygen consumption (VO_2 peak) (b) and maximum strength of the quadriceps (1RM) (c) before (D0), during (D42) and after (D84) the 3-month trial in the placebo and donation groups. Data are expressed as means ± SEM. $n = 15$ in the Placebo group, and $n = 16$ in each of the three donation groups. $^{\#}p$ <0.05, $^{\#\#}p$ <0.01 different from D0, same group.

VHF group; (2) a few minor clinical adverse events in both the HF and VHF group; (3) little to no difference in other biochemical, haematological, physiological and exercise-related parameters.

This is the first randomized controlled trial prospectively investigating the health consequences of repeated plasma donation. Most previous studies in this domain had an observational study design,

TABLE 3 Effects of repeated plasma donation on exercise performance.

		D0	D42	D84
Lactate 190 W (mmol/L)	P	3.5 ± 0.5	3.5 ± 0.5	3.3 ± 0.4
	LF	2.9 ± 0.5	2.8 ± 0.6	3.1 ± 0.6
	HF	3.0 ± 0.2	3.2 ± 0.4	3.1 ± 0.3
	VHF	3.9 ± 0.8	3.8 ± 0.6	3.3 ± 0.4
Lactate post (mmol/L)	P	11.2 ± 0.7	10.2 ± 0.7	10.1 ± 0.8
	LF	9.4 ± 0.7	9.3 ± 0.7	9.4 ± 0.5
	HF	10.1 ± 0.8	9.8 ± 0.6	9.6 ± 0.7
	VHF	11.6 ± 0.5	11.1 ± 0.4	10.9 ± 0.5
HRmax (bpm)	P	185 ± 3	185 ± 2	185 ± 3
	LF	180 ± 5	181 ± 5	180 ± 5
	HF	184 ± 4	185 ± 3	184 ± 3
	VHF	188 ± 2	189 ± 2	189 ± 2
VEmax (L/min)	P	150 ± 8	150 ± 9	145 ± 8
	LF	141 ± 7	145 ± 7	144 ± 9
	HF	145 ± 3	148 ± 4	146 ± 4
	VHF	142 ± 7	140 ± 6	140 ± 5
Oxygen pulse (mL/beat·kg)	P	0.20 ± 0.01	0.21 ± 0.01$^{\#}$	0.21 ± 0.01
	LF	0.20 ± 0.01	0.21 ± 0.01	0.21 ± 0.01$^{\#}$
	HF	0.20 ± 0.01	0.21 ± 0.03$^{\#\#}$	0.20 ± 0.03
	VHF	0.19 ± 0.01	0.19 ± 0.01	0.19 ± 0.01
Max arm strength (kg)	P	43 ± 2	43 ± 2	45 ± 2
	LF	44 ± 2	45 ± 2	45 ± 3
	HF	41 ± 1	41 ± 2	41 ± 1
	VHF	44 ± 2	43 ± 2	43 ± 2

Note: Values are means ± SEM. $n = 15$ in the P group, $n = 16$ in the LF, HF and VHF groups.
Abbreviations: HF, high-frequency; HR, heart rate; LF, low-frequency; P, placebo; VE, ventilation; VHF, very high-frequency.
$^{\#}p$ <0.05; $^{\#\#}p$ <0.01 versus D0, same group.

with different study limitation (e.g., not controlled for confounding), resulting in high uncertainty on the (causal) link between repeated plasma donation and health consequences [20–23]. One previous non-randomized controlled study compared total serum protein, albumin, IgG, IgA and IgM levels after weekly or bi-weekly (>14 days) plasmapheresis for 6 months to levels obtained in regular blood donors [6]. This study showed that total protein and IgG levels in the weekly group were lower than those in the control and the bi-weekly groups, but remained well within the normal ranges. Albumin, IgA and IgM levels were not modified by plasmapheresis. Our HF group, corresponding more or less to the weekly group in Ciszewski et al., had lower plasma ferritin, IgG, IgA and IgM levels 3 months after plasma donation. Our VHF group was even more impacted, with Hb and albumin levels being down-regulated as well compared to the start of plasma donation and compared to the P group. Except for IgG and ferritin in the VHF group, the drop in all other haematological and biochemical parameters in the HF and/or VHF group did not cross the lower acceptable limits, on average. Of note, before the start of the study, IgG levels were slightly lower in the LF and VHF groups compared to the P group but still well within physiological range. All studies that investigated IgG found reduced levels in donors with frequencies from once a month to twice a week, with a higher risk at falling below the normal range [4, 6, 8, 11]. Here, we found that IgG levels were reduced even in the LF group, donating once a month, while IgA and IgM levels were decreased only in the HF and VHF groups. IgG levels dropped below the lower limit of normal in the majority of donors in the VHF group. In the absence of solid evidence demonstrating that induced hypo-IgG is harmless for the donor, VHF donation regimens are not in line with the precautionary principle to avoid harm to the donor. Although Belgian plasma donors donate, on average, only 4–5 times per year, more than 50% of plasma-derived IgG administered to patients in Belgian hospitals originates from Belgian donors, indicating that VHF donation regimens are not essential to obtain self-sufficiency.

Lower ferritin values were previously reported in frequent plasma donors compared to non-donors [9, 11], with its levels being negatively correlated to the number of donations per year [9]. When looking at individual values for ferritin levels, 5 volunteers out of 16 in the VHF group had values <12 μg/L at the end of 3 months. Those results contrast with those of a previous study that retrospectively looked at

ferritin levels over a period of 12 months, during which plasma was donated at frequencies ranging from 0 to more than 70 times [10]. Less than 1% of male donors presented ferritin levels below 12 μg/L even in the group donating at least 70 times over 12 months, approaching the frequency in our VHF group. Divergent results have been reported as well concerning Hb levels, with one study reporting lower levels in frequent plasma donors [9] and another finding no effect [11] even when donating at least once a week for 12 months. In donors donating plasma several times per month, strategies to reduce the loss of red blood cells, such as rinsing back at the end of the procedure, limiting the number of whole blood samples and reducing the number of procedural failures resulting in incomplete return of red cells to the donor, should be considered and tested for their effectiveness.

Alongside determining the effects of repeated plasma donation on haematological and biochemical markers, the second aim of the study was to investigate the functional and physiological impact of repeated donation. We found no effect of 3-month plasma donation on blood pressure, body mass, body composition, markers for endurance performance and maximum strength. SBP and DBP were found to be decreased after 4-month plasma donation at intervals of less than 14 days in donors with high baseline blood pressure levels [5]. Here, in donors with normal blood pressure levels at the start of the study, no change of blood pressure was observed, even in the most intensive groups. Based on the decrease in some haematological parameters and a previous study looking at the effect of one single plasma donation on exercise performance [15], we would have expected a decrease in markers for endurance performance in the VHF group. The maximum power output, maximum oxygen consumption or blood lactate levels were not modified by repeated plasma donation, whatever the intensity of the donation. One previous study looked at the effects of one single plasma donation on the time to exhaustion, maximum oxygen consumption and markers for anaerobic capacity, that is, blood lactate levels and maximum accumulated oxygen deficit [15]. Although the maximum oxygen consumption was unaffected by plasma donation, time to exhaustion, blood lactate levels and maximum accumulated oxygen deficit were all decreased by 10%–20%. Our results suggest that the negative effects of acute plasma donation on endurance performance are not observed in the longer term when donation is repeated and performance is determined a few days after the last donation in basal conditions. It is important to highlight that, despite the down-regulation of key haematological parameters, endurance performance was not affected. We previously found that a partial dissociation and/or delay may be found between the regulation of haematological parameters, and more particularly those related to the iron status, and endurance performance after repeated blood donation [16, 24]. Given the importance of iron status for exercise performance [25], it cannot be excluded that the 3-month period of investigation was too short to induce detectable down-regulation of endurance and strength performance in the VHF group.

Finally, no serious adverse events were reported, and only a few events (anaemia, haematomas, vasovagal reactions without syncope) were present in the HF and VHF groups, which are classically reported by others after plasma donation [4, 12, 13].

VHF donation affects the IgG levels of donors down to a level that may impact their immune system and may affect haematological parameters. Therefore, countries should invest in building large donor bases to ensure a sustainable plasma supply while avoiding potential negative health effect to their donors.

This study has some limitations. First, only middle-aged men were included in this study and only one new donor was recruited. Therefore, the external validity is limited and the present results cannot be extrapolated to new donors or to female or elderly donor populations. Further studies should investigate whether those results are similar in women and older people.

Second, this randomized controlled trial lasted for 3 months. It cannot be excluded that the severe haematological and biochemical changes measured during this period in the VHF group, although not falling below normal values for most of them, will not affect physiological function and exercise performance in the longer term.

Third, the randomization procedure was sub-optimal since allocation to the HF/VHF group was sometimes in conflict with the availability of the participant. Therefore, the donor was assigned to the first available position on the randomization list that did not conflict with his availability. The impact of this sub-optimal randomization procedure was considered limited.

In conclusion, VHF plasmapheresis may result in a large reduction in ferritin and IgG levels. HF and VHF plasmapheresis may result in little to no difference in other biochemical, haematological, clinical, physiological and exercise-related parameters.

ACKNOWLEDGEMENTS

We thank Anna Piperi, Marine Buchet and Elena De Bock for technical assistance and Céline Bugli for statistical analyses. The study was funded by the Science Foundation of the Belgian Red Cross Flanders.

V.C., P.V. and L.D. designed the protocol; A.M, J.K., S.v.D.d.T.R., C.L., N.B., N.A., S.C., V.C. and LD acquired the data; H.V.R., P.V., V.C. and L.D. interpreted the data; A.M. and L.D. drafted the manuscript; all authors contributed to revision of the manuscript and approved the same.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005;142:1–11.

2. Robert P. Global plasma demand in 2015. Pharma Policy Law. 2009; 11:359–67.
3. Administration UFaD. Compliance policy guides manual: plasmapheresis—48 hour period between plasmapheresis procedures. CPG 7123.23; in Administration UFaD, (ed). Rochester, MD. 2000.
4. Schulzki T, Seidel K, Storch H, Karges H, Kiessig S, Schneider S, et al. A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA). Vox Sang. 2006;91:162–73.
5. Rosa-Bray M, Wisdom C, Marier JF, Mouksassi MS, Wada S. The effect of plasmapheresis on blood pressure in voluntary plasma donors. Vox Sang. 2015;108:11–7.
6. Ciszewski TS, Ralston S, Acteson D, Wasi S, Strong SJ. Protein levels and plasmapheresis intensity. Transfus Med. 1993;3:59–65.
7. Amrein K, Katschnig C, Sipurzynski S, Stojakovic T, Lanzer G, Stach E, et al. Apheresis affects bone and mineral metabolism. Bone. 2010;46:789–95.
8. Laub R, Baurin S, Timmerman D, Branckaert T, Strengers P. Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sang. 2010;99: 220–31.
9. Li H, Condon F, Kessler D, Nandi V, Rebosa M, Westerman M, et al. Evidence of relative iron deficiency in platelet- and plasma-pheresis donors correlates with donation frequency. J Clin Apher. 2016;31: 551–8.
10. Schreiber GB, Brinser R, Rosa-Bray M, Yu ZF, Simon T. Frequent source plasma donors are not at risk of iron depletion: the Ferritin Levels in Plasma Donor (FLIPD) study. Transfusion. 2018;58:951–9.
11. Tran-Mi B, Storch H, Seidel K, Schulzki T, Haubelt H, Anders C, et al. The impact of different intensities of regular donor plasmapheresis on humoral and cellular immunity, red cell and iron metabolism, and cardiovascular risk markers. Vox Sang. 2004;86:189–97.
12. Yuan S, Gornbein J, Smeltzer B, Ziman AF, Lu Q, Goldfinger D. Risk factors for acute, moderate to severe donor reactions associated with multicomponent apheresis collections. Transfusion. 2008;48: 1213–9.
13. Buzza M, Marks DC, Capper H, Cassin E, Badcock CA, Reid S, et al. A prospective trial assessing the safety and efficacy of collecting up to 840 mL of plasma in conjunction with saline infusion during plasmapheresis. Transfusion. 2012;52:1806–13.
14. Ghio M, Contini P, Ansaldi F, Ubezio G, Setti M, Risso M, et al. Immunomodulation due to plasma or plasma-platelet apheresis donation: events occurring during donation procedures. J Clin Apher. 2015;30: 204–11.
15. Hill DW, Vingren JL, Burdette SD. Effect of plasma donation and blood donation on aerobic and anaerobic responses in exhaustive, severe-intensity exercise. Appl Physiol Nutr Metab. 2013;38:551–7.
16. Meurrens J, Steiner T, Ponette J, Janssen HA, Ramaekers M, Wehrlin JP, et al. Effect of repeated whole blood donations on aerobic capacity and hemoglobin mass in moderately trained male subjects: a randomized controlled trial. Sports Med Open. 2016;2:43.
17. Purohit M, Berger M, Malhotra R, Simon T. Review and assessment of the donor safety among plasma donors. Transfusion. 2023;63:1230–40.
18. International Society of Blood Transfusion working party on haemovigilance network and the AABB donor haemovigilance working group. Standard for surveillance of complications related to blood donation. Available from: https://www.aabb.org/docs/default-source/default-document-library/resources/donor-standard-definitions.pdf?sfvrsn=21834fa4_0. Last accessed 10 Jul 2023.
19. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. Chest. 2020;158: S12–20.
20. Grgicevic D. Influence of long-term plasmapheresis on blood coagulation. Ric Clin Lab. 1983;13:21–31.
21. Grgicevic D, Pistotnik M, Pende B. Observation of the changes of plasma proteins after long term plasmapheresis. Dev Biol Stand. 1980;48:279–86.
22. Rosa-Bray M, Wisdom C, Wada S, Johnson BR, Grifols-Roura V, Grifols-Lucas V. Prospective multicentre study of the effect of voluntary plasmapheresis on plasma cholesterol levels in donors. Vox Sang. 2013;105:108–15.
23. Salvaggio J, Arquembourg P, Bickers J, Bice D. The effect of prolonged plasmapheresis on immunoglobulins, other serum proteins, delayed hypersensitivity and phytohemagglutinin-induced lymphocyte transformation. Int Arch Allergy Appl Immunol. 1971;41: 883–94.
24. Pachikian B, Naslain D, Benoit N, Brebels R, Van Asch K, Compernolle V, et al. Iron supplementation limits the deleterious effects of repeated blood donation on endurance sport performance but not on iron status. Blood Transfus. 2020;18:334–47.
25. Sim M, Garvican-Lewis LA, Cox GR, Govus A, McKay AKA, Stellingwerff T, et al. Iron considerations for the athlete: a narrative review. Eur J Appl Physiol. 2019;119:1463–78.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mortier A, Khoudary J, van Dooslaer de Ten Ryen S, Lannoy C, Benoit N, Antoine N, et al. Effects of plasmapheresis frequency on health status and exercise performance in men: A randomized controlled trial. Vox Sang. 2024;119:134–43.

Received: 16 August 2023 | Revised: 25 November 2023 | Accepted: 27 November 2023

DOI: 10.1111/vox.13572

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Risk prediction of iron deficiency for plasmapheresis donors in China: Development and validation of a prediction model

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Funding information
CAMS Innovation Fund for Medical Sciences (CIFMS), Grant/Award Number: 2021-I2M-1-060

Abstract

Background and Objectives: The present study aims to evaluate the iron stores in plasmapheresis donors and develop and validate an iron deficiency (ID) risk prediction model for plasmapheresis donors with potential or existing ID.

Materials and Methods: We assessed plasmapheresis donors' serum ferritin (SF) and haemoglobin (Hb) levels. The candidate factors showing significant differences in the multivariate logistic regression analysis were used to establish a risk prediction scoring system. The participants were divided into a training cohort and an internal validation cohort in a 7:3 ratio. Additional plasmapheresis donors from a different station were recruited for external validation.

Results: The SF levels in both male and female donors in the high-frequency group were significantly lower than those of new donors (male: $p < 0.001$; female: $p = 0.008$). The prevalence of ID in female regular donors with a high frequency was significantly higher than that in new donors (33.1% vs. 24.6%; odds ratio = 1.209 [95% CI: 1.035–1.412]). Donation frequency, age, Hb, body mass index and being pre-menopausal were identified as independent risk factors for ID ($p < 0.05$). The developed model exhibited good discrimination ability (area under the receiver operating characteristic curve >0.7) and calibration ($p > 0.05$) in development, internal validation cohorts and external validation cohorts.

Conclusion: A higher donation frequency has been associated with reduced SF levels and an increased risk of ID in women. The developed ID risk prediction model

demonstrates moderate discriminative power and good model fitting, suggesting its potential clinical utility.

Keywords
iron deficiency, iron stores, plasmapheresis donation, prediction model, serum ferritin

Highlights

- Under the current standard of plasmapheresis donation in China, a higher frequency of donation may lead to a reduction in serum ferritin levels and increase the risk of iron deficiency (ID) among women.
- Age, body mass index, donation frequency, haemoglobin levels and menstrual history were highly correlated with the occurrence of ID in female regular donors.
- The risk prediction model for ID in female regular donors has moderate discriminative power and a good model fit, and is of some clinical utility.

INTRODUCTION

Iron deficiency anaemia (IDA) is the most common nutritional deficiency, affecting approximately one-third of the global population [1]. Repeated blood donation, which is often underestimated, is a significant cause of IDA. Research indicated that regular blood donors had a higher risk of developing IDA than first-time donors due to frequent loss of whole blood [2]. In the United States, a study reported that 48.7% of male donors and 66.1% of female donors experienced iron deficiency (ID) or IDA [2].

Men typically lose around 225 mg of iron during whole blood donation, whereas women lose about 217 mg per whole blood donation [3]. This iron loss is primarily due to the significant loss of red blood cells (RBCs). In contrast, plasmapheresis donation only collects plasma, whereas RBCs are returned to the donor. However, there is still a tiny loss of RBCs during plasmapheresis donation, amounting to approximately 30 mL of whole blood per donation. The Association for the Advancement of Blood & Biotherapies (AABB) [4] has recommended that blood banks establish a definition for the number of platelet and plasma apheresis procedures (including incomplete procedures and blood samples) that result in a loss of RBCs roughly equivalent to the loss of RBCs in a single whole blood donation. Based on residuals in the collection kits and losses in testing tubes, it is estimated that this would amount to around four or five plateletpheresis or plasmapheresis donations [5, 6].

Interestingly, some countries have started paying attention to the iron metabolism of plasmapheresis donors. A study conducted in Japan observed that regular plasmapheresis donors had significantly lower serum ferritin (SF) levels compared with new donors [7]. Similarly, a study at the New York Blood Center found that plasmapheresis donors exhibited a significant decrease in SF levels compared with the general healthy population [5].

Notably, Chinese plasmapheresis donation standards differ from those of other countries. China implements a 14-day interval for plasmapheresis donation, and the number of donations within a year shall not exceed 24 times [8]. In contrast, donors in the United States can donate twice a week [9]. Chinese plasmapheresis donors can donate 580 g of anticoagulant-free plasma per donation [8], whereas the range for U.S. donors is 625–800 mL [10]. As a result, conclusions drawn from international studies on plasmapheresis donations may not directly apply to Chinese donors. Therefore, it is essential to conduct research and validation specific to China's circumstances to ensure plasmapheresis donations' effectiveness and safety.

MATERIALS AND METHODS

Study design and population

We performed a multi-centre cross-sectional study from September 2021 to October 2022, focusing on SF and haemoglobin (Hb) in plasmapheresis donors. The study was conducted in six plasmapheresis centres across Sichuan, Hunan, Henan and Yunnan provinces. The Ethics Committee of the Institute of Blood Transfusion, Chinese Academy of Medical Sciences (IBT) approved this study (No. 2021042). All participants gave written consent for the donation. New donors with no plasmapheresis history were recruited as the control group, whereas regular donors were included in the investigator group. To investigate the impact of donation frequency on iron metabolism, we further divided the regular donors into three groups based on the number of plasmapheresis donations in the previous 12 months: 1–8 donations (low-frequency group), 9–16 donations (medium-frequency group), and 17–24 donations (high-frequency group).

Inclusion and exclusion criteria

Donors were eligible to participate after completing a pre-donation health history and physical examination. According to Chinese donor standards, all participants were required to be aged between 18 and 60 years. [10]. Individuals who had experienced moderate to

significant blood loss or had donated whole blood or platelets within the past 12 months were excluded from the study. In addition, those who had taken iron supplements in the previous 6 months were excluded from participation.

Diagnostic criteria for ID

ID is commonly assessed using biomarkers, among which SF is an indicator of total body iron storage [11]. The AABB Iron Deficiency Working Group recently considered the occurrence of iron-deficient erythropoiesis as SF levels below 26 ng/mL [12]. In comparison, the World Health Organization considered the occurrence of ID to be SF levels below 15 ng/mL [13]. To safeguard the health and safety of plasmapheresis donors, we utilized a high-sensitivity diagnostic criterion, defining SF <26 ng/mL as the primary outcome for ID. SF < 15 ng/mL was used as the secondary outcome for ID.

Samples and laboratory testing

Once a donor was deemed eligible for the study, a 1 mL sample of pre-donation blood was collected in sterile tubes for Hb detection (Automated Haematology Analyser, Matenu, China) at local laboratories. A 2 mL sample of pre-donated blood was centrifuged at 3000 rpm for 10 min. Serum samples were separated and stored at −20°C until further analysis. The same batch was tested for SF (full-automatic chemiluminescence instrument, Alinity, USA) in a central laboratory.

Data collection

The number of plasmapheresis donations in the prior 12 months was retrieved by the Donor Management System from each plasmapheresis donation centre. Demographic information, including living place, sex, age, weight, height, female menstrual history and socioeconomic factors such as education and annual household income, were obtained through questionnaires. Lifestyle variables such as smoking, drinking and meat intake were also assessed. Annual household income was calculated in Chinese yuan (CNY) and converted to US dollars (USD) based on September 2021 exchange rates (1 USD = 6.4599 CNY). Annual household income was categorized into three intervals: low (less than 4644 USD), moderate (between US $4644 and US$12,384) and high (greater than 12,384 USD), based on the per capita household income of the study participants. Body mass index (BMI) = weight (kg)/height (m) squared.

Quality control

Training materials were developed to provide standardized and unified instructions before information and sample collection. The plasmapheresis collection centre staff were trained on technical requirements, technical operations and additional related content. After collection, serum samples were chilled to avoid repeated freezing and thawing. The standard curve accuracy and quality control measurements were monitored in real-time during the sample testing phase.

Statistical analysis

We summarized continuous measurements using the mean and standard deviation if normally distributed; otherwise, we used the median and interquartile range (IQR). We gave frequencies and percentages for categorical observations. The Mann–Whitney–Wilcoxon test compared each donation frequency group with new donors. We considered confounding factors that could affect the SF level for more accurate results. Literature-based covariates were identified a priori [14–16]. Multiple linear regression compared SF levels between regular and new donors. In model 1, age and BMI were adjusted. Model 2 also included living place, meat intake, education, smoking, drinking, household income and female donors additionally adjusting their menstrual history. Text and figure legends indicate whether p values retain statistical significance at the $p < 0.0167$ (0.05/3) level after the Bonferroni adjustment. The Benjamini-Hochberg procedure was used as the sensitivity analysis to control the false-discovery rate for multiple comparisons based on the number of time points analysed for each outcome. The p values before and after correction are presented.

We used univariate logistic regression to compare the ID rates between regular and new donor groups. Different ID rates between each regular donor group and the new donor were compared using multivariate logistic regression for confounding factors by establishing model 1 and model 2. If no instruction is given, a p value of 5% is considered significant.

The risk prediction scoring system is a valuable tool for estimating the risk of diseases [17]. The donors were randomly divided into a training and an internal validation cohort, typically in a 7:3 ratio. For external validation, additional plasmapheresis donors from another plasmapheresis station were recruited. Logistic multivariate analysis adopted the stepwise method to determine the independent predictors of ID. The final nomogram model was determined according to the Akaike information criterion (AIC). Model performances were quantified using the area under the receiver operating characteristic curve (AUC) and metrics derived from the confusion matrix accuracy, sensitivity, specificity, positive prediction value (PPV) and negative prediction value (NPV). We used a calibration curve to display the consistency between the predicted probability and the observed probability to evaluate the calibration of the model. Decision curve analysis (DCA) was used to evaluate the clinical benefits and utility of the nomogram [18]. All statistical analyses were performed using the R programming language and environment (R 4.1.3 http://www.r-project.org/, Vienna, Austria), and the following software packages are used: caret, pROC, calibrate, MASS, rms and rmda.

RESULTS

In the study, there were a total of 1493 donors. Among them, 774 were male donors, and 719 were female donors. Of the male donors, 384 were new donors, and 390 were regular donors. Of the female donors, 342 were new donors, and 377 were regular donors (Table 1).

The detected values of SF and Hb for donors with different donation frequencies and their variations are shown in Figure 1. For male new plasma donors, the SF level was 175.92 ng/mL (IQR: 108.98–276.49 ng/mL) and that in the high-frequency group was 139.14 ng/mL (IQR: 86.59–207.73 ng/mL). After adjusting for the confounding factors, the SF level of the high-frequency group was significantly lower than that of the new plasma donors ($p < 0.001$). The SF level of female new plasma donors was 48.04 ng/mL (IQR: 25.28–97.87 ng/mL) and that in the high-frequency group was 36.39 ng/mL (IQR: 18.85–75.41 ng/mL). After adjusting for the confounding factors, the SF level in the high-frequency group was significantly lower than that in new plasma donors ($p = 0.008$) (Table 2). The Hb concentration did not exhibit a statistically

TABLE 1 Baseline data of regular male donors and new male donors.

	Male			Female		
Variables	**New donors**	**Repeat donors**	***p***	**New donors**	**Repeat donors**	***p***
Total number	384	390		342	377	
Living place						
Hunan	78 (20.3)	89 (22.8)	0.601	62 (18.1)	101 (26.8)	0.991
Yunnan	90 (23.4)	100 (25.6)		97 (28.4)	71 (18.8)	
Henan	109 (28.4)	98 (25.1)		92 (26.9)	101 (26.8)	
Sichuan	107 (27.9)	103 (26.4)		91 (26.6)	104 (27.6)	
Age (year)	36 (25–46)	41 (31–50)	<0.001	41 (32–49)	42 (32–50)	0.102
BMI (kg/m^2)	24.48 (21.82–27.10)	25.57 (22.65–28.39)	0.002	23.76 (21.48–26.59)	24.60 (22.06–27.25)	0.018
Education						
Elementary school	50 (13.0)	71 (18.2)	0.001	98 (28.7)	121 (32.1)	0.62
Junior high school	170 (44.3)	190 (48.7)		143 (41.8)	156 (41.4)	
High school	147 (38.7)	100 (25.6)		90 (26.3)	92 (24.4)	
Universities	17 (4.4)	29 (7.4)		11 (3.2)	8 (2.1)	
Meat intake						
None	3 (0.8)	4 (1)	0.302	7 (2)	5 (1.3)	0.019
Occasionally	161 (41.9)	184 (47.2)		192 (56.1)	250 (66.3)	
Frequently	220 (57.3)	202 (51.8)		143 (41.8)	122 (32.4)	
Smoking						
None	112 (29.2)	126 (32.3)	0.012	328 (95.9)	369 (97.9)	0.304
Occasionally	136 (35.4)	100 (25.6)		11 (3.2)	6 (1.6)	
Frequently	136 (35.4)	164 (42.1)		3 (0.9)	2 (0.5)	
Drinking						
None	126 (32.8)	147 (37.7)	0.129	330 (96.5)	352 (93.4)	0.058
Occasionally	245 (63.8)	223 (57.2)		12 (3.5)	25 (6.6)	
Frequently	13 (3.4)	20 (5.1)		0 (0)	0 (0)	
Annual household income						
Low	99 (25.8)	73 (18.7)	0.008	137 (40.1)	125 (33.2)	0.004
Moderate	178 (46.4)	223 (57.2)		140 (40.9)	200 (53.1)	
High	107 (27.9)	94 (24.1)		65 (19)	52 (13.8)	
Menstrual history						
Pre-menopausal	-	-	-	272 (79.5)	294 (78)	0.612
Post-menopausal	-	-		70 (20.5)	83 (22)	

Note: Continuous measurements are expressed as mean ± SD if normally distributed; otherwise, as median (IQR). Categorical observations are expressed as *n* (%).
Abbreviation: BMI, body mass index.

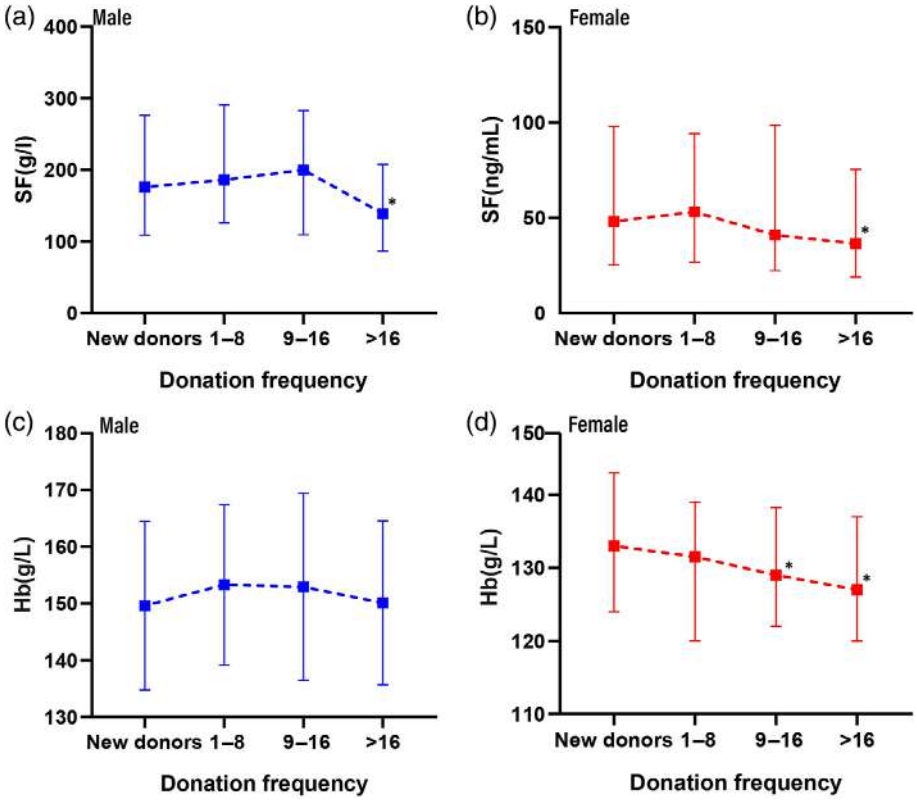

FIGURE 1 SF and Hb levels between regular donors and new donors. SF in male (a) and female (b) groups with different donation frequencies. Hb in male (c) and female (d) groups with different donation frequencies. Hb of male is expressed as mean ± SD. Hb in female and SF in both male and female is expressed as median (IQR). New donors were as control group. *The Mann–Whitney–Wilcoxon test was used to compare each donation frequency group with new donors and significance after Bonferroni correction. Hb, haemoglobin; IQR, interquartile range; SF, serum ferritin.

significant difference between male regular donors and new donors among male donors. The Hb level of female new donors was 133.00 g/L (IQR: 124.00–143.00 g/L). The Hb level of the medium frequency group was 127.00 g/L (IQR: 119.50–138.00 g/L). The difference was statistically significant after adjusting for all confounding factors ($p = 0.003$). The high-frequency group was 125.80 g/L (IQR: 119.00–131.00 g/L). After adjusting for all confounding factors, the difference was statistically significant ($p < 0.001$) (Table 2). The results did not change after the Benjamini-Hochberg procedure (Table S1).

ID rates showed significant gender differences. The ID rate of male new donors was only 1%. The ID rate of regular male donors was 0.5% in the low-frequency group, 0.3% in the high-frequency group and no ID in the medium-frequency group. The number of new female donors with ID was 84, accounting for 24.6%, and the number of female ID donors in the high-frequency group was 54, accounting for 33.1%. After adjusting for all confounding factors, there was a statistical difference between the high-frequency group and new donors (odds ratio [OR]: 1.209, 95% CI = 1.035–1.412, $p < 0.05$) (Table 3). In addition, we repeated the analysis using a cut-off value of 15 ng/mL, whereas the difference was not significant (OR: 1.150, 95% CI = 0.962–1.375, $p > 0.05$) (Table S2).

The training cohort comprised 265 donors, the internal validation cohort comprised 112 donors and the external validation cohort comprised 110 donors. The general data for the training and validation cohorts are shown in Table S4. We identified five independent risks through stepwise multivariate logistic regression analysis, including age, BMI, Hb, menstrual history and donation frequency (Table 4), which demonstrated the lowest AIC value (AIC = 271.92, Table S3). The AUC was 0.798 (95% CI = 0.742–0.854) in the training cohort, 0.763 (95% CI = 0.669–0.858) in the internal validation cohort and 0.703 (95% CI = 0.586–0.820) in the external cohort, indicating favourable discrimination by the model (Figure 2). The accuracies ranged from 62.7% to 74.3%, sensitivities ranged from 68.3% to 87.1%, specificities ranged from 57.0% to 77.1%, PPVs ranged from 35.1% to 57.1% and NPVs ranged from 84.4% to 92.5% (Table S5 and Figure S2). The calibration curve of this model shows a high degree of consistency between prediction probability and observation probability in the training cohort (Hosmer-Lemeshow [HL] test: $p = 0.803$), internal validation cohort (HL test: $p = 0.469$) and external validation cohort (HL test: $p = 0.426$) (Figure 3). The DCA curve shows that the model has certain clinical practicality (Figure 4). Finally, we constructed a nomogram of ID based on the independent predictors of ID screened by a stepwise regression method (Figure 5). The cut-off point was determined using Youden's index (Table S6).

TABLE 2 SF and Hb level between regular donors and new donors.

		Donation frequency (times/per year)			
Model	**New donors**	**1–8**	**9–16**	**>16**	***p* for trend**
Male					
SF (ng/mL, IQR)	175.92 (108.98–276.49)	185.99 (126.20–290.71)	200.12 (109.47–282.71)	139.14 (86.59–207.73)	
Model 1	Reference group	$p = 0.730$	$p = 0.713$	$p < 0.001$	$p < 0.001$
Model 2	Reference group	$p = 0.996$	$p = 0.633$	$p < 0.001$	$p = 0.001$
Female					
SF (ng/mL, IQR)	48.04 (25.28–97.87)	53.01 (26.63–94.20)	40.92 (22.19–98.57)	36.39 (18.85–75.41)	
Model 1	Reference group	$p = 0.57$	$p = 0.378$	$p = 0.002$	$p < 0.001$
Model 2	Reference group	$p = 0.424$	$p = 0.378$	$p = 0.008$	$p < 0.001$
Male					
Hb (g/L, mean ± SD)	149.61 ± 0.75	150.18 ± 0.95	151.10 ± 1.70	145.75 ± 1.68	
Model 1	Reference group	$p = 0.101$	$p = 0.187$	$p = 0.128$	$p = 0.599$
Model 2	Reference group	$p = 0.12$	$p = 0.34$	$p = 0.547$	$p = 0.194$
Female					
Hb (g/L, IQR)	133.00 (124.00–143.00)	132.00 (120.4–139.35)	127.00 (119.50–138.00)	125.8 (119.00–131.00)	
Model 1	Reference group	$p = 0.08$	$p = 0.004$	$p < 0.001$	$p < 0.001$
Model 2	Reference group	$p = 0.008$	$p = 0.003$	$p < 0.001$	$p < 0.001$

Note: Hb of male is expressed as mean ± SD. Hb in female and SF in both male and female is expressed as median (IQR). Model 1 adjusted for age and BMI. Model 2 additionally adjusted for living place, meat intake, education, smoking and drinking, household income, and female donors additionally adjusted menstrual history.
Abbreviations: BMI, body mass index; Hb, haemoglobin; IQR, interquartile range; SF, serum ferritin.

TABLE 3 Relation between the rate of ID and plasmapheresis donation.

		Donation frequency (times/per year)		
Model	**New donors**	**1–8**	**9–16**	**>16**
Male	384	107	109	174
ID, *N* (%)	4 (1.0)	2 (1.9)	0	1 (0.6)
Female	342	108	106	163
ID, *N* (%)	84 (24.6)	24 (22.2)	29 (27.4)	54 (33.1)
Base model (OR [95% CI])	Reference group	0.88 (0.52–1.47)	1.08 (0.84–1.38)	1.15 (1.00–1.32)
Model 1 (OR [95% CI])	Reference group	0.87 (0.52–1.46)	1.10 (0.86–1.41)	1.21 (1.05–1.39)
Model 2 (OR [95% CI])	Reference group	0.94 (0.54–1.63)	1.18 (0.90–1.54)	1.21 (1.04–1.41)

Note: Categorical observations are expressed as *n* (%). Model 1 adjusted for age and BMI. Model 2 additionally adjusted for living place, meat intake, education, smoking and drinking, household income, and female donors additionally adjusted menstrual history.
Abbreviations: BMI, body mass index; CI, confidence interval; ID, iron deficiency; OR, odds ratio.

DISCUSSION

This study observed that the SF level in the higher frequency group was significantly lower than that in the new group. This suggests that the high frequency of plasmapheresis donation under the current Chinese policy has some effect on the SF level of the donors. Similar findings were reported in a Japanese study [7], showing that SF levels in regular donors were significantly lower than in new donors. Specifically, the significant decline in SF levels was seen primarily among female donors who gave more than 21 donations per year. An American study [5] demonstrated a significant decrease in SF levels among male regular plasmapheresis donors compared with the control group. Furthermore, the SF level negatively correlated with the frequency of plasmapheresis donation ($r = -0.4$, $p = 0.007$). In contrast to the above results, George et al. [19] showed that the SF level of female regular donors was higher than that of women who did not donate plasma. The authors attributed this increased SF level in women to their refusal to donate blood due to unqualifying haematocrit levels, leading to the replenishment and growth of SF.

The findings of this study indicated that the rate of ID among female donors in the high donation frequency group was significantly higher than that of new donors. However, ID was rare among male

TABLE 4 Uni- and multivariate analyses of preoperative predictors of ID of female regular donors in training cohort.

			Univariate logistic regression			Multivariate logistic regression		
Group	**No ID**	**ID**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**
Living place								
Hunan	49 (69.0)	22 (31.0)			-			
Yunnan	44 (88.0)	6 (12.0)	0.001	3.45	1.69–7.04			
Henan	57 (77.0)	17 (23.0)	0.187	1.64	0.79–3.43			
Sichuan	47 (67.1)	23 (32.9)	0.129	0.46	0.17–1.26			
Age (year)	45 (32–53)	36 (29–43)	<0.001	0.95	0.92–0.97	0.011	0.96	0.93–0.99
BMI (kg/m^2)	25.0 (22.2–28.1)	23.3 (21.3–25.6)	0.001	0.89	0.83–0.95	0.022	0.91	0.84–0.99
Hb (g/L)	132.0 (124.0–141.0)	121.7 (118.0–131.1)	<0.001	0.93	0.91–0.96	<0.001	0.93	0.90–0.96
Education								
Elementary school	70 (80.5)	17 (19.5)			-			
Junior high school	72 (66.7)	36 (33.3)	0.033	2.06	1.06–4.00			
High school	37 (57.8)	27 (42.2)	0.003	3.01	1.45–6.21			
Universities	4 (66.7)	2 (33.3)	0.426	2.06	0.35–12.19			
Meat intake								
None	3 (60.0)	2 (40.0)						
Occasionally	116 (68.2)	54 (31.8)	0.699	0.70	0.11–4.30			
Frequently	64 (71.1)	26 (28.9)	0.599	0.61	0.10–3.86			
Annual household income								
Low	65 (73.0)	24 (27.0)						
Moderate	92 (67.2)	45 (32.8)	0.349	1.33	0.74–2.39			
High	26 (66.7)	13 (33.3)	0.465	1.35	0.60–3.06			
Menstrual history								
Pre-menopausal	134 (63.2)	78 (36.8)			-			
Post-menopausal	49 (92.5)	4 (7.5)	<0.001	0.14	0.05–0.40	0.02	0.23	0.06–0.79
Donation frequency (times/year)								
1–8	60 (77.9)	17 (22.1)			-			
9–16	52 (67.5)	25 (32.5)	0.15	1.70	0.83–3.48	0.345	1.49	0.65–3.37
>16	71 (64.0)	40 (36.0)	0.042	1.99	1.02–3.86	0.04	2.22	1.04–4.74

Note: Continuous measurements are expressed as mean ± SD if normally distributed; otherwise, as median (IQR). Categorical observations are expressed as *n* (%). Table 1 shows that most women had no history of smoking (97.9%) and drinking (93.4%), so the history of smoking and drinking is excluded from factor analysis.
Abbreviations: BMI, body mass index; CI, confidence interval; Hb, haemoglobin; ID, iron deficiency; IQR, interquartile range; OR, odds ratio.

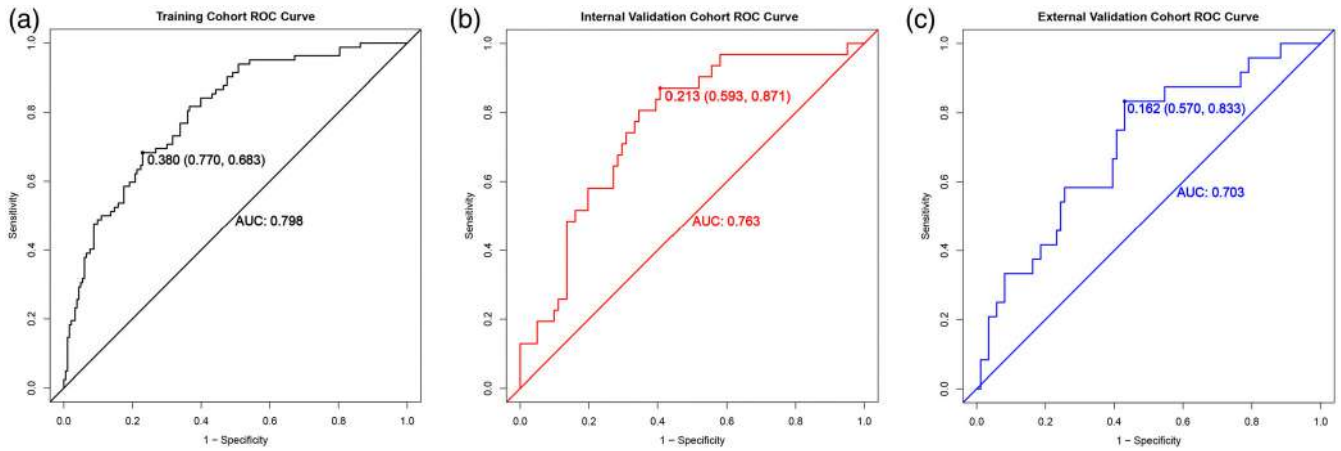

FIGURE 2 ROC curve for evaluating the model's discrimination performance. (a) ROC curve of training cohort. (b) ROC curve of internal validation cohort. (c) ROC curve of external validation cohort. ROC, receiver operating characteristic.

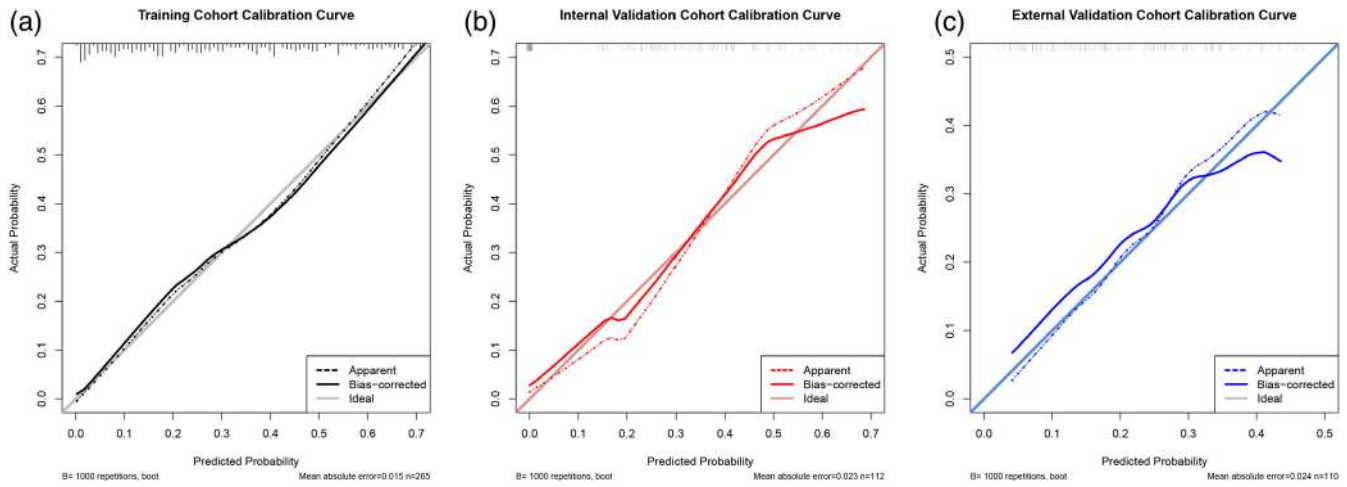

FIGURE 3 Calibration curves depict the calibration of the nomogram in terms of agreement between predicted risks and actual outcomes of ID in female regular donors. The *x*-axis represents predicted probability; the *y*-axis represents actual probability. The diagonal represents the reference line that the predicted value coincides with the actual value, the apparent line represents the actual situation of the prediction model, and the Bias—corrected line represents the actual situation of the corrected prediction model. (a) Calibration curve of the training cohort. (b) Calibration curve of the internal validation cohort. (c) Calibration curve of the external validation cohort.

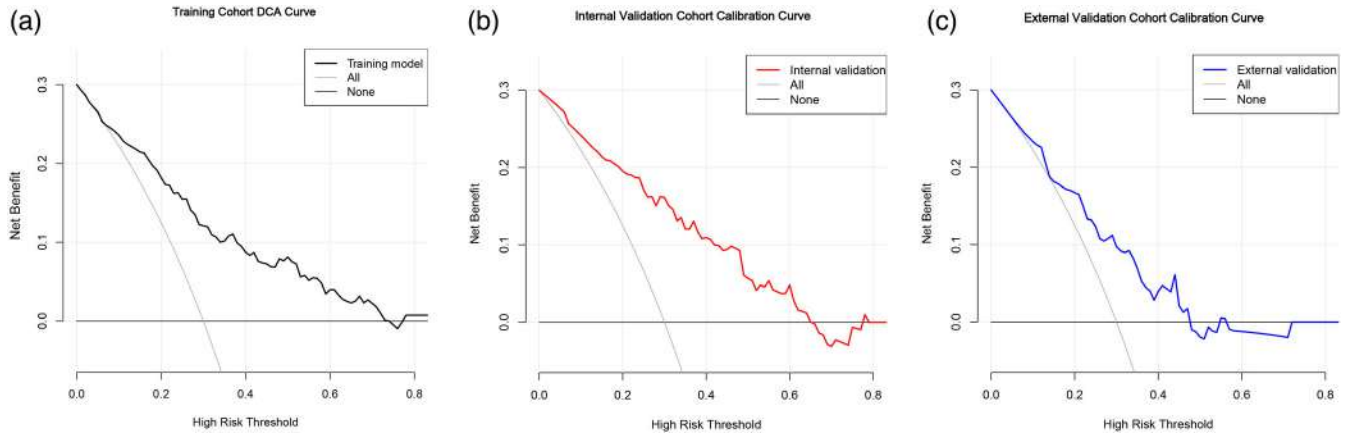

FIGURE 4 Decision curve analysis for the risk prediction of iron deficiency for female regular donors. (a) Decision curve analysis of training cohort. (b) Decision curve analysis of internal validation cohort. (c) Decision curve analysis of external validation cohort. The decision curve plots the standardized net benefit (*y*-axis) across a variety of risk thresholds (*x*-axis) for three scenarios: intervene on all (All), intervene on none (None), or intervene based on predicted risk from the nomogram (blue line). The *y*-axis measures the standardized net benefit, quantifying the total benefit (true-positive rate) minus the total harm (false-positive rate). The *x*-axis represents the threshold probability. The grey oblique line represents the assumption that all donors will be ID and intervene in all. The horizontal black line represents the assumption that no donor will be ID and intervene on none.

donors, possibly due to their higher iron storage and SF level. Although plasma donation caused a reduction in SF, it remained within the normal range. Nevertheless, women who are more susceptible to ID due to their lower SF levels face an increased risk of ID with the high frequency of plasmapheresis donation. In a 2017 trial involving 45,263 whole blood donors randomly assigned to different donation intervals, it was observed that the prevalence of ID among men was 24% in the shortest interval and 12% in the longest interval. Among women, the corresponding prevalence was 27% in the shortest interval and 22% in the longest interval [20]. This suggests that a shorter donation interval increases the risk of developing ID.

We found that younger age and pre-menopausal status were positively associated with ID risk, consistent with previous studies. For instance, a US study [21] demonstrated a positive association between age and ferritin concentration in women, and the association between age and ferritin concentration in women was mainly due to the impact of menstrual blood loss on ferritin. Other studies have indicated that, in post-menopausal women, when oestrogen drops to 10% of its standard value, SF could increase by 2–3 times [22]. Furthermore, a study focusing on SF among female whole blood donors found that SF was higher in the age group of 41–50 (54.31 ± 35.38 μg/L), whereas it was lower in the age group of 18–40

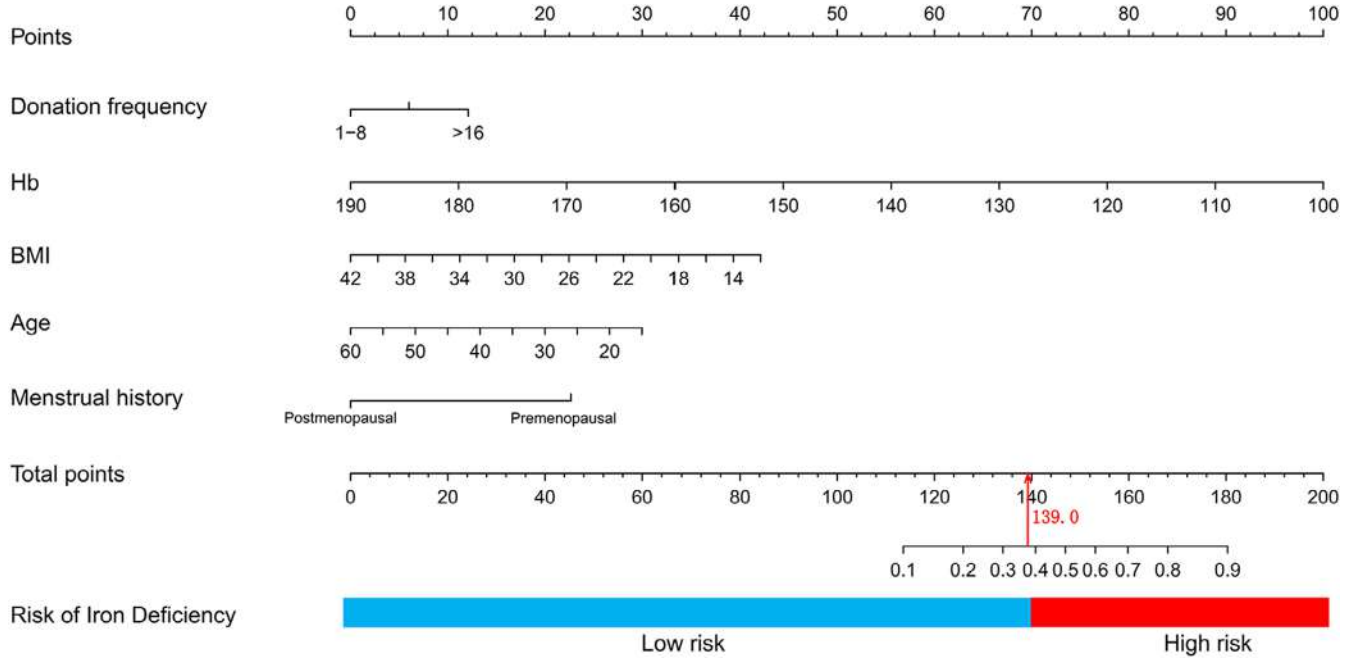

FIGURE 5 Nomogram predicting the probability of ID in female regular donors. The nomogram incorporates age, BMI, Hb, menstrual history and donation frequency to predict ID in regular female donors. Each donor's characteristic was assigned 'Points' based on its position on the respective axis, and the total points were calculated on the 'Total Points' line to determine an individual's probability of developing ID as indicated on the 'Risk of Iron Deficiency' line. The cut-off point (139.0) of the risk of the ID was determined using Youden's index. BMI, body mass index; Hb, haemoglobin; ID, iron deficiency.

(22.60–37.99 μg/L) [23]. In a study involving 1359 Danish women, it was observed that the prevalence of ID (SF < 15 μg/L) was 17.2% in women aged 30–40, 10.3% in women aged 50, and further decreased in women aged 60 (1.6%) [24].

The study revealed a negative association between BMI and the risk of ID. Many studies have reported the relationship between iron levels and BMI. A Chinese study involving 7672 adults found a positive correlation between BMI and ferritin concentration in females (trend test $p < 0.001$) [25]. The positive correlation between BMI and ferritin has yet to be understood [26]. One potential explanation is that a higher meat intake, positively correlated with BMI, can provide a richer source of dietary iron [27]. Furthermore, it has been found that obesity-related inflammatory processes could elevate ferritin levels [25].

Most body iron is contained in Hb (2500 mg) in RBCs [28]. Consequently, the Hb concentration can partly reflect the donor's iron storage status. However, studies have shown that changes in erythrocyte morphological indicators, such as mean erythrocyte volume and mean erythrocyte Hb concentration that are commonly used as part of routine assessments for anaemia, were only associated with changes in the later stages of iron consumption and were poorly correlated with reduced iron levels [29]. Simon et al. [30] tested Hb and ferritin levels in ID donors. They found that Hb did not accurately reflect the ID of donors. Although Hb was associated with the risk of ID, it is not a reliable screening indicator for identifying individuals with ID.

The five aforementioned characteristic variables were incorporated to develop a risk prediction model for ID in female regular donors (Table 4). The model demonstrated moderate discriminative ability in the training cohort (AUC = 0.798), the internal validation cohort (AUC = 0.763) and the external validation cohort (AUC = 0.727). Furthermore, the HL test results indicated that the model fit well in all three cohorts. In summary, the ID risk prediction model holds potential clinical utility for female regular plasmapheresis donors.

This study represents the first investigation in China focusing on the iron metabolism of plasmapheresis donors. It provides a reference for donor health and safety by conducting a preliminary study on the risk factors for ID in women who are regular plasmapheresis donors. Both internal and external validations were performed to evaluate the reliability of the ID risk prediction model. Nonetheless, the study has some limitations. First, donors with low Hb were systematically excluded from our study during the pre-donation examination. This was a limitation to our finding that repeat plasmapheresis donations were not associated with a decrease in Hb. However, the impact of this limitation on the results might be insignificant. According to our previous research in China [31], the proportion of temporary deferral due to low Hb deferral (LHD) is tiny (female donors' LHD rate: 0.15%; male donors' LHD rate: 0.01%), so the potential relationship between plasmapheresis donation intensity and Hb would not determine the result. Second, background information such as educational background, annual household income, meat intake level, smoking history

and drinking history were not adequately quantified, potentially affecting the accuracy of the findings.

In conclusion, under the current standard of plasmapheresis donation in China, a higher frequency of donation may lead to a reduction in SF level and increase the risk of ID among women. Age, BMI, donation frequency, Hb test value and menstrual history were highly correlated with the occurrence of ID in regular female donors. The risk prediction model for ID in regular female donors has moderate discriminative power and a good model fit, which is of some clinical utility. This model has enabled quantitative evaluation of the risk of ID among female regular donors and provided a tool for identifying high-risk groups, thus ensuring their health and safety.

ACKNOWLEDGEMENTS

Thanks to all those who worked on this study. The authors thank Toby Simon for his precious assistance with article revision and language editing. The research was funded by CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant No: 2021-I2M-1-060).

G.X. and Y.W. designed the study. G.X., P.Z. and W.L. carried out formal analysis. C.L., Y.C., H.Z., Y.Y., Y.Z., R.Z., A.L., L.L., L.D., Q.X. and J.Y. contributed to data curation. G.X. and Y.W. contributed to writing—original draft preparation. G.X. and Y.W. contributed to writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

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REFERENCES

1. WHO. Micronutrient deficiency: battling iron deficiency anaemia: the challenge. 2004 Available from: https://apps.who.int/nut/ida.htm. Last accessed 5 Jul 2023.
2. Cable RG, Glynn SA, Kiss JE, Mast AE, Steele WR, Murphy EL, et al. Iron deficiency in blood donors: analysis of enrollment data from the REDS-II donor iron status evaluation (RISE) study. Transfusion. 2011;51:511–22.
3. Chinigi Sab P, Kaur G, Kaur P, Tahlan A, Bedi RK, Mittal K, et al. Assessment of serum iron stores in regular plateletpheresis donors. Transfus Apher Sci. 2022;61:103291.
4. Updated strategies to limit or prevent iron deficiency in blood donors. AABB. Available from: https://www.aabb.org/docs/default-source/default-document-library/resources/association-bulletins/ab17-02.pdf?sfvrsn=55d7caaf_4. Last accessed 7 Aug 2023.
5. Li H, Condon F, Kessler D, Nandi V, Rebosa M, Westerman M, et al. Evidence of relative iron deficiency in platelet- and plasma-pheresis donors correlates with donation frequency. J Clin Apher. 2016;31:551–8.
6. Page EA, Coppock JE, Harrison JF. Study of iron stores in regular plateletpheresis donors. Transfus Med. 2010;20:22–9.
7. Furuta M, Shimizu T, Mizuno S, Kamiya T, Ozawa K, Nakase T, et al. Clinical evaluation of repeat apheresis donors in Japan. Vox Sang. 1999;77:17–23.
8. Technical Operation Procedures for Plasmapheresis Collection Stationin. National Health Commission of the PRC. 2019 Available from: https://max.book118.com/html/2022/0415/6025104112004134.shtm. Last accessed 7 Aug 2023.
9. Requirements for blood and blood components intended for transfusion or for further manufacturing use. Office of the Federal Register, National Archives and Records Administration. Available from: https://www.govinfo.gov/app/details/FR-2015-05-22/2015-12228. Last accessed 7 Aug 2023.
10. Information for plasma donors. National Health Commission of the PRC. Available from: http://www.nhc.gov.cn/yzygj/s7658/202109/ca7e7e1972ec4e939c613aa67f7434e1.shtml. Last accessed 7 Aug 2023.
11. Pfeiffer CM, Looker AC. Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. Am J Clin Nutr. 2017;106:1606s–1614s.
12. Serum ferritin concentrations for the assessment of iron status in individuals and populations: technical brief. WHO. Available from: https://www.who.int/publications/i/item/9789240008526. Last accessed 7 Aug 2023.
13. Cable RG, Glynn SA, Kiss JE, Mast AE, Steele WR, Murphy EL, et al. Iron deficiency in blood donors: the REDS-II donor iron status evaluation (RISE) study. Transfusion. 2012;52:702–11.
14. Jang ES, Jeong SH, Hwang SH, Kim HY, Ahn SY, Lee J, et al. Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. BMC Gastroenterol. 2012;12:145.
15. Tong TYN, Key TJ, Gaitskell K, Green TJ, Guo W, Sanders TA, et al. Hematological parameters and prevalence of anemia in white and British Indian vegetarians and nonvegetarians in the UK Biobank. Am J Clin Nutr. 2019;110:461–72.
16. Alsalman M, Albarak A, Busaleh F, Alshaikh S, Alluwaim M, Busaleh M, et al. Heavy menstrual bleeding awareness among Saudi female population and clinical implications. Health Sci Rep. 2021;4:e244.
17. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16:e173–80.
18. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA. 2015;313:409–10.
19. Schreiber GB, Brinser R, Rosa-Bray M, Yu ZF, Simon T. Frequent source plasma donors are not at risk of iron depletion: the ferritin levels in plasma donor (FLIPD) study. Transfusion. 2018;58:951–9.
20. Di Angelantonio E, Thompson SG, Kaptoge S, Moore C, Walker M, Armitage J, et al. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors. Lancet. 2017;390:2360–71.
21. Liu JM, Hankinson SE, Stampfer MJ, Rifai N, Willett WC, Ma J. Body iron stores and their determinants in healthy postmenopausal US women. Am J Clin Nutr. 2003;78:1160–7.
22. Jian J, Pelle E, Huang X. Iron and menopause: does increased iron affect the health of postmenopausal women? Antioxid Redox Signal. 2009;11:2939–43.
23. Reddy KV, Shastry S, Raturi M, Baliga BP. Impact of regular whole-blood donation on body iron stores. Transfus Med Hemother. 2020;47:75–9.
24. Milman N, Kirchhoff M. Iron stores in 1359, 30- to 60-year-old Danish women: evaluation by serum ferritin and hemoglobin. Ann Hematol. 1992;64:22–7.
25. Hu PJ, Ley SH, Bhupathiraju SN, Li Y, Wang DD. Associations of dietary, lifestyle, and sociodemographic factors with iron status in

Chinese adults: a cross-sectional study in the China Health and Nutrition Survey. Am J Clin Nutr. 2017;105:503–12.
26. Jeon YJ, Jung IA, Kim SH, Cho WK, Jeong SH, Cho KS, et al. Serum ferritin level is higher in male adolescents with obesity: results from the Korean National Health and nutrition examination survey 2010. Ann Pediatr Endocrinol Metab. 2013;18:141–7.
27. Recaredo G, Marin-Alejandre BA, Cantero I, Monreal JI, Herrero JI, Benito-Boillos A, et al. Association between different animal protein sources and liver status in obese subjects with non-alcoholic fatty liver disease: fatty liver in obesity (FLiO) study. Nutrients. 2019;11:2359.
28. Kiss JE, Birch RJ, Steele WR, Wright DJ, Cable RG. Quantification of body iron and iron absorption in the REDS-II donor iron status evaluation (RISE) study. Transfusion. 2017;57:1656–64.
29. Alexander HD, Sherlock JP, Bharucha C. Red cell indices as predictors of iron depletion in blood donors. Clin Lab Haematol. 2000;22:253–8.
30. Simon TL, Garry PJ, Hooper EM. Iron stores in blood donors. JAMA. 1981;245:2038–43.
31. Xiao G, Dong D, Wang Y, Li C, Huang GT, Yang H, et al. The risks of low hemoglobin deferral in a large retrospective cohort of plasmapheresis donors and the influence factors of return for a subsequent donation in China. Peer J. 2023;11:e14999.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Xiao G, Li C, Chen Y, Zhao P, Li W, Xiao H, et al. Risk prediction of iron deficiency for plasmapheresis donors in China: Development and validation of a prediction model. Vox Sang. 2024;119:144–54.

Received: 11 May 2023 | Revised: 7 December 2023 | Accepted: 8 December 2023

DOI: 10.1111/vox.13582

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Using competition for plasma donor recruitment and retention: An Australian university case study

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Using evidence from one Australian university's participation in the Vampire Cup (an 8-week national inter-university blood donation competition), this study aimed to (1) understand important motivators and successful promotional strategies driving engagement in the competition, and (2) determine the impact of competition on the recruitment and retention of young adult plasma donors.

Materials and Methods: We used a sequential explanatory mixed-methods design involving a self-administered survey (Study 1, $n = 64$) and four focus groups (Study 2, $n = 20$) with plasma donors aged 18–29 years who participated in the 2021 Vampire Cup. Also, we used a 12-month prospective comparative cohort analysis (Study 3) of those who did ($n = 224$ 'competition donors') and did not ($n = 448$ control group) present to donate for the Vampire Cup.

Results: Competition was a strong motivator, with 76% of survey participants donating to help their university win the Vampire Cup. The survey and focus groups suggested that successful engagement in the competition was due to peer-led recruitment, leveraging existing rivalries at both the inter- and intra-university level, and using prize draws to create an active online social community promoting blood donation. Competition donors donated plasma significantly more often during the competition but donated at similar rates after the competition, compared to the control group.

Conclusion: Rivalry-based competition strategies, combined with enthusiastic team leaders and an active social media community, can help to recruit, and retain, young adult plasma donors, and motivate an intermittent boost to donation frequency over a short period each year.

Keywords

competition, plasma donor, recruitment, retention

Highlights

- Competition is not only an effective method of donor recruitment but can also encourage new donors to return sooner.
- Competition resonates with younger donors and can motivate increased plasma donation frequency over short periods each year without reducing donation activity between competitions.
- Leveraging existing rivalries at multiple levels and creating an online community that promotes blood donation as a normative behaviour can improve competition engagement.

INTRODUCTION

Ensuring adequate numbers of blood, plasma and platelet donors is essential to maintaining the vital supply of life-saving blood products globally. In Australia, which has a voluntary non-remunerated donation (VNRD) policy, plasma can be donated as often as every 2 weeks, yet donors make only on average 4.1 plasma donations each year [1]. Further, <60% of new donors return to donate, with young adults having the lowest likelihood of returning [2]. Therefore, understanding the factors behind why people donate and how more people may be encouraged to donate and continue donating voluntarily—especially young adults—is important.

The influence of close and/or trusted others (e.g., friends, family, peers) in the decision to donate blood is well documented [3, 4], particularly for young adults and new donors [5, 6]. Sümnig et al. [7] found friends and/or relatives to be the strongest motivational factor for first-time donors. Other studies have shown that peer-driven recruitment of blood donors among college students is more effective than traditional methods, with higher rates of reported motivation and lower rates of discouraging factors towards donation [8]. Although social influence generally ranks lower when compared to intrinsic motivators such as altruism and moral duty [3], motivation to donate is said to shift from external to internal sources as the donor career develops [9]. Thus, although the desire to help others (intrinsic motivation) underpins blood donation throughout a donor's career, the support and encouragement from others (extrinsic motivation) may be particularly important for new and novice donors.

Social identity theory argues a person's sense of belonging to a social group (ingroup) and the extent that belonging is important to them (i.e., high level of identification with their ingroup) can affect their behaviour [10]. This is particularly true in inter-group contexts, where the presence of an outgroup (i.e., those not part of the ingroup) serves to activate the effects of ingroup identification [11]. Social identity theory further postulates that in a competition setting, people are motivated to enhance the status of their ingroup relative to an outgroup on a salient dimension for social comparison (e.g., giving the highest number of blood donations) by undertaking an activity (e.g., donating blood) [12]. Competition (also referred to as a 'challenge campaign' or 'rivalry campaign') has been shown to increase health behaviours (e.g., step challenges) [13] and prosocial behaviour among those with available resources to donate (e.g., money) [14]. Rivalry campaigns are also shown to be more effective at increasing voluntary organ donor registrations than ingroup targeting strategies [15, 16]. We would expect competition to similarly increase plasma donation activity among those able to donate, possibly more so given that people can donate more than once. One paper observed the use of competition in the workplace with anecdotal evidence from donors supporting the program as an important reason to donate blood [17]. However, the impact and success of using competition as a means for blood donor recruitment and retention, as well as the effect on blood donation behaviour post competition, remains unexplored.

Using evidence from one Australian university's team participation in an 8-week national inter-university blood donation competition, this study aimed to (1) understand important motivators and successful promotional strategies driving engagement in the competition, and (2) investigate the impact of competition on the recruitment and retention of young adult plasma donors.

METHODS

Context

One novel initiative that leverages social influence and competition to encourage blood donation is the Vampire Cup (VC)—an annual competition run by the Australian Medical Student Association (AMSA) to see which Australian medical school can donate the most over an 8-week period (https://www.amsavampirecup.com.au/). Although Australian Red Cross Lifeblood facilitates the competition by keeping an electronic record of team donation tallies, the competition and promotional efforts are driven by student representatives from each university using word of mouth, campus activities, social media and prize draws. The winning university team receives an engraved trophy and national recognition through AMSA communication channels.

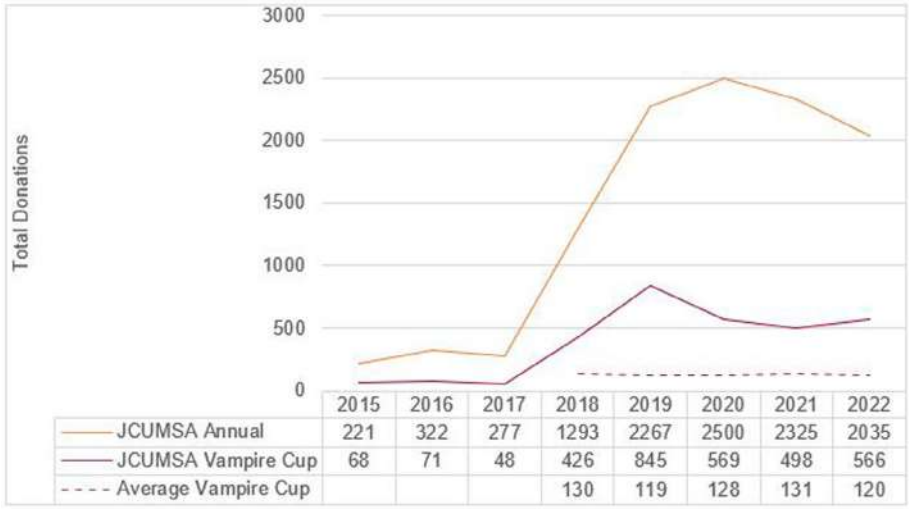
The James Cook University Medical Student Association (JCUMSA) team has competed in the VC and experienced profound growth in donations from 2018 to 2020. The team increased their annual donation tally from below 300 in 2017 to 2500 annual donations in 2020 and led the inter-university competition (Figure 1). During this time, key social media and competition strategies were implemented. In 2018, the JCUMSA team introduced a Facebook group and 'selfie' competition to build an online community that valued blood and plasma donation as a normative behaviour. Intra-university competition between study disciplines in 2018 (e.g., medicine vs veterinary science) and residential colleges in 2019 (on-campus accommodation facilities), having strong existing rivalries, were also introduced to further encourage donations within the larger team.

Research design

This research used a sequential, explanatory mixed-methods design involving three studies:

1. A self-administered survey of donors who participated in the 2021 VC for JCUMSA.
2. Four focus groups with JCUMSA VC participants.
3. A prospective comparative cohort analysis of plasma donors.

Together, these studies enabled triangulated analysis of how the VC and associated promotional strategies influenced donation motivations, intentions and behaviour of young adult plasma donors (aged 18–29) who live and/or donate in Queensland, Australia. Ethical approval for the study was obtained in 2021 from both the



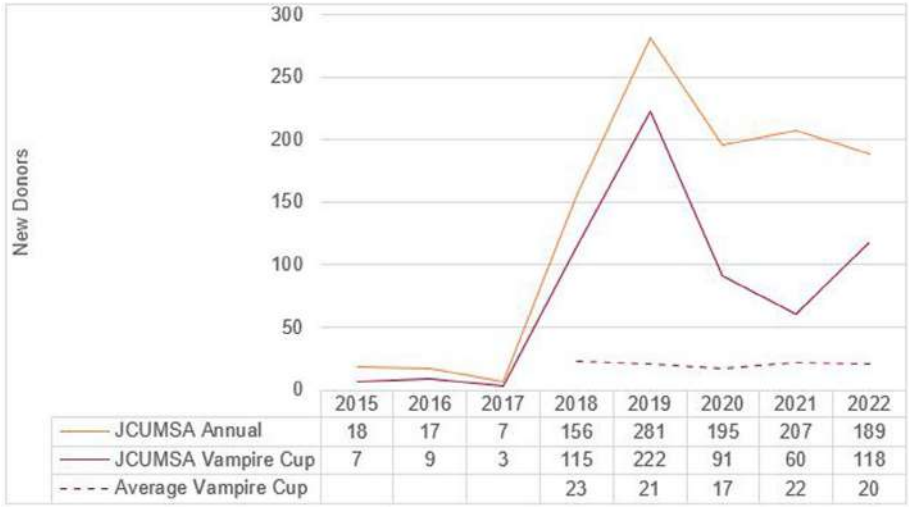


FIGURE 1 The James Cook University Medical Student Association (JCUMSA) Vampire Cup Statistics 2015–2022. JCUMSA Annual, total donations and number of new donors for the JCUMSA team each year; JCUMSA Vampire Cup, total donations and number of new donors for the JCUMSA team during the Vampire Cup each year; Average Vampire Cup, average total donations and number of new donors across all teams (21–23 teams) competing in the Vampire Cup (excluding JCUMSA) each year.

James Cook University (H8376) and Lifeblood Human Research Ethics Committees (Chell 20092021).

Study 1: Survey

Participants and procedure

Donors aged 18–29 years who presented to donate at the Townsville Donor Centre* for the JCUMSA team during the 2021 VC (3 April 2021 to 31 May 2021) were invited by staff to complete a paper-based survey and consent form following their donation. The survey asked donors about their university status (current student, past student, non-student) and study area, past competition participation, how they heard about the competition, what encouraged them to donate during the 2021 VC, future donation intentions and positive word-of-mouth intentions. Donor ID was used to check for duplicate responses and link to donor records to obtain age, gender and donation history. Overall, 224 donors presented to donate (referred to as *competition donors*). Of those, 64 useable surveys were obtained, achieving a response rate of 28.6%.

Analysis

Survey responses were entered into SPSS version 25 and linked to donor records. Descriptive statistics are reported for all items, and *t*-tests were used for sub-group comparisons by course

*Townsville Donor Centre is a regional plasma-only donor centre in Queensland, Australia. The James Cook University medical school is based in Townsville and is located close to the Townsville Donor Centre. Therefore, this donor centre is the primary donor centre for donors in the JCUMSA team. All other Queensland-based donor centres collect plasma and whole blood donations.

(medicine vs. non-medicine), gender, donor status (new vs. returning donor) and past VC participation (once vs. more than once).

Study 2: Focus groups

Participants and procedure

Four in-person, semi-structured focus group ($n = 20$ competition donors) discussions were held to further explore motivations to participate in the VC and effectiveness of promotional strategies used. A stratified purposeful sampling approach, with online and in-person convenience recruitment methods, was used to identify an even representation of new and returning donors in medicine and non-medicine study areas. Focus groups ran for 40–50 min and were audio-recorded and transcribed.

Analysis

Focus group transcriptions were read repeatedly to develop a high level of familiarity with the data (immersion), and then analysed using an inductive thematic analysis approach [18]. Thematic analysis was conducted by T.W. and checked by J.B. for investigator triangulation; differences were resolved through discussion between the authors. The sample size in the study appeared sufficient to allow a point-of-theorysaturation to be reached [18]. Quotes were included in the text if they clearly illustrated concepts held by multiple participants and given a label to indicate participant gender (M = male, F = female), study area and donor status (new donor or returning donor).

Study 3: Prospective comparative cohort analysis

Participants and procedure

A prospective cohort analysis of plasma donation activity compared two cohorts of donors who made at least one plasma donation during the 2021 VC at a Queensland-based donor centre: (1) $n = 224$ *competition donors* (i.e., donating as part of the JCUMSA team), and (2) a comparative control group ($n = 448$). A stratified random sampling approach was used to identify a matched control group whose members were not members of a Lifeblood Team and were not Lifeblood staff. A 1:2 competition versus control group ratio was used, stratified on the basis of donor status (new donor, first-time plasma donor or repeat plasma donor), to account for greater variability in the donor centres attended by the control group.

Analysis

t-Tests were performed to compare sample characteristics between competition and control group donors, and between competition donors who did and did not complete the survey. Analysis of variance and analysis of covariance (controlling for donation recency and donation history) were performed to compare plasma donation activity (collections and return rates) between competition and control group donors at four time periods: (1) during the 2021 VC; (2) 3 months following the competition; (3) 10 months following the competition and (4) during the 2022 VC (see Table 2 for date range). Results were also split by donor status (new donors, first-time plasma donors and repeat plasma donors separately).

RESULTS

Sample characteristics

Overall, $n = 224$ *competition donors* were identified, together contributing 378 donations to JCUMSA's 2021 VC competition tally. At the same time, a control group of $n = 448$ young adult *plasma donors* were identified. Among first-time plasma donors, the control group had donated significantly more recently (last attendance = 101.5 days; $p = 0.021$) and more often (total donation count = 21.5; $p < 0.001$) before the competition compared to the competition donors (last attendance = 249.1 days, total donation count = 9.7). Table 1 summarizes the sample characteristics.

Further, of the 64 competition donors who completed the survey, 61 were current or past students, with 35 (57.4%) from medicine, 16 (26.2%) from veterinary science or nursing and 10 (16.4%) from other non-health disciplines. In terms of VC participation, 2021 was the first competition for 24 (37.5%) donors, while 62.5% had participated in 2–5 VCs. Survey participants also donated more times during the 2021 VC (mean = 2.0, SD = 1.0) than non-participants (mean = 1.6, SD = 0.9; $p = 0.002$). There were no other significant differences between survey participants and non-participants.

Competition motivation and promotional strategies

Motivation to participate in the VC competition

Although helping to win the inter-university and intra-university competitions encouraged donors most (Figure 2), only 30% 'agreed' or 'strongly agreed' that the competitive aspects of the VC was the main reason for donating. When survey participants were asked to describe in their own words why they chose to donate, 50% mentioned altruism (to help others), 26% were already a regular donor and viewed participating in the VC as an 'add on', while 24% described the competition as a needed push to start donating or donate more regularly. Focus group discussions mirrored the underlying importance of altruism in the decision to donate (both during and after the competition).

There were also some significant sub-group differences in the reasons to donate during the 2021 VC. Females more strongly agreed with 'To help my course win the intra-JCU competition' (mean = 3.9)

TABLE 1 Sample characteristics.

	Vampire Cup survey participants	Competition donors	Control group
N	64	224[a]	448
Age on 31 May 2021 (years)			
Range	18–28	18–29	18–29
Mean (SD)	21.1 (2.5)	21.5 (2.7)	24 (3.4)
Median (IQR)	20 (19–22)	21 (19–23)	24 (21–27)
Gender			
Male	25 (39.1%)	88 (39.3%)	212 (47.3%)
Female	39 (60.9%)	136 (60.7%)	236 (52.7%)
Donor status[b]			
New donor	11 (17.2%)	57 (25.4%)	113 (25.2%)
First-time plasma donor	10 (15.6%)	36 (16.1%)	73 (16.3%)
Repeat plasma donor	43 (67.2%)	131 (58.5%)	262 (58.5%)
Plasma donation history[b]			
0	21 (32.8%)	93 (41.5%)	186 (41.5%)
1–5	17 (26.6%)	51 (22.8%)	91 (20.3%)
6–10	12 (18.7%)	22 (9.8%)	68 (15.2%)
11+	14 (21.9%)	58 (25.9%)	103 (23.0%)
Last attendance[b]			
No prior attendance	11 (17.2%)	55 (24.6%)	112 (25.0%)
1–178 days (6 months)	38 (59.4%)	118 (52.7%)	286 (63.8%)
179–365 days (6–12 months)	11 (17.2%)	28 (12.5%)	26 (5.8%
>365 days (>12 months)	4 (6.3%)	23 (10.3%)	24 (5.4%)
Donor career (years)[b]			
Range	0–10	0–12	0–20
Mean (SD)	1.9 (2.3)	2.1 (2.7)	2.8 (3.5)
Median (IQR)	1.5 (0–2.8)	1 (0–3)	1 (0–5)

Abbreviations: IQR, inter-quartile range; SD, standard deviation.
[a]Including survey participants.
[b]Prior to 2021 Vampire Cup. New donor is someone who made his or her first donation during the 2021 Vampire Cup. First-time plasma donor is someone who made his or her first plasma donation during the 2021 Vampire Cup but had donated whole blood and/or platelets previously. Repeat plasma donor is someone who had donated plasma (and possibly whole blood and platelets) before the 2021 Vampire Cup.

than males (mean = 3.7; $t(df) = 2.8(62)$; $p = 0.006$). A 'personal request from a Vampire Cup organiser' was more motivating for those who had participated in a VC more than once (mean = 3.0) compared to those who had participated only once (mean = 2.3; $t(df) = -2.1(62)$; $p = 0.043$).

Importance of existing rivalries

Although most focus group participants reported that they were somewhat competitive by nature, competition was, as expected, a prominent theme underlying participation in the VC. However, feelings of competitiveness and rivalry were more salient at the intra-university level (e.g., between disciplines or colleges within a university) than at the inter-university-level, particularly by those who identified with groups that had a pre-existing rivalry. For example, both Medicine and Veterinary Science disciplines and different campus college halls have a strong history of healthy competition on campus. Linking these existing rivalries to the VC proved to be a successful motivator, and for some was the final push needed to start donating:

> I'd always wanted to donate. I just hadn't got around to it. But then, "Oh, donate for your college, donate for your faculty". College really gave a big push. They're like "You have to beat everyone else." So, I think just that extra push.
>
> [F, medicine student, new donor]

Importance of peer-to-peer communication

Encouragement by friends and being involved in the JCUMSA VC Facebook group were reported as reasons for participating in the competition by over 50% of survey participants. The importance of

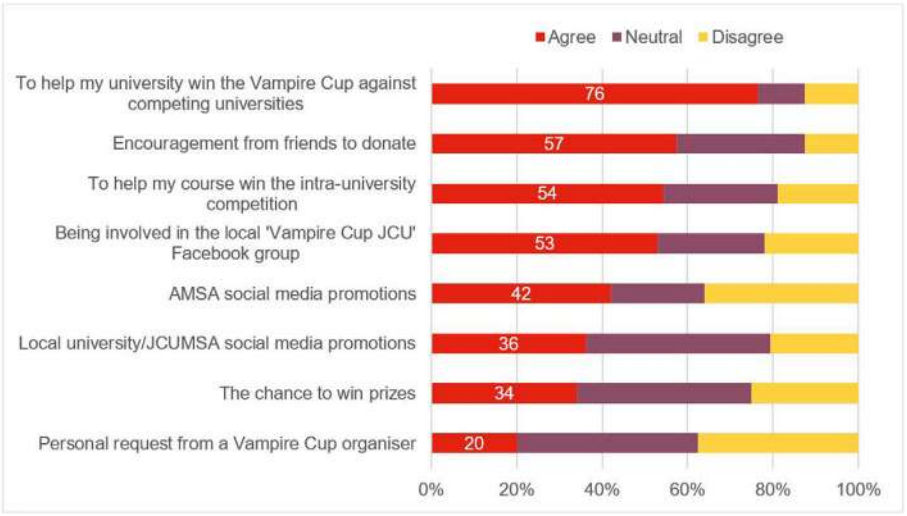


FIGURE 2 Reasons to donate during the 2021 Vampire Cup (survey results). AMSA, Australian Medical Student Association.

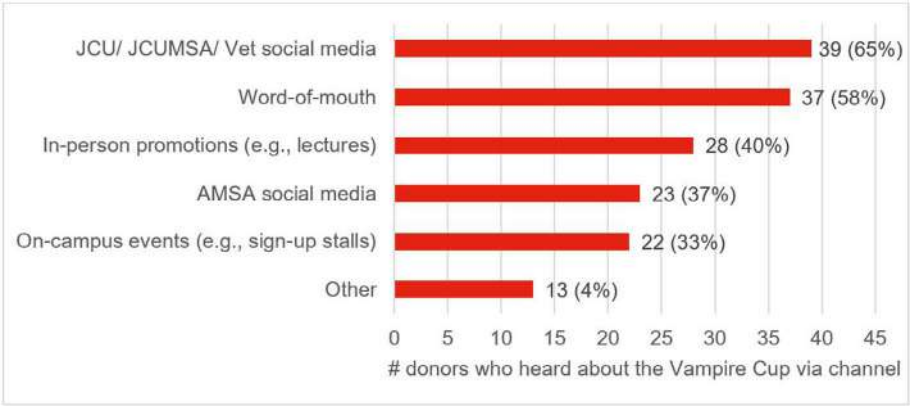


FIGURE 3 Responses to 'How did you hear about the Vampire Cup?'. AMSA, Australian Medical Student Association.

peer-to-peer communication is further illustrated in Figure 3, with promotions via social media and word of mouth being the two most common ways donors heard about the VC. Social media posts by VC organizers primarily highlighted competition details (e.g., dates, process for joining team), prize draws and competition updates (e.g., donation tally compared to other university teams), as well as encouraging user-generated content via a 'donation selfie' competition.

Positive blood donation culture and community

The JCUMSA VC Facebook group was discussed as an effective promotional strategy to create a positive donation culture, sense of responsibility to contribute to the competition and positive peer pressure to donate:

> I think it was really cool [being part of the Facebook group]. And seeing your friends also posting up on there, strangers as well, like everyone sort of seemed to interact with each other's posts and things like that, even if you didn't know them.
>
> [M, non-medicine student, returning donor]

A photo competition was run to encourage activity within the Facebook group, whereby donors posted a photo of themselves donating and used a hashtag representing their course (e.g., #medicine) or college. This not only contributed to keeping track of intra-university competitions but also allowed donors to self-identify with their ingroup and drive online community engagement. While 34% of survey participants agreed that the chance to win prizes was a reason to donate, prizes were offered only for social actions (e.g., posting a "selfie" to the Facebook Group, or tagging friends in Facebook posts) rather than an actual donation (Figure 4). Some existing donors also viewed such prizes as a welcome additional benefit for something they were already doing:

> Definitely there's incentive with the prizes. Because I was already a donor, I was like, 'Yeah, why not sign up

FIGURE 4 The James Cook University Medical Student Association Facebook Group post examples. All participants pictured have provided consent for their image to be used in this publication.

and do it through the Vampire Cup to get prizes?' and I was donating anyway, so why not?

[F, medicine student, returning donor]

The positive donation culture created on the JCUMSA VC Facebook group extends beyond donating, by eliciting word of mouth as a social norm. Most survey participants (>95%) would also engage in opportunistic positive word of mouth about plasma donation. Donors seem more motivated to recruit others when blood donation is linked to a salient social identity (ingroup), thereby changing blood donation from an individual activity to a group effort. Focus group participants suggested that giving positive word of mouth and encouraging others to donate for the VC come with experience and are more likely to actively recruit others when they themselves have participated in the VC:

I think I try to get more people into it now. I have a feeling that's because of the Vampire Cup. Because I've been donating since 2016, but I never really posted much about it or anything until Vampire Cup. Now, even when it's not on, I'm always trying to get other people doing it more.

[F, medicine student, returning donor]

Impact of competition on blood donor recruitment and retention

To understand the impact of competition on blood donor recruitment and retention, donation activity was compared between the *competition donors* and *a control group* during the 2021 VC, 3 and 10 months following the competition and during the 2022 VC. Table 2 summarizes all donation activity and by donor status (new donors, first-time plasma donors and repeat plasma donors).

Donation activity during the 2021 VC

Overall, competition donors donated significantly more often during the 2021 VC compared to the control group, but only among new donors and repeat plasma donors. Further, 29.8% of new competition donors, compared to only 10.6% of new control group donors, returned for a second donation. This suggests that the competition can bring back new donors sooner. However, there was no difference in plasma donation activity among first-time plasma donors during the 2021 VC. There was also some evidence of reactivating lapsed donors, with 10.3% of competition donors having last donated over 12 months before the 2021 competition. Focus group participants suggested that the competition could serve as a reminder to come back:

They had one of the booths at the college I'm at, and the person who was talking, he was someone I knew from the previous year. So, I went over to have a chat, and they told me about the Vampire Cup. And I thought, well, I'd been meaning to get back to doing plasma donation, so I thought, yeah, I'll do that.

[M, medicine student, previous donor]

Donation activity 3 and 10 months following the 2021 VC

Although 94.7% of survey participants 'agreed' or 'strongly agreed' that they intended to donate again within 3 months following the 2021 VC, only 56.3% returned to donate within 3 months and 71.9% returned within 10 months. Return donation behaviour did not significantly differ between competition donors who did and did not complete the survey, or by motivation to participate in the VC

TABLE 2 Donation activity during and after the 2021 VC.

		2021 VC	3-month follow-up		10-month follow-up		2022 VC	
		3 Apr. 2021 to 31 May 2021	1 Jun. 2021 to 31 Aug. 2021		1 Jun. 2021 to 1 Apr. 2022		2 Apr. 2022 to 31 May 2022	
	N	Collections Mean (SD)	Collections Mean (SD)	Return rate	Collections Mean (SD)	Return rate	Collections Mean (SD)	Return rate
Total sample								
Competition	224	1.7 (0.9)	1.0 (1.4)	47.8%	2.9 (3.8)	64.7%	0.7 (1.1)	36.6%
Control	448	1.5 (0.8)	1.1 (1.5)	46.7%	3.1 (4.1)	62.3%	0.5 (1.0)	23.2%
ANCOVA: $F[1,668]$, (p)		12.85 (<0.001)***	0.04 (0.84) ^{ns}	0.52 (0.47) ^{ns}	0.02 (0.89)^{ns}	0.85 (0.36)^{ns}	17.54 (<0.001)***	11.28 (<0.001)***
New donors								
Competition	57	1.4 (0.7)	0.6 (1.0)	35.1%	2.0 (3.2)	54.4%	0.6 (1.1)	31.6%
Control	113	1.1 (0.4)	0.6 (1.1)	31.0%	1.4 (2.5)	43.4%	0.2 (0.5)	13.3%
ANOVA: $F[1,168]$, (p)		9.17 (0.003)**	0.01 (0.94)^{ns}	0.29 (0.59)^{ns}	1.68 (0.20)^{ns}	1.85 (0.18)^{ns}	13.22 (<0.001)***	8.42 (0.004)**
First-time plasma donors								
Competition	36	1.8 (1.0)	0.9 (1.2)	50.0%	2.4 (3.2)	61.1%	0.5 (0.9)	30.6%
Control	73	1.8 (0.8)	1.6 (1.8)	61.6%	4.7 (4.5)	78.1%	0.8 (1.2)	37.0%
ANCOVA: $F[1,105]$, (p)		1.87 (0.17)^{ns}	0.22 (0.64)^{ns}	0.17 (0.68)^{ns}	0.99 (0.32)^{ns}	0.66 (0.42)^{ns}	0.02 (0.89)^{ns}	0 (0.98)^{ns}
Repeat plasma donors								
Competition	131	1.8 (1.0)	1.2 (1.5)	52.7%	3.4 (4.1)	70.2%	0.8 (1.1)	40.5%
Control	262	1.6 (0.8)	1.1 (1.6)	49.2%	3.4 (4.3)	66.0%	0.5 (1.0)	23.7%
ANCOVA: $F[1,389]$, (p)		5.91 (0.02)*	0 (0.95)^{ns}	0.29 (0.59)^{ns}	0.17 (0.68)^{ns}	0.49 (0.49)^{ns}	4.96 (0.03)*	11.83 (<0.001)***

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; SD, standard deviation; VC, Vampire Cup.
Note: Return rate, % who returned to donate; *p <0.05; **p <0.01; ***p <0.001; ^{ns}non-significant.

(i.e., competition and social influence motivations did not significantly vary between those who did and did not return). Plasma collections and return rate 3 and 10 months following the 2021 VC were statistically similar between competition donors and the control group.

Motivational shift following the 2021 VC

Focus group participants stated they felt more 'accountable' to donate during the VC and less motivated to donate as regularly afterwards:

> During the Vampire Cup, I definitely feel more accountable, and try to line up my donations so I can get as many as I can. Because when it's not on, I definitely kind of am not that regular of a donor, as much as I'd like to be.
>
> [F, medicine graduate, returning donor]

Several explanations were put forward for this, with 'donation fatigue' (from frequently donating during the competition) as the most common reason. With a lessened sense of accountability, external life pressures and commitments (that likely occur all year round) were also perceived as more of a barrier following the competition.

> Big push during Vampire Cup … I think most people really try and donate as much as possible for that specific cause. I think if you tried to push it too long, people would kind of get tired.
>
> [F, non-medicine student, new donor]

Participants also mentioned that the donation experience after the competition was less enjoyable without friends and peers in the centre (and more donors from very different demographics), making it less inviting to return:

> It just goes dead in the centres after the Vampire Cup. I can barely get an appointment during it, and then it's just so quiet. And if I go by myself, it's all like old people. Which is great, but you feel like the only young person, so you feel a bit like "Oh, there's no-one else young here".
>
> [F, medicine student, returning donor]

Donation activity during the 2022 VC

Although 88% of survey participants 'agreed' or 'strongly agreed' that they intended to donate again in the 2022 VC, only 47% donated. Competition donors who completed the survey were more likely to return ($n = 76$, 47.4% return rate, $p < 0.05$), compared to those who did not complete the survey ($n = 212$, 33.0% return rate). When comparing collections and return rate during the 2022 VC, competition donors were significantly more likely to return and donate more often than the control group, but only for new donors and repeat plasma donors (Table 2).

DISCUSSION

Using evidence from one team's participation in an inter-university blood donation competition as a case study, this study has helped to better understand why donors engage in a blood donation competition and the impact of competition on the recruitment and retention of plasma donors. The context is particularly important for understanding a young adult population who are often a difficult demographic group to recruit and retain [2]. In doing so, the combined effects of social influence (e.g., peer-to-peer communication, online social community) and social identity in an inter-group competition context were considered [8, 12]. As the first study to empirically examine a blood donation competition, this study strengthens the evidence base suggesting that competition can be used to increase one-off (e.g., organ donor registry, stem-cell registry) and repeatable (e.g., physical activity, blood donation) health and pro-social behaviours [13–16].

Overall, the competition seemed to resonate with younger donors, and positively impact retention and donation frequency of new and repeat plasma donors. Competition donors donated significantly more often during the 2021 and 2022 VCs. New competition donors were also more likely to donate more than once during the competition dates; thus competition can encourage new donors to return sooner. This is important, as people who donate multiple times in the first 12 months of their donor career are more likely to continue to donate regularly compared to those who donate once [19]. However, both groups donated at a statistically similar rate between the competitions. This suggests that competition and related activities can motivate increased plasma donation frequency over short periods each year without negatively impacting donation frequency outside of a competition context. Possible explanations as to why competition donors did not sustain increased donation frequency outside of competition dates include not feeling as accountable to donate, donation fatigue and a less enjoyable (less social) donation experience.

This study suggests that the JCUMSA team's success is built around three key strategies: peer-led activities, leveraging existing intergroup rivalries at multiple levels and creating an online community in which donating and promoting blood donation is a normative behaviour. First, the VC organizers recruiting for the JCUMSA team are longer term student donors (in-group members) who use peer-to-peer communication strategies targeting a younger demographic group (e.g., attending university events and lectures to sign people up). Team leaders also produced engaging videos about the competition and donation process for promotion on social media. Such peer-driven recruitment is important for motivating blood donation among young adults and new donors [3, 8].

Second, social-identity-based competition is used to drive recruitment and engagement at two levels (inter-university and intra-university based on study area or campus accommodation). Salient social identities are more likely to influence behaviour [10, 20];

therefore, identifying salient and meaningful ingroups and outgroups ensured all students felt a spirit of competition. Although this case study was within a university context, blood donation challenges in other sectors can also leverage existing rivalries nationally or locally. National challenges, such as across the healthcare (e.g., hospital vs hospital) or military (e.g., Army vs. Navy vs. Airforce) sectors, are important to optimize resources. However, targeting existing rivalries at a local level (e.g., inter-departmental challenges within a hospital or Army base) with more salient social identities may encourage greater participation. National challenges may be more effective where there is a strong pre-existing rivalry (i.e., salient ingroup and outgroup) at a national level, such as fans of sport teams.

Third, an online community provides team members with social support and peer encouragement to donate and allows further enhancement of the competition aspects and the chance of receiving prizes for posting about their donations. France and colleagues [21] found that belonging to an online community of blood donors over a 30-day period, with content uploaded twice daily by the research team, could improve blood donation intentions but only when paired with other motivational interventions. In addition to motivating blood donations [22], prize draws based on a social action linked to donating (e.g., posting a photo in a donor centre) can provide a motivational alternative in VNRD contexts where prize draws are not allowed or are discouraged. Encouraging donors to share photos of donation activity can benefit the individual (i.e., prize draw) and team by establishing blood or plasma donation as a normative behaviour [23]. When blood donation is considered more of a social (vs individual) activity, donors were more motivated to recruit others to contribute to the group effort, thereby amplifying their impact and group status.

However, it is important to note that the case study methodology adopted for this research examined only one team (JCUMSA) donating at one donor centre (Townsville) within one competition (VC), limiting the generalizability of the findings. Further, this study focused on plasma donations and compared donation frequency and return rates during the 8-week competition period and after the competition. However, only one whole-blood donation could have been made over the same timeframe. Therefore, competition is unlikely to affect whole-blood donation frequency but could improve recruitment and retention of whole-blood donors or the likelihood of responding to invitations to donate at local mobile blood drives. The James Cook University campus is also adjacent to the Townsville Donor Centre, making it more convenient for JCUMSA team members to donate (compared to other university teams). In addition, the survey data is limited by the small sample responding to the survey ($n = 64$) and the self-report nature of responses. The low survey response rate can be attributed to relying on busy donor centre staff to identify and approach eligible donors [24], and so not all competition donors were offered the survey. The 2021 VC was also less successful than of previous years, likely due to COVID restrictions impacting campus activities with fewer students on campus, reducing the competition group sample size.

In conclusion, this study provided preliminary evidence to support the use of competition to motivate plasma donors, particularly for new and younger donors who are often more difficult to recruit and retain. Although altruism still underpins blood donation, rivalry-based competition strategies, in conjunction with peer-led promotions and an active social media community, can be effective methods for plasma donor recruitment, retention and intermittent boosts to donation frequency.

ACKNOWLEDGEMENTS

Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community.

J.B. and T.W. collected and analysed the data for Study 1 and Study 2. T.S.G. and K.C. supervised the research. K.C. facilitated data collection within Lifeblood, and acquired and analysed the data for Study 3. All authors contributed to the design of the study, interpretation of datasets and have read and approved the final manuscript. The authors would like to thank the Townsville Donor Centre staff and Glen Shuttleworth for their assistance with data collection and data extraction.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Thorpe R, Masser BM, Nguyen L, Davison TE. Understanding donation frequency: insights from current plasma donors. Vox Sang. 2020;115:174–81.
2. Priyono A, Masser BM, Dyda A, Davison TE, Irving DO, Karki S. Long-term return and donation pattern of those who begin donating at different ages: a retrospective cohort analysis of blood donors in Australia. Transfusion. 2020;61:799–810.
3. Misje AH, Bosnes V, Gåsdal O, Heier HE. Motivation, recruitment and retention of voluntary nonremunerated blood donors: a survey-based questionnaire study. Vox Sang. 2005;89:236–44.
4. Lemmens KPH, Abraham C, Ruiter RAC, Veldhuizen IJT, Bos AER, Schaalma HP. Identifying blood donors willing to help with recruitment. Vox Sang. 2008;95:211–7.
5. Glynn SA, Kleinman SH, Schreiber GB, Zuck T, McCombs S, Bethel J, et al. Motivations to donate blood: demographic comparisons. Transfusion. 2002;42:216–25.
6. Martin S, Greiling D, Leibetseder N. Effects of word-of-mouth on the behavior of Austrian blood donors: a case study of the Red Cross Blood Donation service. Health Promot Int. 2019;34:429–39.
7. Sümnig A, Feig M, Greinacher A, Thiele T. The role of social media for blood donor motivation and recruitment. Transfusion. 2018;58:2257–9.
8. Al-Riyami AZ, Draz M, Al-Haddadi F, Al-Kabi A, AlManthari A, Panchatcharam SM, et al. Influence of peer-derived donor recruitment on the youth perception on blood donation among college students. ISBT Sci Ser. 2021;16:60–7.
9. France CR, Kowalsky JM, France JL, Himawan LK, Kessler DA, Shaz BH. The blood donor identity survey: a multidimensional measure of blood donor motivations. Transfusion. 2014;54:2098–105.

10. Hogg MA. Social identity theory. Cham: Springer International Publishing; 2016.
11. Lea M, Spears R, Groot D. Knowing me, knowing you: anonymity effects on social identity processes within groups. Pers Soc Psychol. 2001;27:526–37.
12. Shipley A. Social comparison and prosocial behavior: an applied study of social identity theory in community food drives. Psychol Rep. 2008;102:425–34.
13. Wentz JR, Wilhelm SS. Physical activity and social comparison: the importance of group composition in an employee Fitbit intervention. Health Promot Pract. 2023. https://doi.org/10.1177/15248399231160152
14. Zhu N, Hawk ST, Chang L. Unpredictable and competitive cues affect prosocial behaviours and judgements. Pers Indiv Differ. 2019;138:203–11.
15. Hitt R, Gidley R, Smith SW, Liang Y. Traditional vs. social networking routes for organ donation registrations in a competition-based campaign. J Commun Healthc. 2014;7:197–207.
16. Smith SW, Hitt R, Park HS, Walther J, Liang Y, Hsieh G. An effort to increase organ donor registration through intergroup competition and electronic word of mouth. J Health Commun. 2016;21:376–86.
17. Smith A, Matthews R, Fiddler J. Blood donation and community: exploring the influence of social capital. Int J Soc Inq. 2011;4:45–63.
18. Whittaker S. Qualitative research: what is it and how can it be applied to transfusion medicine research? Vox Sang. 2002;83:251–60.
19. Schreiber GB, Sharma UK, Wright DJ, Glynn SA, Ownby HE, Tu Y, et al. First year donation patterns predict long-term commitment for first-time donors. Vox Sang. 2005;88:114–21.
20. Kaikati AM, Torelli CJ, Winterich KP, Rodas MA. Conforming conservatives: how salient social identities can increase donations. J Consum Psychol. 2017;27:422–34.
21. France CR, France JL, Himawan LK, Fox KR, Livitz IE, Ankawi B, et al. Results from the blood donor competence, autonomy, and relatedness enhancement (blood donor CARE) randomised trial. Transfusion. 2021;61:2637–49.
22. Chell K, Masser B, Davison TE, Ferguson E. A typology of strategies that recognize, reward, and incentivize blood donation. Transfusion. 2022;62:2077–85.
23. Cameron AM. Social media and organ donation: the Facebook effect. J Leg Med. 2015;36:39–44.
24. Chell K, White C, Karki S, Davison TE. An Australian trial on the effectiveness of a discount reward to increase plasma donor retention and frequency of donation. ISBT Sci Ser. 2021;16:188–95.

How to cite this article: Bryant J, Woolley T, Sen Gupta T, Chell K. Using competition for plasma donor recruitment and retention: An Australian university case study. Vox Sang. 2024;119:155–65.

Received: 10 August 2023 | Revised: 2 October 2023 | Accepted: 3 October 2023

DOI: 10.1111/vox.13555

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Challenges associated with access to plasma-derived medicinal products in low middle-income and low-income countries

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Plasma-derived medicinal products (PDMPs) are essential to treat many chronic conditions such as haemophilia and primary immunodeficiency. Patients living in low middle-income and low-income countries (LMICs and LICs, respectively) have limited access to PDMPs. The aim of this article is to explore the challenges of accessing PDMPs in LMICs and LICs.

Materials and Methods: A review of the literature and reports on blood safety, plasma production and its utilization to produce PDMPs in LMICs and LICs was carried out.

Results: There is huge wastage of recovered plasma in LMICs and LICs as a result of a lack of good manufacturing practice (GMP) in the production of plasma for fractionation. Together with the high cost of imported PDMP procurement, patients have limited access to such products.

Conclusion: There is a need to improve the situation by using domestically sourced plasma through the initiation of local plasma programmes through a stepwise approach to improve access to PDMPs in LMICs and LICs.

Keywords

access, developing countries, plasma products

Highlights

- There is a great amount of wastage of recovered plasma in low middle-income countries (LMICs).
- This is due to a lack of good manufacturing practice in the production of plasma for fractionation in these countries.
- Therefore, there is a need to establish a stepwise approach for the utilization of domestically sourced plasma for fractionation in LMICs.

INTRODUCTION

Plasma-derived medicinal products (PDMPs) include mainly clotting factor concentrates (CFCs) of FVIII and FIX, intravenous and subcutaneous immunoglobulins (IVIGs and SCIG) and albumin [1]. In addition, hyperimmunoglobulins (Igs) such as anti-D Ig and anti-hepatitis B virus (HBV) Ig are strategic products for prophylaxis from foetal and neonatal haemolytic disease as well as passive immunization against HBV such as in cases of vertical transmission from mother to the new born [2, 3].

FVIII, FIX, IVIG, SCIG and hyper-Igs (anti-D and anti-HB Igs) are on the World Health Organization's (WHO) List of Essential Medicines (LEM) [4]. These products are essential to treat many chronic conditions such as haemophilia, primary immunodeficiency and others [5, 6].

In developed economies, there is sufficient supply of PDMPs to treat patients according to the state of the art, which has helped improve the quality life comparable to their healthy peers. The limited global supply of PDMPs and the high cost have made them mainly accessible to only high-income countries (HICs). HICs consume 70%–80% of the global

production of PDMPs. This leaves only 20% these important therapeutics available to low middle-income countries (LMICs) and low-income countries (LICs), which represent 80% of the global population [7].

To improve the situation in LMICs and LICs, there is a need to understand the challenges that have led to the current situation. To identify these challenges, one should improve the reach and diagnosis of patients who mainly consume PDMPs. Establishing national patient registries as well as national guidelines for management of these patient groups is essential to identify these countries' needs of different treatment products.

On the other hand, points to consider when establishing a plasma fractionation programme are the national blood transfusion programme, established donor programme, study of transfusion-transmitted diseases prevalent in the community in order to assess their risk, the existence of a competent national medicinal authority and, finally, the cost effectiveness of establishing a national plasma fractionation programme.

The aim of this study was to examine the readiness of LMICs and LICs to engage in plasma fractionation programmes to ensure access to safe PDMPs to treat their patients.

METHODS

We conducted a review of the literature through a search of an online database (PubMed) as well as reports from international organizations such as the WHO, World Federation of Haemophilia (WFH), International Patient Organization for Primary Immunodeficiencies (IPOPI) and International Society of Blood Transfusion (ISBT). In addition, specialized publications that follow up regularly on news of the plasma fractionation industry such as *International Blood and Plasma News* (IBPN) or websites such as Statista were consulted. On some points, we relied on personal communication.

The review focuses on the following:

1. Outreach, diagnosis and registries of patients who rely for their management on PDMPs;
2. Structure of the national blood programmes and their elements according to the WHO guidelines;
3. Requirements for the production of plasma for fractionation;
4. Situation of the above-mentioned points in LMICs and LICs;
5. Experiences from LICs and LMICs on projects of domestic plasma fractionation.

RESULTS

Diagnosis and registries of patients who are treated with PDMPs

While hyperimmunoglobulin preparations such as anti-D, anti-hepatitis B and anti-tetanus Igs have public demand, other plasma products on WHO LEM such as coagulation factors (FVIII and FIX) and Igs are used to treat rare diseases such as haemophilia A and B and primary immunodeficiency syndromes (PIDS) [4, 8].

In LMICs and LICs, diagnosis and the establishment of national registries for rare diseases such haemophilia and PIDS is a challenge. Haemophilia A and B prevalence per 100,000 male population is estimated at 17.1 and 3.6. This estimation is based on the number of diagnosed patients in developed countries such as the United Kingdom, France and Canada [9]. This means that we should expect the global number of patients with haemophilia as close to 700,000. The WFH 2021 annual global survey (AGS) indicates that the number of patients diagnosed with haemophilia globally is only 256,840. WFH AGS also indicates that the number of diagnosed patients against the expected number is 83% in Europe, 58% in the Americas and 43% in the Eastern Mediterranean Region (EMR). On the other hand, the number of diagnosed patients against the expected is only 8% in Africa, 17% in South and South East Asia (SEA) and 21% in the Western Pacific Region. These last three regions represent more than 70% of the global population [10]. The prevalence of diagnosed patients with PIDS is reported to be 1.5/10,000 in Scandinavian countries and 1/10,000 in North America and some European countries, while in the EMR it is 1–2/100,000 and in the reporting African and Asian countries it is only 0.5/100,000 [11]. These data demonstrate that there is a problem of under-diagnosis of patients with haemophilia and PIDS, who are the main consumers of the driving products of the plasma industry (coagulation factors FVIII and IX and Igs) in most developing countries. The low number of diagnosed patients does not represent a critical mass that can attract the attention and gain support of both the governments and communities at large. In the meantime, coagulation factor products and Igs are very expensive, which leads to limited procurement of such products. This is particularly true when the health budgets in LMICs and LICs are overwhelmed by the limited to scarce resources and the mandatory prioritization of more prevalent health conditions such as viral infections (viral hepatitis and human immunodeficiency virus [HIV]) and non-communicable conditions such as diabetes and cardiovascular diseases. Patient access to FVIII CFCs is estimated to be 100,000 IU FVIII/patient/year in HICs, while it is only around 16,000 IU/patient/year in LMICs and LICs, where the majority supply comes as humanitarian aid from the WFH Humanitarian Aid Program with very little procurement by the governments of these countries [10].

Similar to the case of CFCs, access to IVIG products is very much limited in LMICs and LICs. In 2021, Germany's use of different Ig products was reported to be around 13 tons [12], while in Egypt it was only 564 kg (author personal communication).

In summary, there are significant challenges in the diagnosis and establishment of national registries for patients relying on CFCs and Ig therapeutics. This will have an impact on the decisions of LMICs and LICs to engage in plasma fractionation programmes locally.

Blood transfusion programmes in LMICs and LICs

WHO requires a national blood programme that has a unit within the Ministry of Health (or other government departments) with

responsibility for governing all activities related to the provision and transfusion of blood and blood products. In addition, there should be an established national blood policy and a multi-year national strategic plan for blood safety. WHO encourages the formulation of a specific legislation or other legal instruments covering the safety and quality of blood and blood products for transfusion. Blood programmes should have a financing system which is either state funded or based on cost recovery. A national blood committee (or equivalent) assists the Ministry of Health in formulating policy and plans, setting standards and advising on key issues [13]. Legislative framework for regulating donors and donation of plasma for fractionation, storage, transport, cross-border movement and registration of manufactured products is mandatory for any country/region to enter into plasma fractionation activities. A qualified national regulatory (medicinal) authority is mandatory for the licensing of plasma collection centres, monitoring epidemiologic prevalence of transfusion-transmitted infections (TTIs) in the general population as well as in donor population, plasma collection, testing and storage activities as well as transport from collection centres to the manufacturing site (domestic or international) [14].

Important findings from the WHO report on blood safety issued in 2021 [13] are given below. The report highlighted the following results on the national blood programmes in a survey that included 170 responding countries from WHO regions:

1. The majority of LMICs and LICs have an established policy and governance, which represents a cornerstone in developing a domestic plasma fractionation programme.
2. Many of the LMICs' and LICs' blood programmes are dependent on international funding and technical assistance, which may raise question about the sustainability of such programmes.
3. Many LMICs and LICs lack systems for inspection, licensing and accreditation.
4. Sixty-four million donations were collected in LMICs and LICs. If these donations were separated into packed red blood cells and plasma according to good manufacturing practice (GMP), there can be 64 million units of plasma (16 million litres) that can be fractionated.
5. Voluntary non-remunerated blood donations account for 62.8% in LICs and 69.5% in LMICs. On the other hand, the blood donations obtained from repeat blood donors account for 37% in EMR, 38% in Africa, 56% in Western Pacific and 57% in SEA.
6. Only 38% in LICs and 75% in LMICs are whole-blood donations processed into blood components.
7. There is a higher prevalence of TTIs among blood donors in LMICs and LICs compared to HICs. There is thus a need to improve the quality of blood screening for TTIs in these countries.

Recovered plasma for fractionation in LMICs and LICs

Of the total of 311,946 L of plasma that was fractionated to plasma products in Africa, recovered plasma was 98% (305,000); of the 126,600 L from SEA, 95% was recovered plasma (120,000); and of the 186,277 L from EMR, 54% (100,000) was recovered plasma. As such, out of the potential 16 million litres of recovered plasma from LMICs and LICs, only about 526,566 L was fractionated.

History of domestic plasma fractionation projects in LMICs

During 1960s and 1970s, driven by the need to treat patients with haemophilia, several small to medium scale projects for the production of low- to intermediate-purity FVIII concentrates were established. South Africa had established plants for two FVIII products, namely low-purity heat-treated FVIII concentrate and intermediate-purity solvent detergent FVIII. The South African Natal Bioproducts Institute (NBI) produces albumin and Igs in addition to FVIII concentrates. Both products could provide small quantities of FVIII concentrates that could fill the gap in supply. A similar project was established by the Thai Red Cross during the 1990s to produce small pools of freeze-dried and heat-treated cryoprecipitates (low-purity FVIII). Cuba and Brazil had similar projects to produce low- and intermediate-purity heat-treated FVIII concentrates [15]. In Egypt, during the last three decades of the 20th century, the Vaccine and Serum Institute (Vac-Sera) had a small fractionation facility for the production of small pools of lyophilized cryoprecipitate, plasma, anti-D Ig, intramuscular polyvalent Ig and albumin. Because of the lack of virus inactivation technologies, WHO recommended discontinuation of production at Vac-Sera by end of 1990s.

DISCUSSION

The development of a plasma fractionation programme for the production of PDMPs was always linked to needs of the patient community to improve therapeutics involved in their management [1]. In the early days, there was a recognition of the risk of transmission of blood-borne viruses to patients who chronically received these products. Several important steps were taken to mitigate this risk, which included virus inactivation of albumin by pasteurization and the introduction of screening of blood to detect various blood-borne viruses (mainly HIV, HBV and hepatitis C virus [HCV]) [14]. Because of the nature of the industry, when large pools of donated plasma are processed in one batch, it was found that the screening of blood was not enough to eliminate the risk, particularly when dealing with emerging or re-emerging new viral agents. This was typically the case for HIV and HCV, which resulted in epidemics among patients with haemophilia during the 1970s and 1980s when they were treated with concentrates that were not viral-inactivated [16]. As such, it was realized that, in addition to various measures to improve the safety of donated plasma, there should be robust technologies for virus inactivation/elimination of PDMPs [17]. This recognition and its implementation could effectively almost totally eliminate the risk of transmission of blood-borne infectious agents through PDMPs [16]. In addition, progressive developments in the separation and purification of various

plasma proteins improved considerably the efficacy of PDMPs and reduced the risks of adverse events.

With these developments in the arena of plasma fractionation, production facilities became extremely sophisticated and, in order to achieve cost–efficiency balance, the industry had to go into mergers and acquisitions to be sustainable. It also reflected on the high cost of modern PDMPs.

The development of domestic plasma programmes has become extremely sophisticated and requires significant resources to match the requirements of safety and efficacy of PDMPs.

In the meantime, the superiority of prophylactic therapy in patients with haemophilia compared to on-demand therapy [18] and the progressive implementation of prophylaxis as a standard of care as stated by the last version of WFH Guidelines on the Management of Haemophilia [19] resulted in a progressive demand on FVIII and IX concentrates. Also, prophylaxis with IVIG in patients with PIDS [6] resulted in progressive increase in the demand on IVIG in HICs. This resulted in the utilization of >70% of PDMPs in HICs.

These realities have largely impacted the availability and accessibility of PDMPs in LMICs and LICs. The challenges in the diagnosis of rare diseases, which are the main consumers of PDMPs, have resulted in the lack of interest of the governments in LMICs and LICs to make these products available to the small number of diagnosed patients. The required blood structure for producing plasma qualified for fractionation is lacking in many of LMICs and LICs [13]. The cost–income balance to establish plasma programmes for the production of PDMPs cannot be achieved in many LMICs and LICs because of the small number of diagnosed patients, small volumes of recovered plasma that can be qualified for fractionation and high cost of sourced plasma.

In spite of the current challenges for establishing programmes for the production of PDMPs in LMICs and LICs, it is still the main solution to fill the gap in availability of safe and effective treatment to many patients. There is a need for international organizations such as the WFH and IPOPI to work with LICs and LMICs to establish national programmes for the detection and diagnosis of these rare diseases. The cooperation should also aim to create national treatment protocols and assessment of country needs of PDMPs. To address the challenges of availability of PDMPs in LMICs and LICs, an out-of-box thinking of new models of access to PDMPs should be considered. The initiative of the Humanitarian Aid Program of WFH to donate CFCs to patients with inherited bleeding disorders in LMICs and LICs is one such example [20]. Blood bank virus inactivation technologies for small volumes of plasma produced according to GMP standards is another option [21, 22]. In countries with the capacity to produce large volumes of plasma, a plasma programme can be built for contract fractionation with a commercial fractionator [23]. Finally, and if cost effective, a long-term plan for establishing a plasma programme with stepwise toll manufacture followed by the establishment of a domestic fractionation facility should be considered, as was possible in South Africa and Thailand.

This last example is also being persuaded in Iran, Brazil and Egypt.

In conclusion, PDMPs are essential medicines to treat many life-long serious clinical conditions. They are largely unavailable to patients living in LMICs and LICs. This unavailability is attributed to several challenges. Limited diagnosis of rare bleeding and immune disorders together with absence of national patient registries, high prevalence of TTIs and the lack of GMP in blood transfusion systems in LMICs and LICs are among these challenges. Complexity of plasma fractionation programmes and the high cost of PDMPs are among the other challenges that limit their availability. There is a need for concerted efforts between industries in developed countries, international organizations and governments of LICs and LMICs to work together to make these important therapeutics available through different means.

ACKNOWLEDGEMENTS

S.D. participated in preparing the search questions and review of literature, E.G. participated in writing the manuscript and F.M. reviewed the manuscript and made necessary edits.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Mousavi Hosseini K, Ghasemzadeh M. Implementation of plasma fractionation in biological medicines production. Iran J Biotechnol. 2016;14:213–20.
2. Runkel B, Bein G, Sieben W, Sow D, Polus S, Fleer D. Targeted antenatal anti-D prophylaxis for RhD-negative pregnant women: a systematic review. BMC Pregnancy Childbirth. 2020;20:83.
3. Zhang L, Gui XE, Teter C, Zhong H, Pang Z, Ding L, et al. Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. Vaccine. 2014;32:6091–7.
4. Peacocke EF, Myhre SL, Foss HS, Gopinathan UE. National adaptation and implementation of WHO model list of essential medicines: a qualitative evidence synthesis. PLoS Med. 2022;19:e1003944.
5. Farrugia A. Product delivery in the developing world: options, opportunities and threats. Haemophilia. 2004;10:77–82.
6. Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. Primary immunodeficiency and autoimmunity: a comprehensive review. J Autoimmun. 2019;99:52–72.
7. Burnouf T, Seghatchian J. "Go no Go" in plasma fractionation in the world's emerging economies: still a question asked 70 years after the COHN process was developed. Transfus Apher Sci. 2014;51:113–9.
8. WHO Model List of Essential Medicines 23rd List 2023. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02. Last accessed 30 Sep 2023.
9. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using National Registries. Ann Intern Med. 2019;171:540–6.

10. Committee, W.F.o.H.D.D. World Federation of Hemophilia Annual Global Survey 2021 [Research Article]. 2021. Available from: www.wfh.org. Last accessed 8 Apr 2023.
11. Condino-Neto A, Sullivan KE. The relevance of primary immunodeficiency registries on a global perspective. J Allergy Clin Immunol. 2021;148:1170–1.
12. International Blood/Plasma Business News Brief, in IBPN; 2023. p. 77.
13. WHO Global Status Report on Blood Safety and Availability. 2021. Available from: https://www.who.int/publications-detail-redirect/9789240051683. Last accessed 11 Apr 2023.
14. WHO Guidance on Increasing Supplies of Plasma-Derived Medicinal Products in Low-And Middle-Income Countries Through Fractionation of Domestic Plasma. Available from: https://www.who.int/publications-detail-redirect/9789240021815. Last accessed 11 Apr 2023.
15. Bird A, Isarangkura P, Almagro D, Gonzaga A, Srivastava A. Factor concentrates for haemophilia in the developing world. Haemophilia. 1998;4:481–5.
16. Farrugia A. Safety and supply of haemophilia products: worldwide perspectives. Haemophilia. 2004;10:327–33.
17. Velthove KJ, Over J, Abbink K, Janssen MP. Viral safety of human plasma-derived medicinal products: impact of regulation requirements. Transfus Med Rev. 2013;27:179–83.
18. Shapiro AD. A global view on prophylaxis: possibilities and consequences. Haemophilia. 2003;9:10–7; discussion 18.
19. Srivastava A, Santagostino A, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26:1–158.
20. Pierce GF, Adediran M, Diop S, Dunn AL, El Ekiaby M, Kzczmarek R, et al. Achieving access to haemophilia care in low-income and lower-middle-income countries: expanded Humanitarian Aid Program of the World Federation of Hemophilia after 5 years. Lancet Haematol. 2022;9:e689–97.
21. Burnouf T, Radosevich M, El-Ekiaby M, Goubran H. Pathogen reduction technique for fresh-frozen plasma, cryoprecipitate, and plasma fraction minipools prepared in disposable processing bag systems. Transfusion. 2011;51:446–7.
22. El-Ekiaby M, Vargas M, Sayed M, Gorgy G, Goubran H, Radosevich M, et al. Minipool caprylic acid fractionation of plasma using disposable equipment: a practical method to enhance immunoglobulin supply in developing countries. PLoS Negl Trop Dis. 2015;9:e0003501.
23. Burnouf T, Epstein J, Faber JC, Smid M. Stepwise access to safe plasma proteins in resource-constrained countries: local production and pathways to fractionation-report of an International Society of Blood Transfusion Workshop. Vox Sang. 2022;117:789–95.

How to cite this article: El Ekiaby M, Diop S, Gouider E, Moftah F. Challenges associated with access to plasma-derived medicinal products in low middle-income and low-income countries. Vox Sang. 2024;119:166–70.

DOI: 10.1111/vox.13599

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