

University of Groningen

Stepwise access to safe plasma proteins in resource-constrained countries

Burnouf, Thierry; Epstein, Jay; Faber, Jean-Claude; Smid, Martin

Published in:
Vox Sanguinis

DOI:
[10.1111/vox.13263](https://doi.org/10.1111/vox.13263)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Burnouf, T., Epstein, J., Faber, J.C., & Smid, M. (2022). 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 Sanguinis*, 117(6), 789-795. <https://doi.org/10.1111/vox.13263>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

REPORT

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

Thierry Burnouf^{1,2}  | Jay Epstein³  | Jean-Claude Faber⁴ | Martin Smid⁵ 

¹Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

²International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

³McLean, Virginia, USA

⁴Association Luxembourgeoise des Hémophiles, Luxembourg City, Luxembourg

⁵Sanquin Consulting Services, Academic Institute IDTM, Amsterdam & Groningen, The Netherlands

Correspondence

Thierry Burnouf, Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, 250 Wu-Xing Street, Taipei 11031, Taiwan.
Email: thburnouf@gmail.com

Funding information

None.

Abstract

Background and Objectives: Actions are needed to improve access to safe plasma-derived medicinal products (PDMPs) in low- and middle-income countries (LMICs).

Materials and Methods: The International Society of Blood Transfusion (ISBT) Working Party for Global Blood Safety organized an on-line workshop during 21–23 September 2021 to advance access to safe plasma proteins in resource-constrained countries, consistent with recent World Health Organization (WHO) guidance documents.

Results: The meeting drew attention to the considerable unmet needs for access to essential PDMPs in LMICs, in particular coagulation factors and immunoglobulins, and stepwise actions to address these deficits. First, improved access to safe plasma protein therapies requires blood component separation with prevention of wastage of recovered plasma. Quality and safety of collected blood and plasma must be assured so that plasma in excess of transfusion needs can be processed into safe plasma proteins. Second, local production of safe plasma proteins can be implemented using available technologies to locally obtain pathogen-reduced plasma and prepare pathogen-reduced cryoprecipitate and immunoglobulins from small plasma pools. Third, when a sufficient, stable volume of quality-assured plasma is available (approximately 50,000 L/year), contract or toll fractionation by a foreign plasma fractionator can expand the supply of PDMPs. Fourth, when the national infrastructure supports high-technology industrial production and stable volumes of quality plasma reach at least 200,000 L/year, technology transfer for domestic fractionation can be considered.

Conclusion: Action is needed including commitments of the organizations that made the workshop possible (WHO, ISBT, World Federation of Haemophilia [WFH], Plasma Protein Therapeutics Association [PPTA], International Plasma Fractionation Association [IPFA], International Patient Organization of Primary Immunodeficiencies [IPOPI] and International Federation of Blood Donor Organizations [FIODS]).

KEYWORDS

haemophilia, immunodeficiency, low- and middle-income countries, plasma, proteins

Highlights

- Patients' access to plasma-derived medicinal proteins (PDMPs) essential for their treatment is still poor or absent in low- and middle-income countries (LMICs) due to the unavailability or unaffordability of the products.
- Stepwise technological actions to process domestic quality plasma can advance the access to safe plasma protein products in LMIC, consistent with recent WHO guidance documents.
- Practical pilot projects to address deficits in PDMPs in LMIC are now planned; implementation will require the continued commitments of the international organizations that contributed to the workshop and the support from technology and equipment suppliers.

INTRODUCTION

A 3-day on-line workshop was organized by the International Society of Blood Transfusion (ISBT) Working Party on Global Blood Safety (WP GBS) during 21–23 September 2021 to discuss 'Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries'. Delegates from 84 countries attended the workshop, which gathered major stakeholders in the plasma product field, including representatives from the World Health Organization (WHO), patient organizations, blood donor organizations, plasma fractionation organizations and technology and equipment suppliers.

Data indicate that unlike in high-income countries, in most low- and middle-income countries (LMICs) patients' access to plasma-derived medicinal proteins (PDMPs) essential for their treatment is still poor or absent due to unavailability or unaffordability of the products. To identify and facilitate new avenues for the supply of plasma protein products, in 2017 the WP GBS published recommendations on pathogen-reduced cryoprecipitate and on plasma for fractionation. More recently, the WHO launched an 'Action framework to advance universal access to safe, effective and quality-assured blood products 2020–2023' under which it published 'Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma' [1] and 'Guidance on centralization of blood donation testing and processing' [2].

The aim of the WP GBS workshop was to 'identify pragmatic technical options for stepwise access to safe plasma protein therapies in resource-constrained countries to support implementation of these WHO guidance documents'.

UNMET NEEDS FOR PDMPs IN LMICs

Significant imbalances exist in global plasma collection, with 65% from the United States, and the need for more regionally balanced collection towards global PDMP sufficiency. To reach 'Treatment for All' as an ultimate goal, additional innovative strategies and actions are necessary. Patients with bleeding disorders (haemophilia A and B, von Willebrand disease and other rare haemorrhagic diseases) and a variety of immunodeficiencies suffer from similar problems: underdiagnoses of patients and short supplies of safe and effective therapeutic products. Inherited bleeding disorders (IBDs) are present

worldwide, but in LMICs only 8% of those are identified because of lack of awareness, inadequate diagnoses and unavailability of treatment products. A striking imbalance between the developed and developing world exists, with 82% of total factor VIII (FVIII) products being used in the Americas and Europe, which comprise only 29% of the global population. In the World Federation of Hemophilia (WFH) Global Survey 2019, the mean FVIII usage reported per capita was 6.01 IU (international units) in high-income countries versus 0.06 IU in LMICs. This gap reflects that many patients are not diagnosed and suffer from early-life haemorrhage or do not have access to treatment including from barriers of cost, leading to the high morbidity and mortality among haemophilia patients in LMICs. The WFH has taken steps to mitigate this unsatisfactory supply situation, which globally affects 70%–80% of haemophilia patients with no improvement in the past 20 years. WFH activities in LMICs aim to improve the level of knowledge through capacity building and data collection, enhance advocacy capacities of different stakeholders and facilitate access to care under a Humanitarian Aid Program (HAP). The HAP provides consistent and predictable access to PDMPs in LMICs through product donations by industry, representing a fine example of solidarity with patients. Making use of optimal treatment paradigms, the HAP provides evidence of the benefits that can motivate governments to support the purchase or production of clotting factor concentrates (CFCs). However, as HAP donations cover less than 1% of global CFC consumption, this programme alone will not resolve shortages in LMICs.

To prevent serious infections, patients with primary immune deficiencies (PIDs) require life-long immunoglobulin (Ig) replacement therapy with individualized product selection and dosages. Access to Igs in the world varies widely, with about 50% of the worldwide Ig consumed in North America alone. The International Patient Organization for Primary Immunodeficiencies (IPOPI) estimates that 80% of PID patients worldwide do not have access to appropriate therapies. Significant disparities exist in PID diagnosis rates and patient access to Ig therapies between regions. Prevalences of diseases differ between regions. Based on a conservatively estimated PID prevalence of 1/1200–1/5000, at least 1.4 million people live with PID worldwide, most of whom require Ig therapy. In 2018, 211 tons of Ig was used worldwide (up from 19.7 tons in 1992), whereas at least 305 tons of Ig are needed to cover PID patient needs only. Demand for Ig is growing at 6%–8% yearly across a broad range of indications, in particular for secondary

immunodeficiencies, and is not forecasted to decrease for years to come. Improved global PDMP sufficiency with better Ig access in LMICs requires collaboration guided by patient needs, donor care, safety of PDMPs, and a better understanding of patient-centred Ig therapies. To overcome existing product shortages, the IPOPI aims to increase the availability of high-quality plasma for fractionation, by improving good manufacturing practices (GMPs) in blood and plasma collection and processing and preventing plasma wastage.

OPTIONS FOR THE FRACTIONATION OF DOMESTIC PLASMA

World Health Assembly Resolutions 58.13 (2005) and 63.12 (2010) urge countries to ensure adequate availability of safe quality blood, blood components and PDMPs. In particular, several PDMPs, including clotting factors and Igs, are included in the WHO Model List of Essential Medicines. Therefore, ensuring a safe, secure, sufficient and ethically obtained supply of essential PDMPs in LMICs is regarded as an important public health responsibility. Plasma collected to improve the sufficiency of PDMPs should meet quality requirements for fractionation. However, a substantial volume of recovered plasma, a valuable source of clotting factors and having, in some LMIC countries, a high content in immunoglobulins, is discarded because quality requirements for industrial fractionation are not met. This wastage is due to deficiencies, which include a fragmented blood collection system, absence of regulations to assure plasma quality and safety, deficiencies in testing, and inadequate infrastructure for plasma freezing, storage and transport. Corrective actions are urgently needed, as the steady increase in whole-blood collection in LMICs to provide for red blood cells may increase the volume of wasted plasma. Thus, the WHO published a high-level guidance document entitled 'Increasing supplies of PDMPs in LMICs through fractionation of domestic plasma'. The guidance provides a strategic framework to assist member states in increasing the volume of quality plasma suitable for fractionation and understanding stepwise approaches for providing safe plasma protein products by local small-scale processing and through industrial fractionation. This guidance is complementary to WHO guidance on centralizing blood donation testing and processing, which is intended to assist member states in deciding whether to centralize blood donation testing and processing. Such centralization can help LMICs gradually increase the availability of quality plasma for fractionation and access to safe plasma protein fractions including PDMPs.

The possibility for fractionation of plasma into PDMPs depends on assurances that the plasma meets international quality standards. Measures are needed to correct non-conformities in quality management systems and/or deficiencies in GMPs as required by plasma fractionators. Key steps and changes can be implemented by blood services to improve the quality of their plasma. A strong commitment from government agencies and adequate funding for GMP implementation are needed. Improvements need to be made throughout the manufacturing chain, from donor selection to shipping of frozen plasma and fractionation. Plasmapheresis as a source of additional

plasma for further processing into plasma fractions can be introduced after GMP compliance is established in blood establishments.

Contract or toll plasma fractionation through an agreement with an established plasma fractionator is a pragmatic and feasible way to obtain PDMPs from domestic plasma. Domestic plasma recovered from whole blood or obtained by plasmapheresis is sent to a fractionator to obtain PDMPs under different contractual agreements. Domestic plasma should comply with mandatory quality requirements from the plasma fractionator and relevant regulatory authorities. This requires implementation of quality management systems for blood, blood components and plasma collection, resulting in a win-win situation for both blood collection and plasma fractionation organizations. With consistent volumes of quality plasma sufficient to be industrially fractionated (estimated to be 50,000 L/year), the decision to initiate contract manufacturing can be made, involving all stakeholders (blood establishments, local authorities, fractionators, the ministry of health and dedicated funding organizations if needed). The PDMPs manufactured through contract fractionation abroad should obtain a license by local or regional competent authorities supervising the country. A quality agreement between blood establishment organizations and the fractionator is a building block that defines all quality, technical and contractual conditions. Such quality management systems can be implemented at the regional level to increase quality plasma volume, perform contract manufacturing and contribute to the availability of PDMPs in the world.

Understanding the complexity of the plasma fractionation industry would help make optimal technical and financial decisions. Plasma fractionation is a complex technology with benefits and limitations. The original process based on ethanol precipitation developed 75 years ago to fractionate albumin is still the core technology today. Countries interested in building a fractionation plant to improve PDMP supplies should consider the WHO guidance recommendations to ensure success and sustainability. Economic considerations, sometimes underestimated, include costs of complex engineering, heavy capital investments, and, typically, technology transfer with a long-term endeavour. For a domestic facility, a minimum targeted annual volume of 200,000 L, ideally expandable to 300,000 L of plasma, is needed.

Thailand is one example where a domestic plasma fractionation programme was implemented to resolve issues of variable costs and insufficient supplies of imported PDMPs and address inequitable access to treatment for patients. The country was running a small-scale plasma fractionation facility, and in 2011 it decided on an industrial plasma fractionation plant to meet increasing local demands for FVIII, intravenous Ig (IVIg), and albumin. In 2013, a technology transfer agreement was signed with Green Cross Corporation (GCC). Construction of the plasma fractionation facility began, followed by technology transfer, qualification, validation and production batch trials. Clinical studies of locally made PDMPs were conducted in university hospitals. The first licensed products were released in 2016, which showed a quality comparable to that of imported products. Critical factors in their success included royal and government support, good diplomatic relationships between Thailand and South Korea, fruitful cooperation among various local health

organizations, the availability of local technical expertise and experienced staff, and a reliable domestic plasma supply. Building such a domestic facility is very costly and requires complex technology transfers. Thus, careful assessment and feasibility studies are needed.

The Hemoderivatives Laboratory (HL) of the National University of Cordoba (UNC), Argentina, was established in 1965 to fractionate plasma from Argentina. In-house plasma fractionation technologies were developed, allowing HL to produce a range of PDMPs. Domestic blood centres supply plasma and receive PDMPs in return as well as equipment and supplies for enhanced blood/plasma quality collection. In addition, HL signed plasma fractionation agreements with Uruguay, Chile and Paraguay. A percentage of the produced PDMPs is returned to the plasma suppliers, while HL keeps excess products to compensate for the fractionation cost, thus improving the availability of PDMPs in Argentina. Insufficient political will for plasma fractionation and insufficient plasma quality initially impeded the development of the plasma fractionation programme. Implementation of the Plasma Quality Assurance Program by HL, which focused on compliant plasma collection procedures and GMP implementation, and better organization of the national blood collection system were vital to the eventual success.

Thus, both sufficient quality and volume of plasma are needed for industrial-scale processing. However, many LMICs struggle to make enough safe blood available, while for small countries the minimum plasma volume needed for a plasma fractionation programme is out of reach, justifying the need to identify pragmatic solutions to increase PDMP supplies at the national or regional level.

OPTIONS TO IMPROVE THE ACCESS TO SAFE PLASMA PROTEIN PRODUCTS IN LMICs

The International Federation of Blood Donor Organizations (FIODS) emphasizes the fundamental role of safe blood and plasma donors in every blood programme. Up-to-date strategies for recruitment and retention of safe blood and plasma donors include “social marketing” with culturally sensitive promotion of donations that focuses on donors’ natural desire to enhance their standing in their own social networks. Thus, the safety and security of the blood supply and voluntary unpaid donations should be priorities, targeting low-risk populations, promoting blood and plasma donation as part of a healthy lifestyle, and protecting donors’ health and rights. Blood donor organizations and associations can play an important role, making a significant contribution to their respective national blood organizations and healthcare systems.

The French Blood Establishment (EFS) reported on the successful use of quarantine/release as an alternative to pathogen reduction (PR) to ensure the safety of plasma for transfusion. Fully tested plasma from whole blood or apheresis is held in quarantine for at least 60 days and released for transfusion on days 61–160 of storage based on a subsequent donation with negative infectious disease test results. Plasma quarantine/release mitigates the infectious risk associated with a donation in an infectious ‘window period’ for tested

agents. However, the practice is feasible only if a large proportion of donors returns for donation during the defined period. The efficiency of plasma quarantine/release depends on multiple factors, including the ability to identify and engage with donors willing to undergo subsequent donations. A robust infrastructure capable of dealing with large volumes of cryopreserved plasma should be available, as well as a robust system of product information and traceability. The sensitivity of donation screening tests (which governs the necessary duration of the quarantine) and the incidence of transfusion-relevant pathogens in donors are relevant elements to consider. Rules and procedures for disposition (i.e., fractionation or destruction) of plasma for which quarantine/release was unsuccessful should be defined. Plasma quarantine in LMICs might not be easily implementable as donor return rates are generally low.

Pathogen reduction (PR) is an option to improve the safety of plasma. Several companies presented their respective PR technologies for blood components. Intercept/Cerus uses amotosalen + ultraviolet A (UVA) to treat plasma (and platelets); at the workshop, feasibility was also claimed for PR of cryoprecipitates and cryo-poor plasma. Mirasol/TerumoBCT uses riboflavin + UVB/A spectra to treat plasma (and platelets); at the workshop, PR of cryoprecipitate was also described. Theraflex/Macopharma uses methylene blue + UVC to treat plasma and cryoprecipitate. VIPS/VIPS uses solvent-detergent (SD) for mini-pool PR of plasma and cryoprecipitate and caprylic acid for mini-pool purification and PR of Ig. At this time, only VIPS offers a PR method for the preparation of Ig. All presenting manufacturers emphasized the safety and efficacy of their technologies. Each of the technologies offers highly significant inactivation of major enveloped viruses relevant to blood safety (human immunodeficiency virus [HIV], hepatitis B virus [HBV] and HCV) but lesser reduction of non-enveloped viruses (i.e., parvovirus B19). Chemical characteristics of treated plasma and cryoprecipitate conform to internationally recognized standards. The companies claim that implementation of their technologies is reasonably quick, with training of staff being critical.

In Jeddah, Saudi Arabia, coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) was successfully prepared using plasmapheresis and Intercept PR. Challenges encountered during implementation of CCP production included regulatory approval for the production of a novel pharmaceutical, labelling of the CCP product, implementation of a plasmapheresis system, operator training, on-site validation of the plasmapheresis system, adjustments of the PR process and on-site validation of the overall process. Additional difficulties specific to the COVID-19 pandemic included scarce resources (supplies, budgets and human resources) and limited availability of sets for plasmapheresis and PR (due to interrupted distribution because of flight cancellations and supply shortages).

Experience from Cairo, Egypt, demonstrated that Mini Pool Plasma Fractionation developed with CE-marked medical devices can enable high-end blood transfusion centres in LMICs (like the national blood transfusion centres) to produce safe alternatives for CFCs and IVIG at affordable costs. Specifically, in Cairo, production of PR cryoprecipitates and Ig was implemented using VIPS technologies to address unmet needs for plasma protein products of patients with

haemophilia A and immune deficiencies. The technology enables production of protein concentrates on a scale that can be adapted to blood transfusion centres in LMICs. To make anti-haemophilic factor, a series of CE-marked sterile medical devices is used to generate approximately 400-ml mini-pools of cryoprecipitate, which are subjected to PR using SD and filtration (F) to produce safe coagulation factors as cryo-SD/F. The product contains concentrated FVIII, von Willebrand factor (VWF), fibrinogen and factor XIII (FXIII). Remarkably, one-third of all FVIII used in Egypt is being produced as cryo-SD/F. A comparable approach was developed to produce safe IVIG fractions. The production process, which models scaled-down fractionation, differs from that for cryo-SD/F but is similar in principle: pooling of plasma, precipitation to get the cryo-supernatant, PR, Ig purification (with caprylic acid), several filtration steps, and conditioning of safe Ig to treat patients with immunodeficiencies. Products have demonstrated both clinical safety and efficacy in the absence of significant adverse reactions. At the same time, recovered plasma is utilized, thus reducing wastage of this valuable resource. All VIPS products are CE-marked as medical devices and comply with local blood bank regulations.

LMICs should implement PR on plasma, cryoprecipitate and cryo-supernatant as part of local production of safe plasma protein products when industrially manufactured clotting PDMPs are unavailable or unaffordable. To render plasma proteins virus-safe, complementary measures are needed, including selection of low-risk blood/plasma donors, testing for specific blood-transmissible agents, and use of validated technologies for virus inactivation/removal. Robust methods for virus inactivation/removal such as SD treatment, pasteurization, dry heat and (nano)filtration have been successfully applied against relevant blood-transmitted viruses such as HIV, HBV and HCV. While there is no single inactivation/removal method that reliably clears all kinds of viruses, a combination of methods offers a high degree of safety against a wide range of potential contaminants that may include unknown or unexpected viruses. Available methods for virus inactivation/removal vary with respect to their range of 'viral kill' as well as to their critical process parameters. Considering that individual inactivation steps could be overloaded by highly viremic donations, it may be preferable to apply virus inactivation on pooled/homogeneous plasma pools rather than to individually treat units for virus inactivation. Nucleic acid testing (NAT) of donations might not be required when the implemented pathogen/virus reduction treatment has demonstrated robustness against viruses of concern.

Regulatory approval of medical devices for pathogen inactivation of plasma from the design phase to clinical use is complex. Objective evidence related to the performance, safety, and efficacy (PS&E) must be provided to a notified body (NB), and the national regulatory authority (NRA). When chemicals are used for pathogen inactivation, the device may be certified either as an integrated set including the chemicals or separately. Certification typically takes several years and is increasingly costly and knowledge-intensive, thus, unfortunately, limiting the availability of medical devices for pathogen inactivation in resource-constrained countries.

SCALE-UP FOR DOMESTIC PROCESSING OF PLASMA: TECHNOLOGICAL OPTIONS, EQUIPMENT AND OVERSIGHT

Small-scale processing technologies in single-use devices and equipment from industry suppliers may help fill technical gaps in locally supplying safe plasma proteins. Validated protein purification and virus reduction methods adapted to small-scale plasma processing fit a stepwise approach for preparing virus-safe plasma products such as FVIII/VWF/fibrinogen, and Ig. This ramp-up phase can help familiarize local stakeholders and the workforce with specific requirements of plasma processing.

Industry suppliers representing Sartorius, Merck Millipore and Asahi Kasei Medical presented examples of pragmatic, scalable single-use technologies for various types of chromatographic processing, filtration, tangential flow filtration and virus removal by nanofiltration. Single-use processing can increase the flexibility and efficiency, lower contamination risk, avoid heavy capital investment, and facilitate process implementation and scale-up for domestic plasma processing, including for purified virus-inactivated Igs and cryoprecipitate. Suppliers indicated that they have technical support teams dedicated to LMICs to assist process implementation and performance optimization.

Within a short time frame, Intas Pharmaceutical, India, implemented a dedicated purification process of severe acute respiratory syndrome coronavirus (SARS CoV)-2 Ig from CCP collected by local blood banks. This process included steps for virus inactivation and removal. A concrete example of the production of plasma-derived Igs from small plasma pools was given from the angle of the manufacture of antivenom polyclonal IVIGs in Costa Rica. Antivenom manufacture uses GMP-compliant processing methods analogous to those used in the human plasma fractionation industry to purify Igs. The experience developed by several LMICs in the fractionation of antivenom Igs illustrates the feasibility of domestic production of plasma-derived biologicals that may provide a roadmap for the supply of human plasma fractions in LMICs.

THE WAY FORWARD

The workshop concluded with a presentation of models for technical assistance and technology transfer followed by a panel discussion which focused on identifying practical next steps.

Consistent with WHO guidance documents [1], access to plasma protein products can be approached stepwise (Table 1). First, and most fundamental, is to ensure the quality of blood and plasma collection and processing. Second, as plasma is increasingly generated from component separation of whole blood, it becomes important to eliminate wastage of plasma that is not utilized for transfusions. Local production of small-scale virus-inactivated cryoprecipitate and Igs can be considered using available technologies. Third, as more stable, quality-assured plasma becomes available (approximately 50,000 L/year), collaboration with a plasma fractionator through contract or toll fractionation becomes possible to expand the supply of plasma protein products. Subsequent technology transfer

TABLE 1 Stepwise access to safe plasma protein products in resource-constrained countries where commercial concentrates are unavailable or unaffordable

Step	Volume of quality plasma (L)	Safety measures
1	<50,000	<ul style="list-style-type: none"> • Quarantine or holding period of plasma donations • Validated pathogen reduction of plasma, cryoprecipitate and cryo-poor plasma
2	<50,000	<ul style="list-style-type: none"> • Validated preparation of mini-pools of virus-inactivated cryoprecipitate or immunoglobulins • Small-pool, scalable, plasma fractionation
3a	≥50,000	<ul style="list-style-type: none"> • Consider contract/toll fractionation by a licensed fractionator abroad
3b	≥200,000	<ul style="list-style-type: none"> • Consider domestic or regional plasma fractionation

for the development of domestic fractionation is an option when stable volumes of quality plasma reach a level of 200,000–300,000 L/year and there is a national infrastructure to support high-technology industrial production. Establishment of a national fractionation plant may eventually lead to collaboration with other countries of the region to provide contract or toll fractionation, enabling economies of scale for a national fractionation plant while expanding access to industrially prepared plasma protein concentrates across the region.

A key issue in advancing access to plasma protein products is justification for promoting plasma production when collections of whole blood are insufficient to meet patient needs for transfusion. A major barrier in LMICs exists from the under-diagnosis of rare disorders, since authorities face difficulties prioritizing budgetary needs of very small patient populations. Awareness should be raised of public health decision makers through scientific-evidence-based advocacy about the importance of plasma collection to care for patients whose lives depend on plasma protein products. The WHO could play a larger role in advancing this message globally. For example, World Blood Donor Day could be re-invented as World Blood and Plasma Donor Day. Advocacy for plasma quality also advances the quality and safety of blood components for transfusions and is linked to promotion of a safe and stable blood donor base. Raising awareness of the need for plasma proteins helps to increase the willingness of donors to donate.

Wastage of plasma and failure to generate plasma and cryoprecipitate by component separation from whole blood are missed opportunities and should be supported in countries where treatment with PDMPs or safe plasma components is lacking. A first step is improving blood collection systems to meet transfusion needs while promoting the quality of component separation according to WHO guidance such that plasma ultimately can fulfil the requirements for fractionation. Short of fractionation, with the production of quality plasma, various patient needs can be met through local production of

small-scale plasma protein products. For example, cryoprecipitate has proven value in treating peripartum haemorrhaging and massive bleeding in trauma cases, and can also be used to treat patients with haemophilia A and von Willebrand disease. Ensuring viral safety of cryoprecipitate is paramount to expanding its use. In general, scientific evidence of safety and efficacy is central to advocating for the local production of small-scale plasma protein products. Depending on the product, with tests in place to prevent transfusion-transmitted infections and methods of PR, for example, SD treatment, it might be possible in some settings to obviate the need for NAT to ensure viral safety. Local patient organizations can support investments in locally generated treatments.

Technology suppliers have the ability and willingness to provide technical assistance starting at the early stages of plasma preparation and throughout the ‘plasma value chain’ from donation to fractionation. Technical assistance at the level of plasma preparation is relatively easy and can include training and help with implementation of quality standards and controls; equipment set-up, validation, and maintenance; and material procurement. Assistance at this level can facilitate operation of blood establishments under GMPs and preparation of plasma that meets regulatory standards while also improving the quality and safety of labile blood components for transfusion.

When preparation of quality plasma is managed under a nationally coordinated and well-regulated blood system, contract fractionation becomes an efficient option for access to industrially manufactured products. The partnering fractionator can take steps to ensure that locally generated plasma fulfils all requirements for quality based on GMPs through audits and inspections by both the fractionator and relevant regulatory authorities. This process of assessments concurrently provides valuable domestic learning on how plasma collection and preparation should be done. Limitations of contract fractionation include the likelihood of a narrow range of products, dependence on a third party with importation of finished products, and costs.

Creation of a national or regional fractionation plant can be considered when there is certainty to provide >200,000–300,000 L/year of quality-assured plasma as needed to enable economies of scale. Such plants may eventually provide contract fractionation services to neighbouring countries in the region. Building a fractionation plant is a long-term enterprise of 5–10 years taking at least 3–4 years from planning to operation. Owing to the skills, time and effort required, as well as the current regulatory requirements of technology transfer, technology licensing from an established fractionator is preferred over building up a system from scratch, potentially by expansion of a prior relationship with a contract fractionator. Additionally, there must be the necessary political, public health, economic and social infrastructure and commitments. Clinical studies are also needed to support product registration with competent regulatory authorities.

International plasma fractionators are generally interested in collaboration with LMICs to establish contract fractionation and are willing to provide developmental assistance. In general, it is futile to pursue contract fractionation when the country lacks sufficient blood

collection to satisfy transfusion needs. Under the Achilles Project, the WHO focused on providing assistance to Indonesia and South Africa as individual countries with large populations that could generate large volumes of plasma recovered from whole blood. The approach was comprehensive, including restructuring of the blood supply system, for example, through centralization of some functions, advancement of blood regulation, and implementation of quality systems at blood establishments. However, fractionators can accept pooling of plasma volumes from multiple countries in a region when the countries have common quality standards and the regulators mutually agree on acceptance criteria for plasma and final products.

The way forward from the guidance provided in the foundational WHO documents and the knowledge shared during the workshop is to launch practical pilot projects based on a stepwise approach in line with recent WHO guidance and available plasma resources (Table 1) [1]. In a country with severe shortages of plasma proteins, a pilot project for local production of viral-inactivated cryoprecipitate is an option. Other countries may additionally benefit from small-scale production of Igs. Pilot projects for the local production of small-scale plasma protein products can simultaneously be pursued in multiple countries with consideration of local conditions and overall lessons learned. Successful pilot programmes can lead to expansion through replication of strategies that have worked. In yet other countries, pilot projects for plasma fractionation comparable to the Achilles Project in Indonesia and South Africa may be feasible. To make these pilot projects possible, the local situation should be supportive. First, the pilot project needs a person who is trusted in the local environment and has good connections with key local and international stakeholders. Support from stakeholder organizations is needed, including the scientific and medical communities. In all countries, including high-income countries, development of fractionation is a gradual and stepwise process. Hence, the appropriate time to begin considering small-scale local plasma processing and/or contract fractionation is when a country identifies its need for PDMPs.

In conclusion, practical solutions are needed to resolve problems in LMICs where patients with haemophilia and PIDs are not diagnosed and plasma protein products are unavailable or unaffordable. There are many hurdles, but action is urgently needed. The continued

collaboration of organizations that made the workshop possible (WHO, ISBT, WFH, IPOPI and FIODS) can be a great help in supporting stepwise improvements for patients who depend on treatments with plasma proteins. At all stages of such an effort, government support is mandatory and crucial.

ACKNOWLEDGEMENTS

T.B., J.E., J.-C.F. and M.S. (members of the organizing committee of the Global Blood Safety Working Party of the ISBT) were the organizers of the workshop, contributed to the writing of this report, and approved the final version. The authors gratefully acknowledge the inputs of all moderators and speakers, discussants and attendees of the workshop, and thank the ISBT Central Office staff for the outstanding support in its organization. Presentations at the workshop are available on the Global Blood Safety ISBT webpage: <https://www.isbtweb.org/working-parties/global-blood-safety/workshop-recordings>

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Thierry Burnouf  <https://orcid.org/0000-0002-0507-9243>

Jay Epstein  <https://orcid.org/0000-0003-2293-9062>

Martin Smid  <https://orcid.org/0000-0001-8487-0043>

REFERENCES

1. WHO Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma [cited 2021 Dec 24]. Available from: <https://apps.who.int/iris/handle/10665/340171>
2. WHO Guidance on centralization of blood donation testing and processing [cited 2021 Dec 24]. Available from: <https://www.who.int/publications-detail-redirect/9789240020825>

How to cite this article: Burnouf T, Epstein J, Faber J-C, 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.