Plasma is a strategic resource

Paul F.W. Strengers[1,2] and Harvey G. Klein[3]

Plasma-derived medicinal products (PDMPs) such as immunoglobulins and clotting factors are listed by the World Health Organization as essential medicines. These and other PDMPs are crucial for the prophylaxis and treatment of patients with bleeding disorders, immune deficiencies, autoimmune and inflammatory diseases, and a variety of congenital deficiency disorders. While changes in clinical practice in developed countries have reduced the need for red blood cell transfusions thereby significantly reducing the collection volumes of whole blood and recovered plasma suitable for fractionation, the need for PDMPs worldwide continues to increase. The majority of plasma supplies for the manufacture of PDMPs is met by the US commercial plasma industry. However, geographic imbalance in the collection of plasma raises concerns that local disruptions of plasma supplies could result in regional and global shortages of essential PDMPs. Plasma, which fits the definition of a strategic resource, that is, "an economically important raw material which is subject to a higher risk of supply interruption," should be considered a strategic resource comparable to energy and drinking water. Plasma collections should be increased outside the United States, including in low- and middle-income countries. The need for capacity building in these countries is an essential part to strengthen quality plasma collection. This will require changes in national and regional policies. We advocate the need for the restoration of an equitable balance of the international plasma supply to reduce the risk of supply shortages worldwide. Strategic independence of plasma should be endorsed on a global level.

Plasma is a vital fluid. Comprising more than half of total blood volume, blood plasma plays a critical role in the maintenance of intravascular volume as well as the circulation and homeostasis of proteins, electrolytes, and hormones. Plasma for transfusion and such plasma-derived medicinal products (PDMPs) as clotting factor concentrates FVIII and F IX, immunoglobulins, and hyperimmune globulins (rabies, hepatitis B, RhIG) are included on the World Health Organization (WHO) Model List of Essential Medicines (EML).[1] EML listing is crucial for low- and middle-income countries, since governments often consult the EML to guide allocation of scarce healthcare resources.[2] Importantly, a recently published randomized multicenter clinical study reported that recombinant FVIII is almost twice as likely as plasma-derived FVIII containing von Willebrand factor to induce anti-FVIII–inhibiting antibodies in previously untreated severe hemophilia A patients arguing for the continued availability of plasma-derived FVIII as a therapeutic choice.[3,4] After separation of whole blood into components (red blood cells [RBCs], platelets, and plasma for transfusion), developed countries collect more plasma than is needed for transfusion and send the balance of recovered plasma for further manufacture of PDMPs.

ABBREVIATIONS: EML = List of Essential Medicines; PDMP(s) = plasma-derived medicinal product(s).

From [1]Sanquin Plasma Products and the [2]International Plasma Fractionation Association, Amsterdam, The Netherlands; and the [3]Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland.

Address reprint requests to: Paul F.W. Strengers, MD, Sanquin Plasma Products, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands; e-mail: p.strengers@sanquin.nl.

The opinions expressed are those of the authors and do not represent the positions of the National Institutes of Health, the Department of Health and Human Services, or the US Government.

Received for publication August 6, 2016; revision received September 19, 2016; and accepted September 21, 2016.

doi:10.1111/trf.13913

© 2016 AABB

TRANSFUSION 2016;56;3133–3137

However, plasma prepared in developing countries is frequently unsuitable for fractionation and commonly discarded.[5] PDMPs must be imported. In developed countries, PDMPs are generally available, albeit at considerable cost due to the high cost of plasma and the degree of sophistication of the plasma fractionation process to ensure quality and safety. Changes in medical practice such as minimally invasive surgery and restrictive transfusion policies have resulted in a marked decline in RBC transfusion.[6] These changes also affect the plasma supply. Decreased RBC use has resulted in fewer whole blood collections and a consequent decline in supply of recovered plasma for fractionation. In the latest national survey in the United States, some 4.3 million units of plasma (approx. 1 million liters) were collected from volunteer donors, and 3.6 million units were transfused, 26.8% fewer units produced than in the previous survey.[7] The NHS Blood and Transplant Service reports that in the United Kingdom, RBC use has fallen from 43 units per 1000 population in 1999 to 2000 to 31.5 units in 2014.[8] Other European countries have experienced similar reductions. Decreasing volunteer plasma supply raises a critical issue for developed and developing countries alike: the vulnerability of the global plasma supply needed for preparing PDMPs.

PDMPs AND THE IMBALANCE IN PLASMA SUPPLY

Plasma for producing PDMPs derives from two sources: plasma recovered from the separation of whole blood collections into components (recovered plasma) and plasma obtained by plasmapheresis (apheresis plasma or source plasma). Most source plasma comes from the commercial plasma industry. Even as whole blood collections and the volume of recovered plasma suitable for fractionation decline, global needs for PDMPs are increasing.[9] The World Federation of Hemophilia estimates that 400,000 people are living with hemophilia and only 25% receive adequate treatment. An estimated 1 in 2500 Americans has inherited α-1 antitrypsin deficiency, and as many as 3% of patients diagnosed with chronic obstructive pulmonary disease may have undetected α-1 antitrypsin deficiency and be eligible for α-1 antitrypsin augmentation therapy.[10] The International Patient Organization for Primary Immune Deficiencies calculates that 70% of patients with primary immune deficiency lack treatment due to inadequate programs and insufficient immunoglobulin supplies.[11] Some developing countries put off diagnostic screening for these disorders since they will be unable to provide treatment to patients so identified.

Whereas whole blood collections in developed countries are declining, collections in low- and middle-income countries are growing. The US Centers for Disease Control and Prevention reports that annual blood collections by national programs in 14 African countries increased 19%, from 1,856,334 units in 2011 to 2,203,190 units in 2014 and by as much as 147% in Ethiopia.[12] Continued collections growth in low-income countries is likely, since the rate of collections (an estimated 3.9 units/1000 population) remains well below WHO's minimum target for adequacy (10 units/1000) and far below the approximately 30 units/1000 population in developed countries.[13] Unfortunately most of the growth in whole blood collections will not translate into additional recovered plasma and PDMPs; most of the plasma, often prepared from donors inadequately screened and in facilities lacking Good Manufacturing Practices and a lack of freezing and storage capacity of plasma, does not meet quality criteria for fractionation and is discarded.

In contrast to the diminishing supply of recovered plasma, in developed countries source plasma collection has increased considerably (Fig. 1). The majority of this increase comes from the US commercial plasma industry, which historically has dominated international plasma markets. This plasma provides not only for the PDMP needs of US patients but also for international export. The Plasma Protein Therapeutics Association reports that the volume of source plasma has increased from 11,000,000 L in 2004 to 34,000,000 L in 2014.[14] Source plasma was collected by 552 commercial plasmapheresis centers of which 80% are located in the United States. Sixty percent of this plasma originates from US paid donors, the majority contribution to the worldwide supply (Fig. 1). Other regions contribute considerably less (Fig. 2). Although US source plasma is crucial for meeting increasing international needs, reliance on any single country or region to supply the bulk of the world's plasma raises significant concerns. Any disruption in supply could devastate vulnerable patient populations such as those with coagulation or immune deficiency disorders. Patients in low-income countries, for whom recombinant protein preparations are not a practical alternative due to high cost, shortages, or lack of marketing interest of suppliers, are at particular risk.

POTENTIAL THREATS TO AN IMBALANCED PLASMA SUPPLY

Several situations might lead to plasma supply interruptions. Regional plasma shortages may arise from the emergence of unexpected transfusion-transmissible infections, economic and political factors, military conflicts, commercial consolidation, changes in demand, and the flow of medicines from countries with lower prices to countries with higher prices. The appearance of human immunodeficiency virus in the 1980s resulted in an historic interruption of blood services. Detection of a novel transfusion-transmissible pathogen in the United Kingdom in 1996, a prion causing variant Creutzfeldt-Jakob

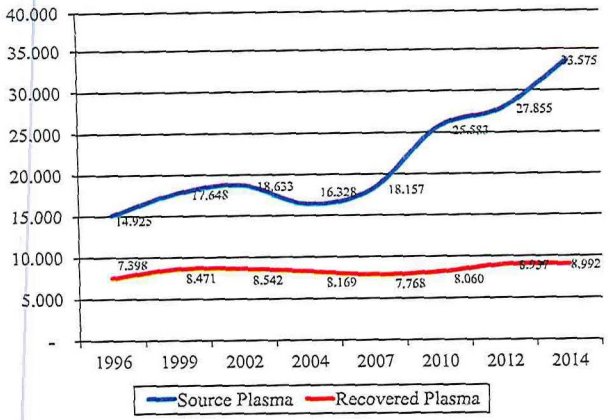


Fig. 1. Worldwide plasma processed (×1000 L) by collection source (1996-2014), commercial companies and nonprofit organizations. Total in 2014: 36,792,000 L. Source with permission: Marketing Research Bureau, Inc., Orange, CT.

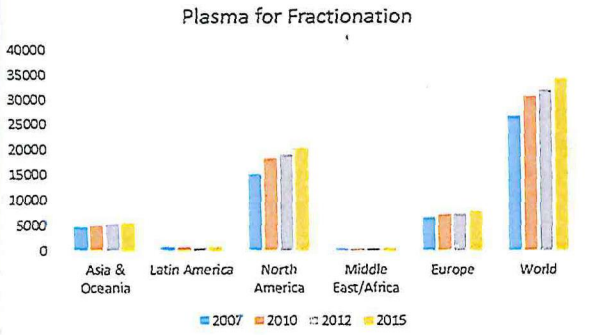


Fig. 2. Global plasma collection volume (×1000 L) by geographic region (2007-2015). Source with permission: Marketing Research Bureau, Inc., Orange, CT.

disease, resulted in termination of all plasma collections in the United Kingdom and Ireland and necessitated plasma importation from the United States to meet UK patient needs.[15] The US Food and Drug Administration acted quickly and prudently to protect US patients by prohibiting US distribution of all PDMPs manufactured from non-US plasma, further amplifying the imbalance in global plasma supplies. Despite modern safety measures and international surveillance for emerging blood-borne pathogens, the blood supply of the French island of La Réunion was interrupted during the past decade by the unexpected appearance of Chikungunya virus as were blood collections more recently in the US territory of Puerto Rico by epidemics of Dengue and Zika viruses. Future epidemics are unpredictable but highly likely.[16] Should some novel transmissible agent appear in the United States, a prion or a virus resistant to inactivation or removal technology used in the plasma fractionation industry, US plasma collections could face a serious threat with disastrous consequences for global supplies of plasma.

Changes in market conditions have also resulted in regional and spot shortages of plasma and PDMPs. National health services that depend on importation become vulnerable to regulatory actions such as recalls and market withdrawals. Such actions have occurred with several PDMPs, most recently with intravenous immunoglobulin. Imbalance in supply of a strategic raw material may create other serious risks such as unwanted price dependency, disruptions in supply due to natural disasters, and flow of medicines from countries where prices are lower to countries with higher prices.

PLASMA AS A STRATEGIC RESOURCE

The European Union (EU) defines strategic resources as "economically important raw materials which are subject to a higher risk of supply interruption."[17] What makes these materials critical for a region or a country is insufficient domestic production and/or inability to guarantee supply through importation. National industries can become dependent on importation, particularly during periods of expanding market demand. The imbalance in the supply of strategically vital energy resources resulted in the worldwide oil crisis in the 1970s and in the Russian threat to the supply of gas to Europe in 2014.[18] Clean and safe drinking water is so scarce that nearly 1 billion people in the developing world are at risk from a lack of access.[19] Worldwide consensus and advocacy exist for special attention to and management of strategic resources.[20]

Plasma fits the definition of a "strategic resource." There is need for improved and equitable balance of the international plasma supply to reduce the risk of supply shortages worldwide. We propose that blood and plasma be considered strategic resources comparable to energy, water, and other products and services deemed important for national or regional independence. The aim is to highlight the importance of balanced and diverse collection and preparation and to minimize the risk of shortages of plasma and essential PDMPs upon which patients' lives depend. Measures should be taken by governments or regulatory bodies to mitigate the existing risk of dependency on the supply of plasma from any single country or region. The United States currently enjoys an enviable position of "strategic independence" through its collection of plasma in excess of domestic needs. However through exclusion of plasma from non-US sources, the United States, too, is vulnerable to potentially catastrophic supply failure in the event of new emerging transfusion-transmissible infections.

MOVING FROM A MARKET-DRIVEN TO A PUBLIC HEALTH APPROACH

The World Health Assembly resolution WHA63.12 directs the WHO to promote self-sufficiency in the supply of safe blood components using voluntary blood donations whenever possible and advocates "security of supply" as an important goal to prevent blood shortages and to meet national transfusion requirements.[21] Self-sufficiency assures that a nation's patient needs for safe blood products are met in a timely manner, that patients have equitable access to transfusion services and blood products, and that these products are obtained ideally from donors of national or regional origin. However, placing medicines on the EML does not guarantee timely patient access, but represents only a first step in a policy to assure availability of these medicines.[22] The current European Directive 2002/98/EC on human blood and blood components directs that "Member States should take measures to promote Community self-sufficiency in human blood or blood components and to encourage voluntary unpaid donations of blood and blood components."[23] In the EU, however, some countries still have not reached self-sufficiency in immunoglobulin and albumin, such as Greece, Italy, and Spain. The US National Blood Policy of 1973 endorsed four principles: adequate supply; high quality; access by everyone in need regardless of economic status; and efficiency in collection, processing, storage, and utilization.[24] Although these principles form the basis of blood and plasma supply policies in the EU and in the United States, the EU and United States regulate blood components primarily to assure safety and efficacy, but have taken few steps to assure access and availability.

We believe that these goals will be best achieved through increased plasma collection in countries and regions outside the United States including in low- and medium-income countries where an estimated 9.3 million liters of plasma are discarded each year.[5] Developed countries must first recognize and understand the risks inherent in exclusively market-driven strategies. The status of plasma should be elevated to that of a strategic resource with appropriate sector supervision, governance, control, and sustainable management. National and regional policies should be developed to increase the contribution of non-US countries to the worldwide plasma supply and to regulate the export of plasma during periods of threatened shortage. Realization of these objectives will require the cooperation of stakeholders at national and international levels of policy making and regulation.

The global supply of plasma and PDMPs is and will remain critically dependent on US supply. Strategic independence does not imply a need to reduce this contribution. Market-driven and public health approaches need not be mutually exclusive. Blood and plasma are highly valued by the general public and the prevention of potential shortages should become part of national political agendas. Blood for transfusion is already managed by these principles in most countries. If national authorities would endorse the concepts of strategic independence for plasma, the supply of the "raw material" for manufacturing PDMPs would become better secured for their patients.

Strategic independence poses special problems for developing countries, where annually millions of liters of plasma are discarded as unfit for fractionation, a loss that is both economically and morally inexcusable. Improving this condition requires investment to assure that plasma from these regions meets standards of quality and safety accepted by international regulations. Suitable plasma could then be manufactured into PDMPs by contract fractionation where excess capacity exists and returned to the collecting regions. High-income countries have the resources, experience, and capability to manage blood and plasma as strategic resources. What is lacking is the political will. Low- and middle-income countries need assistance with resources and training to develop blood systems capable of preparing safe, high-quality blood components. A primary objective of WHO's blood program has been to provide support to these countries to enable them to prepare recovered plasma suitable for fractionation.[25] Efforts to establish blood and plasma as strategic resources should better assure access to essential medicines worldwide. Such efforts must be pursued.

ACKNOWLEDGMENTS

The authors like to thank Dr Bob Perry and Mr Patrick Robert for their valuable comments.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

1. Klein HG. Should blood be an essential medicine? N Engl J Med 2013;368:199-201.
2. Essential medicines and health products [Internet]. 2016 [cited 2016 Nov 5]. Available from: http://www.who.int/medicines/publications/.
3. Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of Factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med 2016;374:2054-64.
4. Burnouf T, Strengers PF. Risks of inhibitors to recombinant Factor VIII: a quarter of a century to reach the conclusion. J Thromb Haemost 2016;14:2073-74.
5. Improving access to safe blood products through local production and technology transfer in blood establishment

[Internet]. Geneva: World Health Organization; 2015 [cited 2016 Nov 5]. Available from: http://www.who.int/phi/publications/blood-prods_technology_transfer.pdf.
6. Murphy MF, Goodnough LT. The scientific basis for patient blood management. Transfus Clin Biol 2015;22: 90-6.
7. Chung KW, Basavaraju SV, Mu Y, et al. Declining blood collection and utilization in the United States. Transfusion 2016;56:2184-92.
8. National survey red cell use [Internet]. London: NHS Blood and Transplant [cited 2016 nov 5]. Available from: http://hospital.blood.co.uk/media/27581/anonymous-nrcs.pdf.
9. Mahony BO, Turner A. The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang 2010; 98: 447-50.
10. Stoller JK, Aboussouan LS. A review of α1-antitrypsin deficiency. Am J Respir Crit Care Med 2012;185:246-59.
11. PID principles of care implementation package [Internet]. Estoril: International Patient Organisation for Primary Immunodeficiencies; 2011 [cited 2016 Nov 5]. Available from: http://www.ipopi.org/index.php?page=others.
12. Chevalier MS, Kuehnert M, Basavaraju SV, et al. Progress toward strengthening national blood transfusion services — 14 countries, 2011-2014. MMWR Morb Mortal Wkly Rep 2016;65:115-9.
13. Blood safety and availability [Internet]. Geneva: World Health Organization; 2015 [cited 2016 Nov 5]. Available from: http://www.who.int/mediacentre/factsheets/fs279/en/.
14. United States total collections 2006-2015 [Internet]. Annapolis (MD): Plasma Protein Therapeutics Association; 2016 May [cited 2016 Nov 5]. Available from: http://www.pptaglobal.org/images/Data/Plasma_Collection/Total_Yearly_Collections_2006_-_2015.pdf.
15. Measures currently in place in the UK to reduce the potential risk of vCJD transmission via blood [Internet]. London: Department of Health; 2013 Apr 29 [cited 2016 Nov 5]. Available from: https://www.gov.uk/government/news/measures-currently-in-place-in-the-uk-to-reduce-the-potential-risk-of-vcjd-transmission-via-blood.
16. Glynn SA, Busch MP, Dodd RY, et al. Emerging infectious agents and the nation's blood supply: responding to potential threats in the 21st century. Transfusion 2013;53:438-54.
17. A review of national resource strategies and research [Internet]. London: Department for Environment, Food and Rural Affairs; 2012 Mar [cited 2016 Nov 5]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/69526/pb13722-national-resource-strategies-review.pdf.
18. Oil embargo, 1973-1974 [Internet]. Washington (DC): Office of the Historian, Bureau of Public Affairs, U.S. Department of State [cited 2016 Nov 5]. Available from: https://history.state.gov/milestones/1969-1976/oil-embargo.
19. Water scarcity & the importance of water [Internet]. Concord (NH): The Water Project; 2016 [cited 2016 Nov 5]. Available from: http://thewaterproject.org/water_scarcity.asp.
20. Essential medicines and health products information portal [Internet]. Geneva: World Health Organization; 2016 [cited 2016 Nov 5]. Available from: http://www.who.int/medicinedocs/en/d/Js19998en/.
21. Self-sufficiency in blood and blood products based on voluntary non-remunerated blood and plasma donations [Internet]. Geneva: World Health Organization; 2011 [cited 2013 Aug 12]. Available from: www.who.int/bloodsafety/transfusion_services/self_sufficiency/en/index.html.
22. Gray AL, Wirtz VJ, 't Hoen EF, et al. Essential medicines are still essential. Lancet 2015;386:1601-3.
23. 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. Brussels: European Union; 2003 Aug 2 [cited 2013 Aug 12]. Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF.
24. Hutt P, Merrill, R. Food and Drug Law: Cases and Materials. Westbury, New York: The Foundation Press, Inc., 1991.
25. WHO Expert Committee on Biological Standardization. Sixty-third report. WHO technical report series 980. Geneva: WHO Press; 2015, p. 21-5.

CORRIGENDUM

Strengers PFW and Klein HG Plasma is a strategic resource. Trans 2016; 56(12): 3133-3137

The authors wish to correct the following data. The numbers cited in the figures and body of the manuscript for plasma volumes represent plasma collections rather than plasma volumes which are approximately 18% lower for the year 2015. This change does not affect the conclusions of the paper. We thank Mr. Joshua Penrod of PPTA for bringing this to our attention.

doi:10.1111/trf.14222
© 2017 AABB