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An Economic Analysis of Global Policy Proposals to Prohibit Compensation of Blood Plasma Donors

HENRY G. GRABOWSKI and RICHARD L. MANNING

ABSTRACT *Human blood plasma and its derivative therapies have been used therapeutically for more than 50 years, after first being widely used to treat injuries during World War II. In certain countries, manufacturers of these therapies – known as plasma-derived medicinal products (PDMPs) – compensate plasma donors, raising healthcare and ethical concerns among some parties. In particular, the World Health Organization has taken a strong advocacy position that compensation for blood donations should be eliminated worldwide. This review evaluates the key economic factors underlying the supply and demand for PDMPs and the evidence pointing to the policy options that are most likely to maintain a reliable supply of life-sustaining therapies. It concludes that compensated plasma donation is important for maintaining adequate and consistent supplies of plasma and limits the risk of under-treatment for the foreseeable future.*

Keywords: Economics; Compensation; Blood Plasma; Plasma-Derived Medicinal Products; Plasma Donation; Plasmapheresis.

JEL classifications: I11; I18; L38; L65; O38.

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Introduction

Human blood (“whole blood”) contains four components: red blood cells, white blood cells, platelets, and plasma. Donated whole blood has been used for blood transfusions since the 1800s to treat individuals with severe blood loss and other chronic bleeding conditions (ARC 2014). In addition to such transfusions, each component of blood can be used individually to treat specific medical conditions.

Due to changes in surgical procedures that limit blood loss and changing standards of medical practice with regard to whole-blood transfusions, the utilization of blood for transfusions has declined in the United States and other developed countries, and is anticipated to continue to decline in the future (Wald 2014). With these changes, the demand for whole-blood donation will undoubtedly follow a similar course.

Historically in the United States and other developed countries, it was not uncommon for whole-blood donors to receive financial compensation. However, today in the United States, such compensation is essentially nonexistent, and a large share of whole blood is collected through nonprofit organizations that sometimes offer prizes and nonmonetary forms of compensation (FDA 2011).¹

Human blood plasma contains nutrients, electrolytes, albumin, clotting factors, hormones, and other components. Plasma-derived medical products (PDMPs) have been used therapeutically for more than 50 years, after first being used on a widespread basis to treat injuries during World War II (WHO 2013b). In contrast to whole blood, PDMP use has expanded substantially over the past several years, and is likely to continue to grow. PDMPs and whole blood play very different roles in medical care, and economically they have the characteristics of distinct, albeit related, markets.

PDMPs are predominantly manufactured from plasma that has been collected by commercial enterprises that compensate plasma donors (typically small amounts). The process of plasma collection differs substantially from that of whole-blood collection, and imposes substantially greater burdens on donors.

A seminal study by Titmuss (1970) advocated prohibiting compensation for blood products on the grounds that it would crowd out voluntary donors, lead to lower blood quality, and violate basic ethical principles. In 1975, the World Health Assembly passed a resolution urging countries to develop blood collection and utilization systems based on voluntary donations.

Controversy around compensating blood and plasma donors intensified during the 1980s as donated blood and plasma became sources of transmission of HIV, hepatitis C, and hepatitis B. During this time frame, serious concern arose that compensation (and/or pressure to engage in familial donation) might keep infected people from accurately disclosing health conditions or behaviors that would lead their blood or plasma to be unsuitable for transfusion or manufacture into PDMPs. However, as the transmission mechanism for HIV became more fully understood, processes were developed to improve the screening of donors, test donated blood products, and deactivate or remove viruses from donated blood and plasma. These new processes and techniques have left the blood and PDMP supply in the United

States and most developed countries exceptionally safe (GAO 1997; Skinner, Hoppe, Tachdjian, Crone, and Youngner 2016).

In the face of concerns about the safety and sustainability of the global whole-blood and PDMP supply, and motivated by certain ethical principles, the World Health Organization (WHO) has taken a strong advocacy position over time that compensation for blood and blood-component donations should be eliminated worldwide. This position applies to donations of both whole blood and of plasma for manufacture into PDMPs (WHO 2013a, 2013b). As of 2013, this position had gained the support of Ministries of Health in 51 countries from all regions of the world, and in December 2014, the provincial government of Ontario, Canada, enacted legislation prohibiting compensation for blood or plasma donation (Legislative Assembly of Ontario 2014), joining many other countries around the world. Only the United States and a few European countries, principally Germany and the Czech Republic, currently permit compensation for plasma donation. These countries supply a large share of the world's supply of PDMPs.

In view of the important role PDMPs play in the treatment of critical illnesses and the potential disruption in the PDMP market if compensated donation were severely restricted, it seems appropriate to evaluate the underlying economics of the market for PDMPs and the role that compensation plays in the global supply of plasma and PDMPs. A companion paper addresses the ethical principles associated with compensation of plasma donors (Skinner, Hoppe, Tachdjian, Crone, and Youngner 2016).

Demand- and Supply-Side Factors Affecting Blood Plasma Availability

The Demand for Plasma: A Unique and Growing Need

PDMPs provide important benefits to patients. More than 200 different therapeutic uses have been identified for these products, including replacing blood lost during surgery or trauma, treating immunodeficiencies and autoimmunity, preventing and treating infections, and controlling bleeding in congenital and acquired coagulation factor deficiencies (MRB 2015). Table 1 provides a partial list of common uses of the most widely used PDMPs. Many of the conditions treated with these products are rare and chronic. Patients often require life-long treatment, and often there are no clinically equivalent therapies (NHS 2015; Scheinfeld 2015).

Although 20 of the 1000 or more proteins in human plasma are currently used for therapy, three products drive overall demand: immunoglobulin, albumin, and factor VIII (MRB 2014). Figure 1 illustrates the composition of global plasma demand, showing that in 2012, the three largest-selling proteins accounted for 48% (or 53%, including specific immunoglobulins), 13%, and 11% of sales, respectively.

Neither the level nor the composition of demand for PDMPs has been static over time. As new PDMPs have been developed and their use has expanded, the demand for plasma has grown. As illustrated in Figure 2, albumin drove early plasma utilization as a replacement for blood and proteins lost through burns and trauma. Plasma-derived factor VIII, which is used as a clotting factor replacement therapy for the treatment of hemophilia A, became the dominant product in the 1980s and 1990s. As recombinant factor VIII

Table 1. Selected conditions using PDMP

Plasma Component	Condition	Estimated Prevalence
Albumin	Burns	
	Cardiopulmonary bypass	
Coagulation factors	Cirrhosis complications	
	Major surgery	
	Shock	
	Trauma	
	Plasma exchange treatments	
	Acute Respiratory Distress Syndrome	
	Bleeding/trauma	
	Hemophilia A (factor VIII deficiency)	1 in 10,000
	Hemophilia B (factor IX deficiency)	1 in 25,000
	Liver disease	
Immunoglobulins	Other factor deficiencies (factor II, V, VII, X, XI, XIII and fibrinogen)	Between 0.33 in 1000.000 to 1 in 10,000,000
	Anticoagulant overdose	
	Von Willebrand Disease	1.25 million (US), 6.9 million (worldwide)
	Chronic Inflammatory Demyelinating Polyneuropathy	1.5–3.6 per million people
	Acute Inflammatory Demyelinating Polyneuropathy (Guillain–Barre)	1–2 per 100,000
	B-Cell Chronic Lymphocytic Leukemia	1 in 200 (US, 2014)
	Multiple Myeloma	1 in 143 (US)
	Cytomegalovirus	1 in 1000 births (US, 2011)
	Hepatitis A, B	
	Idiopathic thrombocytopenia purpura	9.5 per 100,000
	Kawasaki Disease	67.3 per 100,000 children under 5 (incidence)
	Multifocal Motor Neuropathy	0.3 per 100,000 (Japan, 2012)
	Organ and bone-marrow transplants	
	Pediatric HIV	
	Primary Immunodeficiency	250,000 (US)
	Rabies	
	Rh disease	6 in 1000 (US)
	Tetanus	
	Varicella	
Protease inhibitors	AAT Deficiency	100,000 (US)
	AT-III Deficiency Congenital and Acquired	1 in 2000 to 1 in 20,000 (Congenital)
	Hereditary angioedema	1 per 50,000-150,000

Sources: ACS (2015, 2016); CDC (2009, 2013); Frank (2015); GBS-CIDP Foundation International (n.d.); Hirsch, Piovela, and Pini (1989); IDF (n.d.); Matsui (2012); Moise (2008); and Skinner (2012).

became available and as numerous immune deficiency treatments involving immunoglobulin have been developed, immunoglobulin has become the primary demand driver. Moreover, recent introductions of immunoglobulin therapy in areas such as neurology, oncology, dermatology, and rheumatology suggest that immunoglobulin use will continue to grow (Robert 2009, 359–360).

As mentioned, blood collections in the United States have fallen in recent years, declining from 17.3 million units in 2008 to 15.7 million units in 2011

Figure 1. Shares of worldwide PDMP sales, 2012.

Source: MRB (2014).

Figure 2. Worldwide plasma utilization: albumin, factor VIII, and immunoglobulin (1975–2014).

Source: MRB (2014).

Figure 3. United States: whole-blood and plasma collections.

Sources: HHS (2011b) and PPTA (2015b, 7).

(HHS 2011b). In Canada, demand for red blood cells decreased 1.9% from 2011–2012 to 2012–2013, and Héma-Québec reported that red blood cell deliveries to hospitals declined 5.6% between 2012–2013 and 2013–2014 (Canadian Blood Services 2014, 17; Héma-Québec 2014). A declining supply of whole blood as a potential source of plasma for manufacture of PDMPs presents a clear challenge in the face of growing demand for these medicines.

Demand for PDMPs Likely to Grow

Utilization of PDMPs will grow for three primary reasons. First, current *per capita* use is low in low-income countries relative to middle- and high-income countries (WHO 2013b), suggesting that as incomes grow over time, there will be a natural tendency for medical care to improve and for more patients to receive appropriate treatment with PDMPs. The WHO states that “In view of improving access to medical care in the developing world, particularly in emerging economies, the trend to increased use is likely to continue for the foreseeable future” (WHO 2013b, 33).

Demand for PDMPs will likely grow in developed countries as diagnostic capabilities improve and as PDMPs are more widely prescribed to under-treated or under-diagnosed patient populations. For example, levels of factor VIII and immunoglobulin use across Europe suggest that some Europeans with hemophilia, primary immunodeficiency, and other immunoglobulin-treatable conditions receive less treatment than is appropriate based on clinical models

(PPTA 2015a), suggesting room for expanded use. Similarly, Stonebraker, Brooker, Amand, Farrugia, and Srivastava (2010) and Stonebraker, Bolton Maggs, Brooker, Farrugia, and Srivastava (2011) find that factor VIII and factor IX were more commonly used in higher-income countries but that their use varied considerably across countries – suggesting potential underutilization and future growth in both developed and developing countries.

The potentially most important source of increased demand for PDMPs lies in the discovery and development of new uses for plasma proteins. Many such new treatments are the subject of ongoing R&D. Table 2 highlights selected

Table 2. Selected PDMP indications under development

Protein	Disease	Estimated Incidence (US Unless Otherwise Noted)
Transferrin/ Apo-transferrin	Congenital deficiency	10–20 (worldwide)
	β Thalassemia	1000
	Sickle-cell anemia	70,000–90,000
Ceruloplasmin	Congenital deficiency (aceruloplasminemia)	315
	Wilson disease	3000–12,000
	Menke Disease	1200–2700
Factor H	aHUS (atypical Hemolytic-uremic syndrome)	15,000–60,000
	Dry Age-Related Macular Degeneration	12,700,000
	Wet Age-Related Macular Degeneration	1600,000
Factor V	Congenital factor V deficiency	163
	Congenital factor V/factor VIII deficiency	100–300
Fibronectin	Wound healing	
	Cancer (leukemia)	44,600
Haptoglobin	Diabetic Neuropathy	
	Coronary artery disease in type 1 diabetes	25,000–50,000
	Crohn's disease	400,000–600,000 (North America)
High Density Lipoproteins	Acute coronary syndrome	1.255 million new or recurrent coronary attacks and 450,000 deaths annually
	Congenital HDL deficiency (Tangler disease)	50 (worldwide)
IgA	Selective IgA deficiency	500,000–1000,000
	Celiac disease with IgA deficiency	4000
Plasmin	Acute peripheral arterial occlusion	100,000
	Ischemic stroke	360,000
Plasminogen	Ligneous conjunctivitis	210
Protein S	Congenital Protein S deficiency	100,000
	Acquired protein S deficiency	3600–7200 with ischemic stroke and DVT

Source: Robert (2013).

new therapeutic uses currently under development, some of which could be appropriate for large patient populations.

One particularly intriguing possibility lies in Alzheimer's disease. While success against this disease has been hard to come by, and results are mixed, studies have suggested that intravenous immunoglobulin (IVIG) therapy may benefit patients with Alzheimer's disease (Relkin 2014; Villeda et al., 2014; Weill Cornell Medical College 2013).² One market research firm suggests that the annual growth rate in demand for IVIG would increase from approximately 6% to 12% per year if IVIG were approved to treat Alzheimer's, and that more than 50,000 Alzheimer's patients could be treated during the first five years after approval (Robert 2011). In addition to trials involving IVIG, other approaches to Alzheimer's have targeted other PDMPs, such as albumin. One study under way is evaluating whether replacing an Alzheimer's patient's existing albumin with "new" albumin can reduce the concentration of beta amyloid plaques in the patient's system and thus reduce the disease's main symptoms (Boada, Ramos-Fernández, Guivernau, Muñoz, Costa, Ortiz, Jorquera, Núñez, Torres, and Páez 2014).

Another potentially important demand shock for immune globulin products is the recent spread of the Zika virus and other emerging diseases. Although the most publicized likely impact of Zika infection is microcephaly – the underdevelopment of the fetal brain – another emerging concern is the onset of Guillain-Barre syndrome (GBS) following infection (Broutet, Krauer, Riesen, Khalakdina, Almiron, Aldighieri, Espinal, Low, and Dye 2016; Cao-Lormeau et al. 2016). GBS is an acute and debilitating neurological condition affecting adults and children. IVIG is a primary treatment for GBS (Willison, Jacobs, and van Doorn 2016), suggesting the potential for substantial increases in demand if the Zika virus continues to spread and its link to GBS is confirmed.³

Plasma Supply: Obtaining Plasma and Manufacturing PDMPs is Complex, Capital-Intensive, and Highly Regulated

Safely collecting suitable plasma, fractionating it into its component proteins, and manufacturing PDMPs is a complex process involving challenges and costs not generally found in the traditional pharmaceutical industry. The entire production process – from plasma collection to product formulation – must comply with FDA and other international health authority regulations for product licensure and facility inspection. This unique dual regulatory oversight of both starting material and final therapy results in a product for which the cost of goods accounts for approximately 63% of total costs, compared with 38% in the traditional pharmaceutical industry.⁴

The higher manufacturing cost percentages incurred by PDMP manufacturers are driven by the capital- and time-intensive plasma collection, testing, storage, and manufacturing processes that account for approximately 70% of total manufacturing costs (PPTA 2013). Further, PDMP manufacturers also implement numerous safeguards to maintain a consistent and safe supply of plasma (Curling, Goss, and Bertolini 2013; Penrod and Farrugia 2015).

The Role of Compensation in Global Supply and Trade of PDMPs

Approximately 85% of the 14.1 million liters of US-collected plasma intended for PDMP manufacture (typically referred to as source plasma) is obtained through plasmapheresis, which is the process of directly removing plasma from the donor's blood and returning the red blood cells to the donor. The remaining 15% of plasma (typically referred to as recovered plasma) is separated from whole blood after the donation is complete. In other middle- and high-income countries, which along with the United States collect the vast majority of plasma for fractionation, a high proportion of the total plasma collected is obtained through plasmapheresis (WHO 2013b, 26). Additionally, the percentage collected as source plasma worldwide has increased from 67% in 2004 to 76% in 2012 (MRB 2012).⁵

Plasmapheresis typically requires one to two hours to complete. A healthy donor can undergo the procedure as frequently as twice per week, although average donation frequency is much lower than this (Schreiber 2013). Regulations limit plasmapheresis to 625–800 mL, depending on donor weight, in the United States, and to 625 mL, regardless of weight, in most of Europe (Williams 2013, 9). Plasmapheresis donors are typically compensated approximately \$35 per donation in the United States, an amount that roughly corresponds to the median hourly wage (BLS 2016; CSL Plasma 2015).⁶ In contrast, the whole-blood donation process typically takes about 75 minutes to complete and yields only about 250–300 mL of recovered plasma. A healthy individual can also only donate whole blood once every two to three months (ARC 2015).

Countries that allow compensated donation tend to collect large shares of plasma as source plasma and tend to collect more plasma per person. In countries that permit some degree of compensated plasma donation, 76% of plasma is collected as source plasma, compared with 42% in countries without compensated donation (WHO 2013b). Data presented in Figure 4 show that the top three countries in terms of *per capita* plasma collections in 2011 all allowed compensated plasma donation. Of course, restrictions on compensation of donors are not the only difference across these countries. Most countries also place much more stringent restrictions on donation frequency and volume than the United States does (Council of the European Union 1998), which contributes to the lower *per capita* plasma levels observed outside the United States. Nevertheless, if the prohibition on compensating blood donors in upper- and middle-income countries were eliminated, and this increased *per capita* plasma donations to levels prevailing in Germany or the Czech Republic, this would have a large positive effect on global plasma supplies. Specifically, if all upper-middle- and high-income countries collected plasma at the same rate *per capita* as it was collected in the Czech Republic or Germany in 2011, supply could meet projected global demand for immunoglobulin over the next 20 years, assuming future demand growth at the rate of 4% per year, and it would further allow some cushion in supply capacity for new indications and demand shocks from emerging diseases.⁷

To get a sense of the potential impact of expanding compensated donation, we can look to trends in plasma collections in countries where compensation is practiced and where it is not. The European Committee on Blood Transfusion reports plasma collection data for 46 countries over the period from 2001 to

Figure 4. Plasma for fractionation by country.

Sources: Plasma volume data come from Council of Europe (Janssen, van Hoeven, and Rautmann, 2015) and the Marketing Research Bureau (PPTA, 2014, 35) for non-European countries. Plasma volume data are for 2011 with the following exceptions: the US, Japan, and China are from 2012; Canada from 2012/2013 and Brazil from 2010. Compensation status by country is from the Council of Europe supplemented with WHO data when the former is not available; compensation status information for Latvia and China is ambiguous.

2011. Eleven of these countries have a full series of data over this time period (Janssen, van Hoeven, and Rautmann 2015). Data for nine of these countries is presented in Figure 5.⁸ Two countries stand out in these data: the Czech Republic and Germany, both of which allow compensated plasma donation (Janssen, van Hoeven, and Rautmann 2015). Importantly, Germany's collections have increased steadily since 2005, and collections in the Czech Republic increased dramatically after compensation was introduced in 2007. Early in the decade covered here, the Czech Republic provided plasma at among the lowest rates in Europe. By the end of the decade it was providing plasma at more than double the rate *per capita* of most other European countries.⁹

International trade involving PDMP exports originating from a few countries currently exists because many countries do not have a sufficient domestic supply. Many countries purchase PDMPs on the global market that are produced largely from plasma collected from compensated donors. Specifically, 90% of the 28.7 million liters of plasma for fractionation collected worldwide in 2011 was collected in ten countries (WHO 2013b, 25).

Figure 5. Liters of plasma for fractionation per 1000 population.

Source: Janssen, van Hoeven, and Rautmann (2015).

A specific example of the importance of compensated donation in the international trade of PDMPs is Quebec, where, from 2013 to 2014, 85.5% of immunoglobulin consumed was produced from US-collected plasma (Canadian Blood Services 2014; Héma-Québec 2014, 10). It is interesting to note that Quebec prohibits compensated plasma donation within its borders and imports a large share of the PDMP needed for its population from the United States.

International trade in PDMPs helps meet needs that otherwise could not be met. However, the reliance on plasma from a small number of countries to supply the needs of most of the world raises some potential concerns. Among these concerns is the risk that a supply disruption of some sort in one of the major supplying countries could have widespread impacts on patients around the world. In addition, demand shocks for increased PDMPs associated with infectious disease epidemics such as that posed by the Zika outbreak or new uses of PDMPs for chronic conditions could produce difficult rationing decisions by manufacturers and policy makers. Although these risks do not appear imminent at the present time, they would arguably be diminished if plasma supply were more diversified across countries. Moreover, there is good reason to believe that the therapeutic value of PDMPs could be enhanced by a more diverse donor base, which would result in a greater supply of antibodies not typically present in plasma collected from donors in a small number of countries.

Compensated Donation versus Other Methods of Assuring Adequate Plasma Supply

As mentioned, the WHO has adopted a policy recommendation to eliminate compensated plasma collection (WHO 2013a). In view of the existing volumes of plasma that are collected through compensated donation, the implementation of such a restriction seems very likely to result in shortages of source plasma and to complicate the manufacture of PDMPs (most likely resulting in higher prices). Of course, one way to offset such shortages might be to boost plasma collections from non-compensated donors. It is far from clear how such efforts would be accomplished and how successful or efficient they would be.

A key driver of the reliability of compensated supply is the incentive provided to individual donors. Compensation provides an incentive for individuals to donate repeatedly and consistently at the same center or network of centers. Where donors are repeatedly seen in the same setting or within the same network, the health of repeat donors and the safety of their donations can be monitored.

Compensation motivates and remunerates individuals for spending the additional time needed to donate plasma. As mentioned, it may also be that compensation allows the production of higher-quality immunoglobulin products because it provides incentives for a wider range of individuals to donate plasma than might otherwise be the case. As such, the pool of donated plasma is more likely to contain important antibodies that are not present in everyone's blood.

Supply limitations resulting from restrictions on compensated donation could also negatively impact the research and development of new PDMPs for as-yet-untreated diseases. Conversely, new indications for existing PDMPs could lead to shortages that threaten the availability of treatment for those who currently rely on these products. Each of these likely outcomes from discouraging compensated plasma donation through legislation, regulation, or policy would raise significant concerns, as they would likely create an avoidable but real and detrimental impact on the lives of thousands of people.

Efforts to increase the supply of plasma from non-compensated donors by more actively recruiting donors and/or converting volunteer whole-blood donors to source plasma donors have been limited in scope and success. For example, in November 2013, Héma-Québec opened its first center focused on collecting plasma for fractionation "to deal with the challenges of recruiting donors and achieve a competitive cost for the collection of plasma" (Héma-Québec 2014, 10). Even if this effort reached its annual goal of collecting 10,000 liters of plasma for fractionation (approximately 2000 collections were made at the center in its first five months), Québec would have produced only 17.1% of needed immunoglobulins based on the volume of plasma collected and immunoglobulin demand in 2013–2014 (Héma-Québec 2014).

Other efforts to increase the use of plasma recovered from whole blood in developing countries (e.g., WHO's Achilles Project) or to convert whole-blood donors to source plasma donors (e.g., the recent initiative by BloodSource) have also experienced limited success and seem unlikely to achieve substantially different results in the near term (BloodSource 2015; Padilla 2009).

Indeed, significant obstacles exist to motivating sufficient numbers of non-compensated donors to replace the current volume of compensated plasma donation. Among these is the fact that whole-blood donations result in less plasma recovery and can only be done a few times per year. Hence, the number of voluntary whole-blood donors would have to be expanded significantly beyond the number that currently receives compensation for donating plasma to produce the same level of plasma supply. Although various nonmonetary strategies for recruiting whole-blood donors have been identified, it would likely be very costly to replace the current pool of compensated plasmapheresis donors either by expanding the number of whole-blood donors or by replacing compensated with non-compensated plasmapheresis donors, or some combination of these two strategies.

As an example of efforts to identify nonmonetary means of inducing blood donations, Glynn, Williams, Nass, Bethel, Kessler, Scott, Fridey, Kleinman, and Schreiber (2003) found that incentives most likely to encourage donation among American whole-blood donors included cholesterol screening, prostate-specific antigen screening, and blood credits. Of course, cholesterol and prostate-specific antigen screenings are not needed on a regular basis, suggesting that those would not likely be able to serve as consistent incentives for plasmapheresis donation. Such tests are also not free, so the type and degree of in-kind compensation necessary to encourage sufficient donations could end up being as or more costly than direct financial compensation.

It is important to note that studies of in-kind donation (Lacetera and Macis 2010; Goette and Stutzer 2008; Iajya, Lacetera, Macis, and Slonim 2013; Lacetera, Macis, and Slonim 2012) have not explored the cost of getting non-compensated donors to undergo the time-intensive plasmapheresis procedure consistently, so the applicability of even these studies is questionable. Whether and what type of “marketing” efforts would be adequate to entice a sufficient number of donors to donate plasma consistently without compensation is unknown.

Based on the patterns and trends we observe, it seems clear that compensated plasma donation through plasmapheresis is more likely to meet future needs than available alternatives. The obstacles to either expanding recovery of plasma from whole-blood donation or inducing sufficient non-compensated plasma donation to ensure an adequate and consistent supply of plasma seem very large.

Compensation Has Not Crowded Out Voluntary Donations

Critics of compensated donation hypothesize, referencing (Titmuss 1970), that allowing compensated donation “crowds out” or decreases the volume of non-compensated donation, a notion that has been disputed on economic welfare grounds (Arrow 1997, 1972; Solow 1971). Contrary to the hypothesis of Titmuss, the empirical literature suggests that the *total* supply of compensated and non-compensated blood donated appears to increase in the presence of compensation, so that non-compensated and compensated plasma donation structures can effectively coexist.

For example, in the Czech Republic, whole-blood donations *increased* substantially after compensated plasma donation was introduced in 2007, and

collections tended to increase *more* in regions with plasma donation centers (Beck 2011). Additionally, relying on aggregated WHO data, Png (2008) found that a 1% increase in incentivized (including direct compensation) blood donation was associated with a 0.55–0.71% decrease in non-compensated blood donation, suggesting a 0.45–0.29% *net increase* in supply. Finally, in 2011, collections of whole-blood units per capita and liters of plasma for fractionation per capita were positively correlated (correlation coefficient of 0.472) among European countries (Skinner, Hoppe, Tachdjian, Crone, and Youngner 2016).

Conclusion

The body of evidence surrounding the global supply trends of PDMPs clearly points to the fact that permitting compensated donation leads to a greater supply of PDMPs and reduces the likelihood of a serious public policy and ethical problem – patients being unable to obtain life-enhancing or life-sustaining treatment. Furthermore, by increasing potential donors' options and allowing them to decide how to donate, a compensated donation system expands options for those who prefer to be compensated, but it makes no one worse off. Those who prefer to donate without compensation can still do so (Arrow 1972).

Recent drug shortages in the United States have highlighted the plight of patients who rely on specialized medicines and revealed the vulnerability of the US healthcare system to supply disruptions (HHS 2011a; Stein 2011). There is also evidence of shortages involving certain plasma proteins (Farrugia, Evers, Falcou, Burnouf, Amorim, and Thomas 2009, 95; Robert 2008, 168).¹⁰ Expanding the use of compensated plasma donation would more likely prevent and mitigate similar shortages because compensated donation results in a greater total supply and provides a mechanism that can be used to motivate donations in response to unanticipated developments in demand or supply.

This review of the available evidence paired with economic theory indicates that compensated donation is a key element in ensuring an adequate and consistent supply of plasma for manufacture into medicinal products and avoiding PDMP shortages that, in and of themselves, raise serious policy concerns. In the present, compensated donation is more likely to ensure an increasing and reliable supply of PDMPs in the face of worldwide under-diagnosis and under-treatment. In the future, as new uses for plasma are developed and demand for whole blood continues to decline, compensation-based plasmapheresis offers the best hope of providing an adequate supply of PDMPs to meet demand. Moreover, if PDMPs are shown to be effective against debilitating diseases such as Alzheimer's, and if the threat of neurological conditions resulting from Zika infections grows, the demand for plasma and its derived products will accelerate rapidly. Restricting the available supply of PDMPs by suppressing compensated donation under such circumstances is almost certain to lead to price increases and shortages for key products, with many who could benefit from these products unable to obtain them.

Notes

1. However, in other countries and in lower-income countries in particular, whole-blood donations are often either compensated or “encouraged” from family members of the individual in need of a transfusion (WHO 2013b).
2. Although primary outcomes of a phase III clinical study of IVIG in mild to moderate Alzheimer’s patients were negative, certain subgroups showed favorable improvement on a cognitive test, and further research is planned. Another study found that administering blood plasma taken from younger mice to older mice improved the older mice’s cognitive function.
3. Despite the fact that Zika infection is understood to be transmitted via blood (typically through mosquitoes), the US Food and Drug Administration (FDA) has determined that the virus is eliminated from plasma in approved PDMP manufacturing processes (FDA 2016).
4. The comparison is based on 2013 financial reports from 3 large plasma- and 13 research-based pharmaceutical manufacturers.
5. Another evident trend in the production of PDMPs is the increasing role of commercial as opposed to non-profit plasma fractionation to meet global patient needs. Globally, commercial fractionation capacity has grown from 24.24 million liters in 1999 to 40.48 million liters in 2012, while non-profit capacity has declined somewhat from 9.74 million liters to 8.95 million liters over the same period (MRB 2012).
6. Note, in making the comparison to the median hourly wage, we do not suggest that plasma donation is a means to make a living; such would be impossible. The comparison is useful, however, to place plasma donation in the context of other time-allocation tradeoffs that individuals make.
7. As shown in Figure 2, worldwide immunoglobulin requirements increased by 2.27 million liters per year between 2008 and 2014. Population data come from WHO; income groups as defined by the World Bank (July 2014).
8. Data for Croatia and the Slovak Republic are suppressed in Figure 5 for ease of presentation. Those two countries report less than 10 liters of plasma donated per 1000 in every year reported.
9. Compensated plasma donation is also available in Austria, but consistent data on donation levels for that country is not available from the Council on Europe. However, other sources indicate that Austria has a relatively high level of plasma donation.
10. For example, Brazil was unable to purchase immunoglobulin on the global market, and there was a shortage of immunoglobulin in the United States when several manufacturers were forced to slow production to comply with stricter FDA regulations in the late 1990s.

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