NISKANEN CENTER

THE CASE FOR COMMERCIAL COMPENSATED PLASMA COLLECTIONS

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EXECUTIVE SUMMARY

- Blood plasma is essential for meeting the medical and therapeutic needs of vulnerable patients.
- This paper compares the main models of plasma collection used around the world and examines the policies that have an impact on these models. This includes a non-commercial model – private or public – that does not compensate donors for their plasma, a commercial model that does compensate donors, and a public-private partnership with donor compensation.
- Every country that permits the commercial model to operate within its borders has surplus plasma, which helps meet the therapeutic needs of patients abroad. Every country that prohibits the commercial model or donor compensation has plasma collection deficits which have only grown over the past decade. There are no exceptions.
- The United States alone provides more than 70 percent of the plasma for the world's plasma therapies. While the U.S. could plausibly provide enough plasma to meet the growing global demand for therapies, both a precautionary approach and possible political and legal uncertainties recommend a greater regional balance in collections.
- The best way for countries to collect enough plasma to ensure that every patient who needs a plasma therapy has access to it is to permit commercial compensated plasma collections within their own borders rather than relying on imports from countries that already allow it.

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INTRODUCTION: THE POINT OF PLASMA COLLECTION

The primary point of collecting blood plasma is to meet the medical and therapeutic needs of patients. We collect blood and plasma in order to ensure that we can preserve and promote the health of current and future patients.

Blood plasma is the yellow or straw-colored part of our blood. While it is mostly water, about 7 percent of it is made up of a variety of essential proteins like antibodies or immunoglobulins, albumin, a variety of coagulation or clotting factors, fibrinogen, and others. These proteins help us fight infections when we get sick, help our blood clot when we are injured, and do many other things. We collect blood plasma primarily to make medicine for patients who have rare diseases, like primary or secondary immunodeficiency, autoimmune disorders, a variety of neurodegenerative diseases like multifocal motor neuropathy, rare blood disorders like hemophilia or von Willebrand disease, and many others. The point of collecting blood plasma is to ensure that these patients have safe, secure, and reliable access to medicines that save and improve their lives.

Simply put, policy discussions should prioritize patients and the therapies they need. And the most important policy question is: Are we collecting enough plasma to ensure uninterrupted, safe, and sufficient access to quality-of-life-improving and often life-saving therapies for the current and future patients whose lives and health depend upon it?

MODELS OF PLASMA COLLECTION

To answer that question, we need to compare the main models of plasma collection used around the world and the policies that impact which of these models emerge. One model is a non-commercial model, either private or public, that does not compensate donors for their plasma. The other model is a commercial model that does compensate donors.[1]

Most countries have adopted policies that have legally enshrined a single model – a domestic non-commercial model that does not compensate donors for plasma. This includes the United Kingdom, New Zealand, Australia, and Canada's most populous provinces: Ontario, British Columbia, and Quebec. This also includes 23 of the 27 countries within the European Union. A handful of countries – Germany, Austria, Hungary, the Czech Republic, and the United States – have at least a decade's worth of experience with policies that permit both models to operate within their borders.[2]

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1. Beginning in 2020 in Egypt, soon to be operational in most of Canada, and with efforts afoot in Romania through Donam Plasma, a third model – a public-private partnership with donor compensation – has also emerged. Egypt's partnership with Grifols ("Grifols Egypt for Plasma Derivatives") will result in 20 plasma collection centers (see Grifols Egypt 2021). A new partnership in Canada between Canadian Blood Services and Grifols will also see additional compensated plasma collections in provinces outside of Quebec. This partnership is expected to allow Grifols to also operate in Ontario and BC which, unlike the other provinces, passed laws to prevent organizations other than Canadian Blood Services from compensating donors. The goal will be to reach 50 percent self-reliance (see CBS 2022). In Romania, the plan is to open 10 plasma centers (see Donăm Plasmă 2022).

2. Ukraine and Egypt also permit commercial compensated plasma collections, but these arrangements are much more recent. Ukraine changed its blood and plasma collection laws on September 30, 2020, which opened the door to commercial compensated collections. In 2021, Biopharma opened eight centers in that country that collected nearly 250,000 liters of plasma, and had plans to open 25 centers by 2025, hoping to reach 800,000 liters of plasma. However, the war in Ukraine resulted in temporary closures of several centers, which are just now beginning to be re-opened. Ukraine will be an interesting country to watch over the next decade (Mulyarchuk 2022).

The most important bottom line results are these:

- Every country that permits the commercial model to operate within its borders has *surplus* plasma collections. They collect more than enough plasma to meet the therapeutic needs of their own patient communities and so help meet the therapeutic needs of patients outside of their borders.
- Every country that prohibits the commercial model or donor compensation has plasma collection *deficits*. These deficits have grown over the past decade. These countries do not collect enough plasma to meet the therapeutic needs of their patient communities, and so to meet their patients' needs they rely on imports of therapies made from plasma collected using commercial, compensated plasma collections in the aforementioned handful of countries. Countries that ban the commercial model nevertheless are dependent upon it.

There are no exceptions.[3]

We also now have more than two decades' worth of evidence demonstrating that permitting non-commercial, non-compensated blood and plasma collection to coexist with commercial, compensated plasma collection has ensured a safe, reliable, and sufficient quantity of plasma to meet the therapeutic needs of every patient.

The same cannot be said for countries that have banned commercial, compensated plasma collections. While the therapies produced through the non-commercial, non-compensated plasma collection model are equally safe, this model has been unreliable, expensive, and has failed to collect sufficient plasma everywhere it is in place. As Canadian Blood Services has said: "Self-sufficiency is not operationally or economically feasible in a volunteer, unpaid model" (CBS 2015: 36).[4]

The commercial model is effective and does not adversely affect non-compensated blood and plasma collections for transfusions. It has operated in countries without evidence of reducing or undermining altruism or solidarity, harming donors, or wrongfully exploiting them.

This evidence has resulted in patient-centric policy changes in the province of Alberta and by Canadian Blood Services. These changes are promising. Australia, New Zealand, and the UK should take a similarly patient-centered approach and modernize their legal frameworks to permit commercial and non-commercial sectors to coexist.

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3. Over the last 20 years, there has been, to my knowledge, only one country that was fully self-sufficient in plasma for therapies without relying on the commercial sector. This was nearly a decade ago, in 2014, when New Zealand held that distinction. Since then, New Zealand's collections have been insufficient to keep up with increases in demand, so it started importing therapies in 2015 and continues to rely on imports to make up for its on-going shortfall.

4. The full quote is: "Given that self-sufficiency is not operationally or economically feasible in a volunteer, unpaid model, Canadian Blood Services strives to maintain a sufficiency of 30 per cent for Ig [immunoglobulin]." In its 2012-13 report, CBS wrote: "As self-sufficiency is not operationally or economically feasible in a volunteer, non-remunerated model, Canadian Blood Services strives to maintain a sufficiency of 30% for Ig" (2013: 43).

GLOBAL SUPPLY

Germany, Austria, Hungary, the Czech Republic, and the United States provide close to 90 percent of the plasma used to manufacture plasma therapies to meet the global needs of patients. All other countries combined – including Canada, Australia, New Zealand, the U.K., EU members, and others – manage to collect only enough plasma to meet 10 percent of the global need.

The United States is home to more than 80 percent of the world's plasma collection centers and provides more than 70 percent of the plasma used to manufacture plasma therapies for the world (Jaworski 2020). It is the 11th largest industry in the U.S., with exports of therapies or plasma representing about 1.9 percent of total U.S. exports in 2019 (Greenberg 2019). Globally, the industry is valued at more than $30 billion, and it is projected to reach over $45 billion by 2027 (BCC Research 2023).

The U.S. supplies Canada with more than 80 percent of the plasma it needs for therapies, and about 15 percent of New Zealand's. Americans have provided nearly 100 percent of the plasma needed to make therapies for the U.K. since 1998. Australia, which is home to CSL Behring, the second-largest plasma company in the world, does not allow CSL to collect plasma domestically, so it depends on CSL plasma collections in the U.S. for nearly half of its therapies.

Approximately 300,000 patients rely on therapies made from plasma in the EU. The four countries that permit commercial compensated plasma collections supply more than a third (38 percent) of total EU plasma used to make therapies, while the remaining 23 countries together supply about a quarter (24 percent). The remaining deficit of more than a third (38 percent) is covered by donors in the United States. Table 1 provides an overview of the extent to which some European countries depend on imports.

Table 1: Extent of plasma self-reliance, by country, 2017-2020

Self-reliance	2017	2018	2019	2020
Germany	>100%	>100%	>100%	>100%
Austria	>100%	>100%	>100%	>100%
Hungary	>100%	>100%	>100%	>100%
Czech Republic	>100%	>100%	>100%	>100%
Italy	73%	76%	n/a	n/a
France	n/a	n/a	n/a	~50%
Denmark	30%	34%	n/a	n/a
Norway	0%	0%	n/a	n/a
Belgium	n/a	n/a	~50%	n/a
Spain	44%	35%	33.5%	33.5%
Netherlands	n/a	n/a	n/a	45%

Sources: De Meester, Bourgeois, Devriese, and San Miguel 2020; WHO 2022; Ministerio de Sanidad (Spain) Various years; Canadian Blood Services Annual Reports; National Blood Authority Annual Reports; New Zealand Blood Services Annual Reports; NHS England National Immunoglobulin Database Annual Reports

Table 2: Plasma self-reliance in Canada, Australia, New Zealand, the United Kingdom, and the US, 2017-2019

Self-reliance	2017	2018	2019	2020
Canada	18.2%	17%	15.8%	15.9%
Australia	56%	52.6%	48.4%	46%
New Zealand	88.5%	88.2%	87.5%	88.8%
UK	0%	0%	0%	0%
US	>100%	>100%	>100%	>100%

Source: Canadian Blood Services annual reports, National Blood Authority annual reports, New Zealand Blood Services annual reports, NHS England National Immunoglobulin Database Annual Reports

Collections are anticipated to grow faster in the U.S. than anywhere else, and so the proportion of plasma provided by the U.S. to meet global therapy needs will rise. Over the next five years, U.S.-supplied plasma is likely to rise to at least three-quarters of global collections. These absolute figures are even starker when we compare rates of plasma donation measured in liters per 1,000 residents. Within the EU, the four countries that permit commercial compensated plasma collections have rates that are at least twice those of countries that don't.

The Netherlands had the best-performing non-commercial, non-compensated plasma collection system in Europe in 2019 according to the available data, but it was still not collecting enough to meet the needs of its patient community.[5] Collections in the Netherlands stood at 18 liters per 1,000 residents that year, half that of Germany's 40 liters per 1,000 residents, and merely a third of the Czech Republic's 65 liters collected per 1,000 residents.

Australia has probably the best-performing non-commercial, non-compensated plasma collection system in the world. Red Cross Lifeblood managed to collect 29 liters per 1,000 people in 2019. But not only was that not enough to meet the needs of its patient community, it was also less than half the Czech Republic's and just a bit more than half of Germany's. Australia met only 48.4 percent of the needs of Australian patients that year.

New Zealand had the next best performing system among Canada, Australia, New Zealand, and the United Kingdom (CANZUK), but managed to collect only 14 liters per 1,000, relying on imports for 12.5 percent of its patient community needs in 2019. Canada's non-commercial blood operators (Canadian Blood Services and Héma-Québec) together collected 7.6 liters per 1,000 residents. That number rose to 10.3 liters per 1,000 if we include estimates for commercial plasma collections, and so Canada was more than 80 percent dependent on other countries for its plasma supplies (just under 80 percent when estimated commercial collections are included). The U.K. did not collect plasma for therapies in 2019, relying on imports for 100 percent of its patient needs.

The United States collected 163 liters per 1,000 residents in 2019 (130 and 149 liters per 1,000 in 2017 and 2018). This is more than twice the rate of the next-best performing country, the Czech Republic, and more than nine times that of the Netherlands. These collections backstop the poorly

5. France did not submit data to the European Directorate for Quality Medicine (EDQM) for 2019.

performing systems in most of the rest of the world. Tables 2 and 3 provide further information about plasma collection among these and other countries.

Table 3: Rate of plasma collection per 1,000 residents in the EU, 2017-2019

Plasma L/1,000	2017	2018	2019
Germany	36	38	40
Austria[6]	59.4	53.8	53.3
Czech Republic	61	62	65
Netherlands	17	17	18
Finland	10	10	10
Denmark*	13.8	14.9	n/a
Norway	10	9	10
Sweden	11	11	10
Switzerland*	7.5	7.2	n/a
Italy	13	14	n/a
Spain	8	8	8

* WHO 2022.

Source: European Directorate for Quality Medicine Various years unless otherwise stated.

Table 4: Rate of plasma collection per 1000 in Canada, Australia, New Zealand, the United Kingdom, and the US, 2017-2019

Plasma L/1,000	2017	2018	2019
Canada*	8.8	9.7	10.3
Australia	26	27	29
New Zealand	14	14	14
UK	0	0	0
USA	130	149	163

*Includes author's estimates of plasma collection at commercial plasma centers.

Source: Canadian Blood Services annual reports, Héma-Québec annual reports, National Blood Authority annual reports, New Zealand Blood Services annual reports, NHS England National Immunoglobulin Database Annual Reports

GLOBAL IMBALANCE

The plasma collection figures represent an unacceptable imbalance in the global supply chain for plasma protein therapies. While the U.S. could plausibly provide enough plasma to meet the growing global demand for therapies, both a precautionary approach and possible political and legal uncertainties recommend a greater regional balance in collections.

6. The data for Austria includes only plasma collected at commercial centers affiliated with the European Plasma Protein Therapeutics Association, and is sourced from correspondence with the European PPTA.

The current pandemic provides just the latest example of the precarious situation facing patients when we are over-reliant on American plasma collections. The pandemic reduced plasma collections in the U.S. by around 20 percent. Separately, an unexpected decision by U.S. Customs and Border Patrol to treat the donation of blood plasma as "employment" meant a further reduction in collections of approximately 10 percent as visitors to the country could no longer donate (Lind and Dodt 2021) – at least until September 2022, when a U.S. District Court granted a preliminary injunction preventing enforcement of this decision, thereby allowing visitors to again donate (Immune Deficiency Foundation 2022).

The reductions in the U.S. led to a significant global reduction in the availability of plasma, which reduced the availability of immunoglobulin. France and Italy both expressed concern about their ability to provide immunoglobulin replacement therapy for their patient communities, as did patients in Spain (Lluch 2021; Infosalus 2021). England limited the use of immunoglobulin in the face of this "critical situation."

Immunoglobulin therapy was rationed in Canada for a time. Elsewhere in the world, some new patients were unable to access the therapy that would have been best for their specific condition. One immunologist from Sudan explained that of her nearly 100 patients with primary immunodeficiency, about a quarter died from lack of access to immunoglobulin.[7]

For more than two decades national blood operators around the world have worried about the possibility of a crisis. Concerns in Canada about over-reliance on American plasma collections have been expressed since at least the founding of Canadian Blood Services in 1998. New Zealand Blood Services has been raising the alarm, as has the National Blood Authority in Australia, and NHS Blood and Transplant in the U.K. The situation was described as "steaming towards an iceberg" in *Current Opinion in Allergy and Clinical Immunology* in 2020 (Prevot and Jolles 2020).

In June of 2020, an unnamed official at the European Directorate for the Quality of Medicines and Healthcare (EDQM) was quoted as saying, "This situation exposes European patients to the risk of sudden interruptions of plasma supplies from the U.S." In 2019, when the world was facing an acute shortage of immunoglobulin, John Boyle, then-president of the U.S.-based Immune Deficiency Foundation, wrote an article that was subtitled "The sky is not falling but the world needs more plasma" (Boyle 2019). The very same article could have been written every year for the past decade.

RISING DEMAND, MORE INDICATIONS

The European Union managed to collect 108 percent of the plasma it needed for its immunoglobulin use as recently as 2011, excluding the U.K. However, growth in demand for immunoglobulin has seen the EU deficit grow from 16 percent in 2014, to 24 percent in 2017, to the current 38 percent (Bencharif 2022).

7. Personal conversation at the International Patient Organization for Primary Immunodeficiency Stakeholder meeting in Cascais, Portugal, June 2022.

Australia was 100 percent self-reliant in plasma for plasma therapies in 2004. Since then, the country has seen a fairly steady decrease in self-reliance to a low of 46 percent in 2020, but rising to 57.8 percent in the latest annual report. In 2004, Australia used approximately 1.35 million grams of immunoglobulin, a rate of around 66 grams per 1,000 residents. By 2022, Australian patients used 8.05 million grams, or 310 grams per 1,000 residents.

Although Australia is amongst the highest users of immunoglobulin, its experience in steady and significant growth in immunoglobulin use is not unique. Over the last two decades, demand for immunoglobulin has been rising by 6 to 10 percent per year around the world. The EU saw 8.3 percent growth in demand from 2010 through 2019. Australia and Canada experienced many years of double-digit demand growth, with similar growth in demand in the UK. The latest annual report from New Zealand Blood Services (2021) puts the growth in that country's demand for immunoglobulin at 12 percent.

Experts have been noting the significant growth in demand for at least two decades. In a 2006 article for the *New Zealand Journal of Medicine*, David Hutchinson, Richard Charlewood, Peter Flanagan, and Terry Mitchell wrote:

> The steady rise in demand for IVIG in NZ over the past decade matches the experience in other developed nations. Utilisation in Australia rose by an average of 14.8 percent per annum over the period 1995–2005, and in Canada it rose by an average of more than 15 percent per annum over the period 1992 to 2001. A continued rise in demand is inevitable with the improved management of antibody deficiency and the completion of new studies establishing the efficacy of IVIG in diverse inflammatory disorders. (Hutchinson, Charlewood, Flanagan, and Mitchell 2006).

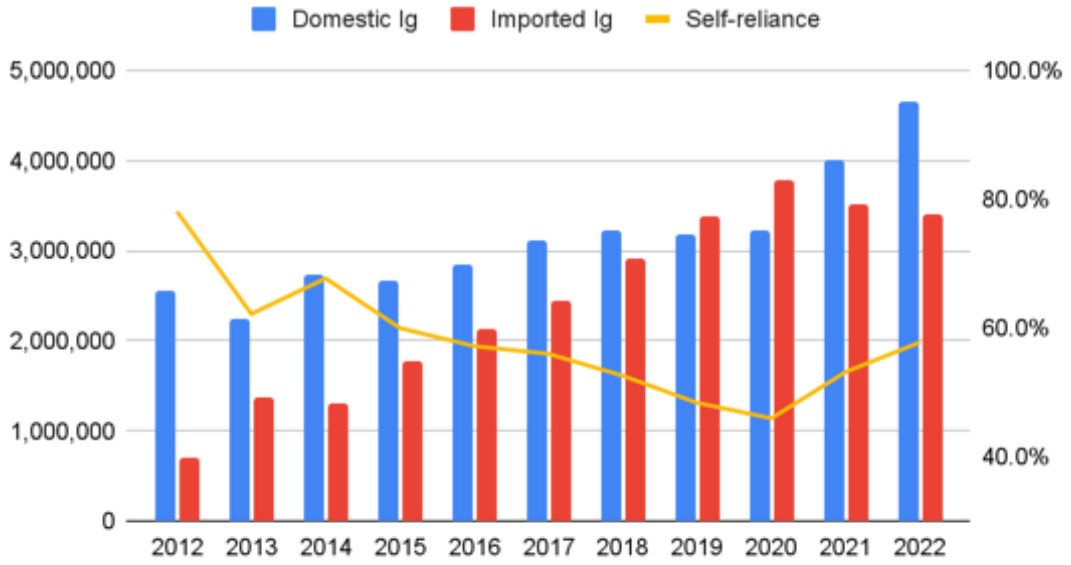
Despite more than two decades of warnings, crises, and occasional shortages, and more than two decades' worth of evidence regarding the effectiveness of commercial, compensated plasma collections and the ineffectiveness of non-commercial, non-compensated plasma collections, most countries have either ignored the evidence or have failed to take action while not giving sufficient consideration to permitting at home what they all rely on from abroad.

CANADA, AUSTRALIA, NEW ZEALAND, AND THE UNITED KINGDOM

Over the past 10 years, Canada, Australia, New Zealand, and the United Kingdom have become increasingly dependent on American plasma collections as a result of the steady increase in immunoglobulin use in each country. There was a temporary drop in dependence in 2022 as a consequence of the pandemic and the aforementioned drop in plasma donations in the United States. Of these countries, only Canada is likely to buck the trend in the next few years and see a significant reduction in this dependence.

As mentioned, Australia has the best performing non-commercial, non-compensated plasma collection system in the world. Australia was 14 percent dependent on the U.S. in 2011, then 42.8 percent in 2016, and 46.8 percent in 2021 (Figure 1).

Figure 1: Australia's immunoglobulin self-reliance, 2012-2022

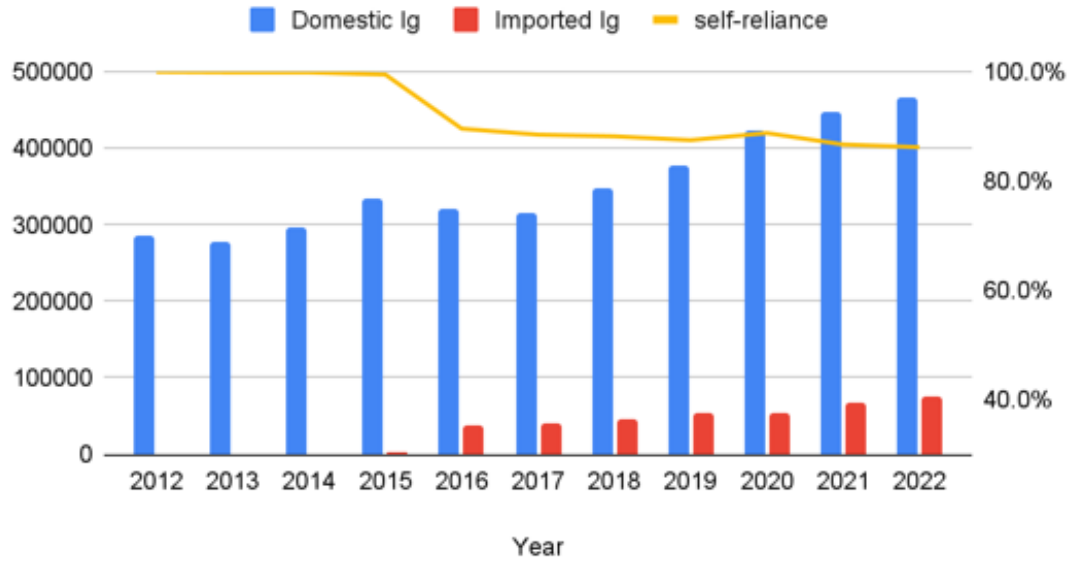


Source: National Blood Authority annual reports

New Zealand had the distinction of being exclusively reliant on domestic non-commercial, non-compensated plasma collections in 2012. This distinction is marred somewhat by the country's likely underuse of immunoglobulin. While neighboring Australia was using 173 grams of immunoglobulin per 1,000, New Zealand was using only 66.2 grams per 1,000. (In 2021, Australia used 293 grams per 1,000, while New Zealand used 100.5 grams per 1,000.)

By 2015, however, despite the lower use, New Zealand's non-commercial, non-compensated plasma collection system began to show signs of inadequacy. New Zealand imported 1,828 grams of immunoglobulin, representing just 0.5 percent of patient needs that year. The hope that this was only temporary and New Zealand would soon be fully self-reliant again was in vain. Instead, New Zealand became just over 10 percent dependent on imports in 2016, and 13.3 percent dependent by 2021. The demand for immunoglobulin also spiked by 12 percent in 2022, auguring poorly for a return to self-sufficiency (Figure 2).

Figure 2: New Zealand's immunoglobulin self-reliance, 2012-2022

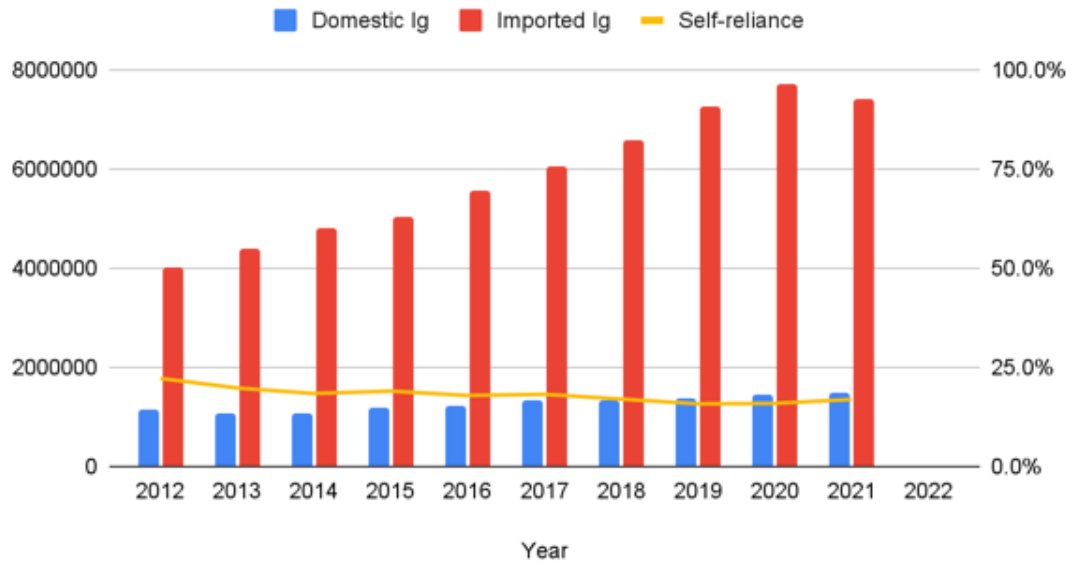


Source: New Zealand Blood Services annual reports

From 1998 until 2021, the U.K. did not collect plasma for therapies and so was entirely dependent on commercially-sourced therapies, overwhelmingly from the U.S. Use of immunoglobulin within the U.K. was also significantly lower than in Canada, Australia, or the United States, but the U.K. is slowly catching up as well. Since the ban on the manufacture of plasma therapies from domestic plasma collections, the U.K. has been discarding approximately 250,000 liters of recovered plasma for the past several years. They will now be able to use that plasma for the manufacture of therapies. This, along with 11 new plasma collection centers, will likely make the U.K. approximately 20 percent self-reliant by 2024, and may reach self-reliance levels as high as 30 percent by 2025. This is an improvement, but clearly inadequate.

In 2015, Canada was 81 percent dependent on U.S. plasma collections. Six years later, in 2021 (the year for which we have the most recent data), that number had increased slightly to an 83.1 percent dependency on plasma collected in the U.S. However, if we include estimates for the three commercial plasma collection centers operating in Saskatoon, Winnipeg, and Moncton, the 2021 figure drops to 78.4 percent (Figure 3).

Figure 3: Canada's immunoglobulin self-reliance, 2012-2022



Source: Canadian Blood Services Annual Reports

EXPENSE

Apart from possibly asking too much of volunteer donors, an additional explanation for inadequate plasma collections is the expense involved in operating a non-commercial, non-compensated plasma collection system. Compared with the commercial alternative, non-compensated plasma collections typically cost between two to four times more, according to a 2018 Health Canada expert panel (Health Canada 2018).

Australia releases more fine-grained data on costs than does Canada or New Zealand. In 2022, each gram of immunoglobulin from its non-commercial, non-compensated plasma collection system cost AUD$118.99. That same year, imported immunoglobulin cost Australia AUD$75.59 per gram, which indicates that the cost for non-commercial immunoglobulin included a 57 percent premium (Table 4). However, prior to 2022, a year with unusually high costs for commercial immunoglobulin, one non-commercial gram of immunoglobulin cost at least 2.25 times more than a commercially-sourced gram.

Table 5: Cost of domestic vs. commercial immunoglobulin in Australia, 2019-2022

AUSTRALIA	2019	2020	2021	2022
Cost per gram Ig (domestic)	143.72	141.98	133.03	118.99
Cost per gram Ig (imported)	45.90	47.36	59.25	75.59
% Difference	3.131 times (213%) more expensive	2.998 times (199.8%) more expensive	2.245 times (124.5%) more expensive	1.574 times (57.4%) more expensive

Source: National Blood Authority Annual Reports

Hypothetically, if Australia were to source immunoglobulin entirely from the commercial sector, the total cost in 2022 would have been AUD$608.6 million, as compared with the actual total cost of AUD$810.4 million. The Australian healthcare system would have saved a little more than AUD$200 million that year. Back in 2018 economist Robert Slonim also estimated the cost savings from using commercial immunoglobulin at "over AUD$200 million" per year. According to Slonim, "Likely culprits for the higher domestic costs include the Red Cross Blood Service's monopoly powers and not compensating donors. Since not offering compensation limits donations, it likely increases other costs, including recruiting donors" (Slonim 2018). Indeed, the primary driver of the higher cost is the lower volume of plasma collected at non-compensated centers compared with compensated centers which have similar annual operating costs.[8]

The Australian data captures both the costs of collection as well as the costs of fractionation, or producing the medicine. In Canada, we have evidence about the collection costs specifically. Hoping to open and operate 40 non-compensated plasma collection centers, Canadian Blood Services (CBS) requested from the federal government $855 million dollars over seven years in 2017, with an ongoing annual operating budget of $248 million each year thereafter; its goal was to reach 50 percent self-reliance (Grant 2017). These figures translate into an annual ongoing operating cost of $6.2 million per center, with expected collections of 15,000 to 20,000 liters per center, for a total of about 600,000 to 800,000 liters collected per year. Using CBS's own estimates and ignoring all costs other than ongoing operational costs, this works out to an effective average collection cost of $310 to $413 per liter.

That same year Canadian Plasma Resources (CPR), a Canadian commercial compensated plasma company, made its third offer to supply CBS with plasma at a cost of $220 per liter.[9] This price would have been 41 percent cheaper than the lowest cost estimate, or 88 percent cheaper than the higher estimate. If Canada were to rely entirely on commercial compensated plasma collections the cost would be $176 million per year compared with $248 million if it were to rely entirely on CBS non-compensated collections. The annual operational cost savings amount to at least $72 million.

CBS has not accepted any of CPR's offers. As CBS is the only entity legally permitted to purchase plasma in the country outside of Quebec, its decision has forced CPR to find other buyers for its plasma, which it did in the form of Biotest in Germany.[10] CBS initially explained that the volumes CPR was offering were too small. But this explanation ceased to be relevant in CPR's subsequent offers, which promised to supply the exact volumes CBS was hoping to achieve with its own plasma collection plan.

8. Non-commercial, non-compensated centers typically average between 10,000 to 20,000 liters of plasma collected per year. In the United States in 2019 the average collection volume across 832 centers was 64,342 liters for a total of 53,532,216 liters. In 2020 that average dropped to 46,740 liters per center across 929 centers, and then to 42,076 across 1,031 centers in 2021 (see "Plasma Collections" at PPTA 2022).

9. CPR offered its plasma to CBS in October 2016, June 2018, May 2019, and again in December 2020. In the 2020 offer, CPR once again indicated that its "primary business objective has always been to collect Canadian plasma to make finished plasma protein products to treat the medical needs of Canadian patients" (CPR 2020, 2). The 2020 offer price per liter was $225, or US$175, less than the international price of plasma from August 2020 estimated at US$194 per liter. The offer promised 600,000 liters by 2025.

10. In the political debate, opponents of commercial compensated plasma collections argued that this was "plasma for export," suggesting that the plasma would go to the "highest bidder." This criticism did not make sense given that CPR offered plasma to CBS at a discount compared with global prices and that it made repeated efforts to sell plasma to CBS. In April of 2022, Grifols purchased Biotest, and since Grifols supplies Canada with plasma, the plasma collected by CPR will be used in therapies for Canadian patients (see Grifols 2022).

To collect enough plasma to meet the needs of Canadian patients in 2019 would have cost provincial governments $1.7 billion in collection costs alone. Canada would still need to pay for fractionation. Meanwhile, the cost of the plasma protein products Canada used between 2018 and 2019 was $656 million, according to the CBS annual report (CBS 2019).[11] It is easy to see why provincial governments declined the budgetary request, offering enough funds to open just 11 plasma collection centers.

If the costs cited above are accurate, and if the global situation is as described, why haven't Canada, Australia, and New Zealand opted to permit domestic collections of commercial compensated plasma?

"ENCROACHMENT" OR "CROWDING OUT"

The most important reason is the theoretical concern of "encroachment," or what is sometimes called "crowding out." The worry for governments is that compensated plasma collections, used to manufacture therapies, may adversely affect non-commercial, non-compensated blood collections used for transfusions. This worry dates to at least the publication of Richard Titmuss' *The Gift Relationship* in 1970.

The European Blood Alliance insists: "Payments to blood and plasma donors by commercial suppliers erode the current community-based, non-remunerated, donor population… In countries with dual systems (where unpaid and paid collection coexist), blood establishments who collect components for transfusion encounter increasing difficulties in recruiting and retaining unpaid donors" (EBA 2016). Bernardo Rodrigues, an advocacy officer with the European Blood Alliance, has said that when people are drawn by the cash incentive to give plasma instead of blood, "it's what we call crowding out" (Bencharif 2022).

It is hard to see the basis of the European Blood Alliance's claim. Over a span of 60 years, we still have no studies demonstrating encroachment or "crowding out" from the presence of commercial compensated plasma collections. There is no study showing this in any of the countries that permit a parallel commercial, compensated plasma collection system.[12]

The European Directorate for the Quality of Medicines and Healthcare (EDQM) reports discussed earlier do not show that countries that permit commercial, compensated plasma collections have markedly fewer non-compensated donors (Table 5). They do not appear to show any negative relationship between compensated plasma collections and non-compensated blood and plasma collections.

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11. According to the Nova Scotia Ministry of Health's annual report on immunoglobulin use in the Atlantic provinces, the average cost of immunoglobulin therapy in the Atlantic provinces was $44.32 per gram in 2018-19, down from $64.83 the year prior (Nova Scotia Provincial Blood Coordinating Program 2019: 9).

12. There are surveys and at least one experiment in Sweden. The surveys ask donors if they would donate plasma if they were paid, and some people say "no." But this does not matter since what does matter is whether or not enough people would do it to meet the needs of patients for the different uses for blood or plasma. Even if 90 percent of people wouldn't donate plasma for compensation, 10 percent of the population actually donating plasma would result in significant plasma collection surpluses. Some surveys ask current non-compensated donors how they would feel if compensation were introduced. This is even less interesting, since we need to know what would attract non-donors to donating, not how the 3 to 4 percent of people who like the current system enough to donate blood and plasma might feel about being offered compensation.

Table 5: Number of whole blood donors per 1,000 residents in selected EU countries, 2017-2019

Donors per 1,000 residents	2017	2018	2019
Austria	36	34	35
Czech Republic	25	25	26
Germany	28	28	28
Hungary	39	26	n/a
Netherlands	19	20	21
Finland	22	22	21
Norway	19	18	18
Sweden	21	20	20
Italy	28	28	28
Spain	25	25	25
Greece	48	48	38

Source: European Directorate for Quality Medicine Various years.

Consider the specific case of the Czech Republic. Following the introduction of commercial compensated plasma collections in late 2007 there was no decrease in non-compensated collections. Over a 10-year period from 2006 through 2016, plasma sent for fractionation went from 82,900 liters (8.05 liters per 1,000 residents) to 613,600 liters (58 liters per 1,000). Despite that more than seven-fold increase in collections, there was no corresponding change in the rate of whole blood collections.[13] While Germany contributes the highest volume of plasma for fractionation in the EU, the most recent EDQM report shows the Czech Republic leading all of Europe in the rate of plasma collection at 65 liters per 1,000 residents in 2019.

The Czech Republic also follows the general EU standard of permitting one plasma donation every two weeks, up to a limit of 34 per year. Austria permits 50 donations per year (once every three days, up to twice a week and up to three times every two weeks), while Germany allows up to 60 donations a year (once every two days). The United States, Canada, and Egypt permit twice weekly donations, with at least 48 hours between donations, up to 104 donations per year. However, only 0.3 percent of donors donate the maximum amount, with 49 percent of donors donating 10 or fewer times in 12 months. The average number of donations was 21.4 in a 12-month period (Schreiber and Kimber 2017).

Amongst the countries that allow parallel commercial plasma collections, the Czech Republic had the lowest proportion of whole blood donors at 26 per 1,000 in 2019, but that rate is nevertheless higher than Finland, Sweden, Norway, and the Netherlands. It was also higher than the median rate of 22 donors per 1,000 residents within the EU, and only slightly lower than Italy's rate of 28 per 1,000.

13. The rate of whole blood donations did not decrease in the intervening period. Instead, the opening of commercial centers correlated with an increase in the rate of whole blood donations, which has since returned to the current levels. Interestingly, plasma collections in the Czech Republic increased at both commercial and non-commercial plasma collection centers.

At the aggregate level, there is no evidence of "encroachment" or "crowding out" in the Czech Republic. There is also no such evidence at the aggregate level in Austria. There are no systematic studies showing a negative impact from compensated plasma collections on whole blood collections in either of these countries.

Germany and Hungary are more complicated because, in the case of the former, there are compensated blood collections running in parallel with non-compensated collections, while in the latter there are laws requiring a once-yearly whole blood donation prior to being permitted to donate plasma. However, the German Red Cross, which does not compensate donors, continues to be the largest whole blood collector despite the presence of not only compensated plasma collections, but also compensated blood collections. And at least some in Germany deny that there has been a negative effect on whole blood donations after the introduction of compensated plasma collections. According to Dr. Franz Weinauer of the Bavarian Red Cross, for example, they hadn't witnessed encroachment from compensated plasma collections: "blood and plasma donors are not part of the same donor population," with older people giving non-compensated blood and younger people giving compensated plasma (Wetzel 2018).

When Canadian Blood Services asked its counterparts in Germany, Austria, Hungary, and the Czech Republic if they had witnessed "encroachment," the conclusion was: "no evidence of VNRBD [Voluntary Non-Remunerated Blood Donation] being tangibly impacted by remunerated source plasma operations" (Bédard 2020).[14]

The aggregate data in the EU and the evidence available so far suggests that "encroachment" or "crowding out" is an interesting theoretical concern without much empirical support.[15] There is not much support for such a concern in Canada or the United States either. In a study I conducted with my colleague, William English, we found the introduction of compensated plasma donation opportunities in three cities in Canada and three cities in the US had no effect on non-compensated blood donations (English and Jaworski 2020). On the contrary, there was a very small, positive effect on blood donations, more pronounced in Canada than the U.S.

What explains these results?

First, there may be an advertising spillover effect from the introduction of a plasma collection center. The more centers that collect blood or plasma in a jurisdiction, the more aware people will be of the need for both. Second, different populations are attracted to these opportunities for different reasons. Some people are not interested in opportunities to give plasma for compensation, while others are not interested in donating either blood or plasma unless it is compensated. Others may wish to donate, but the costs associated with donation are too high, which are made

14. In 2018 CBS also had ProGuide conduct a study entitled Potential Encroachment of Source Plasma Operators into the Blood Industry in the United States and Europe in which it surveyed executive-level leadership of non-compensated blood collectors. The general response was: "It seems sensible to conclude that this phenomenon exists but more data is needed." More specifically, of 17 surveyed executives, two were categorized as "Seems to exist (no proof)," 10 were placed in the "Makes sense (no analysis)" category, four were "Doubtful," and one said "Definitely none."

15. The default hypothesis should instead be that different populations are drawn to these different organizations, a hypothesis supported by a scan of the demographic profiles of whole blood and plasma donors for transfusion as compared with source plasma donors for plasma therapies. (See also Healy 2020 on how organizations create their donors.)

up for by the compensation. Some are motivated by image or reputational considerations[16] – they wish to appear to be altruistic.

Finally, the overlap in the population, the place where we do anticipate competition, is with people who are motivated by the lives they might save. Both non-compensated blood donations and compensated plasma donations save lives and help patients. So genuinely authentically altruistic people who are less interested in how their behaviour is perceived will be attracted to both opportunities.

In combination, these explanations suggest that we should anticipate increases in both blood and plasma donations from the parallel operation of compensated plasma collections, up to a certain threshold point of saturation.

To illustrate, suppose that there are 100 people with the following desires and motivations: 60 will not donate, either because they are unable for medical or other reasons, or they are not interested. Of the remaining addressable market of 40 potential donors, 15 will do it for compensation (potential dedicated plasma donors), 15 will do it for the sake of saving lives (open to being either blood or plasma donors), and 10 will do it out of image motivation (potential dedicated blood donors). With perfect awareness of the opportunities, at least 10 will be dedicated blood donors, and at least 15 will be dedicated plasma donors. Of the remaining 15, some will donate blood while others will donate plasma, and they may switch sometimes.

With imperfect awareness, it is possible that a blood center is currently only attracting eight of their potential dedicated 10 donors. A new plasma center may increase general awareness, and so a blood center may see one or more additional dedicated blood donors when a plasma center opens. Advertising for a plasma center may function as a reminder to those who are aware of both opportunities, and so may spur some of the 10 potential dedicated blood donors to make a blood donation.

In this population, encroachment could happen if there were perfect awareness and sufficient opportunities to donate in convenient ways. A blood center would draw all 10 of the dedicated blood donors, plus some from the 15 who are motivated by saving lives. At the limit, they would have 25 blood donors. A new plasma center may draw some of the 15 from the blood center, and so lower blood donations in the jurisdiction.

I suspect that most jurisdictions are not like the hypothetical jurisdiction with perfect awareness and sufficiently convenient donation options, and so we think that it is more reasonable to expect not encroachment but enlargement of the donor population at both blood and plasma centers.

ALBERTA BOUND

At the end of 2020 Alberta chose to repeal the 2017 Voluntary Blood Donations Act that had prevented commercial compensated collections in order to preserve a monopoly on blood and plasma

16. Dan Ariely, Anat Bracha, and Stephan Maier (2009) call this "image motivation."

collections by public sector unions. Since the Act's repeal, three commercial centers have opened in the province, one in Calgary (2021), one in Edmonton (2021), and one in Red Deer (2022), with plans for a fourth in Lethbridge (2023). Together, these centers will contribute approximately 250,000 liters of plasma from commercial collections by 2024 (at maturity these four centers should collect closer to 300,000 liters per year).[17]

The CBS' non-compensated plasma collection center in Lethbridge is expected to collect 15,000 liters, while recovered plasma from whole blood donations in Calgary, Edmonton, and Red Deer should result in an additional 15,000 liters. Thus, the total amount of plasma collected should be approximately 285,000 liters in 2024, or a rate of 60.4 liters per 1,000 in a population of about 4.7 million people. Collections would be nearly twice Germany's, and comparable to the Czech Republic's (although still less than half of that in the United States).

Meanwhile, assuming 4.7 grams per liter, these collections would yield 1.34 million grams of immunoglobulin. In 2022, Alberta had the highest rate of immunoglobulin use in Canada at 293 grams per 1,000 residents, or 1.33 million grams.

By 2024, Alberta is likely to be the only jurisdiction in Canada that will be collecting enough plasma to make it very nearly 100 percent self-reliant. It will collect more plasma than any other province, including Quebec or Ontario, which have two and three times Alberta's population, respectively. Alberta will also be the only jurisdiction within CANZUK to reach this objective. Despite a smaller population, Alberta's collection volumes will outpace all of New Zealand's. Were New Zealand to follow Alberta's example, it, too, would be in a position to return to self-sufficiency quickly and cost-effectively.

Just four years after the repeal of a law that favoured unions and their jobs over patients and their therapies, Alberta is likely to exceed total plasma collections in the rest of Canada *combined*. This should raise questions about what would have happened in Canada had provincial governments listened to patients rather than public sector unions[18] and so never enacted the Voluntary Blood Donations Act in Ontario (2014), then Alberta (2017), and finally in British Columbia (2018). One very likely possibility is that Canada would now be a net contributor to the global supply of plasma, like the Czech Republic, rather than a net drain on that supply.

In the wake of Alberta's decision to repeal the Voluntary Blood Donations Act, the publication of two separate reports — the Health Canada Expert Panel report (2018) and the Ontario Auditor General's report (2020) — both of which urged increased domestic plasma collection, and an unwillingness on the part of provincial governments to fund 40 plasma collection centers, Canadian Blood Services has decided to create a partnership with Grifols. The partnership will see Grifols open and operate several commercial compensated plasma collection centers as an "agent"

17. The Calgary and Edmonton centers are expected to contribute approximately 80,000 to 90,000 liters each, Red Deer another 40,000 to 50,000 liters, and Lethbridge 30,000 to 40,000 liters by the end of 2024.

18. The Network of Rare Blood Disorder Organizations, an umbrella organization of the 15 national patient organizations whose membership depends upon blood, plasma, and the therapies made from plasma, opposed bans on commercial compensated collections in Ontario, Alberta, and British Columbia. They issued a unanimous policy position statement on compensated collection of plasma in 2018, writing: "with no evidence of safety risks, and no evidence of threats to the voluntary collection of blood, compensated collection of plasma can help with the global and Canadian plasma supply shortage, helping to ensure patients can access plasma-derived medicinal products when they need them" (NRBDO 2018).

of Canadian Blood Services. All plasma collected by Grifols will be collected exclusively for CBS and CBS retains the right to veto any collection center location decision by Grifols. Both organizations expect that the Voluntary Blood Donations Act in Ontario and British Columbia will not prevent Grifols from operating there on the grounds that, as an agent of CBS, Grifols will enjoy the exemption written into those laws for Canadian Blood Services. The partnership should result in significant increases in plasma collection, and so Canada's dependence on the US for plasma should decrease quickly.

CONCLUSION

On June 11, 2009, the World Health Organization issued "the Melbourne Declaration," a report formally entitled *100% Voluntary Non-Remunerated Donation of Blood and Blood Components*. The WHO declared a commitment by 2020 to achieve global reliance on exclusively "non-remunerated" blood and blood components, including plasma therapies. Australia, New Zealand, the UK, and Canada each approved of the declaration.

It is now well past 2020, and no countries have met the goal. Instead, since 2009, reliance on compensated or remunerated plasma collections has only increased to the current level of more than 80 percent.

Clearly, once upon a time it was conceivable that non-compensated plasma collections could succeed at meeting the needs of patients. But such a proposal was unrealistic by 2009 – not because people became less willing to donate plasma, but because the number of such donations necessary to meet the needs of patients had ballooned beyond what could be reasonably expected of even the most altruistic of countries.

In addition, the arguments against compensated plasma collections appear to be very weak. We have barely any evidence that compensated plasma donors have an adverse effect on altruism or solidarity, or that they adversely affect non-commercial, non-compensated blood and plasma collection for transfusion. In fact, hardly any of the objections to commercial compensated plasma collections withstand minimal scrutiny.

First, consider safety. Every country in the world uses plasma from the United States. Countries would not use therapies made with U.S. plasma if they were less safe.[19]

Second, consider claims of wrongful exploitation. Exploitation is best understood as either presenting someone with undue risk, undue pressure, or an unfair division of the benefits from trade. There is no undue risk when it comes to plasma donations at European frequencies, and little evidence of any harm at the legally-permitted higher Canadian and American frequencies. We encourage people to give plasma. It is not a risky procedure. There is also no undue pressure. In Europe, donors receive Đ30 to Đ50 for the time and effort required to give plasma, which can last up to an hour and a half, while in Canada and the U.S. donors get between $50 and $75 per dona-

19. The CEO of Canadian Blood Services, Dr. Graham Sher, has said: "Paying plasma donors is not an issue of safety. The finished products that come from the commercial paid plasma industry are inordinately safe, and there has been no documented evidence of any viral transmission for almost three decades or more from these products" (CBS 2016).

tion. This payment represents the largest cost for plasma collection companies. Donors receive more as a proportion of revenue per liter than the company does in profit. This is not only not unfair; it is a good deal.

As for altruism and solidarity, few arguments could be more beside the point. The point of a plasma collection system is not to give donors an opportunity to express their altruism or to promote community solidarity. The point of a plasma collection system is to collect enough plasma to ensure that every patient who needs plasma therapy has access to it. Perhaps more importantly, what truly threatens community solidarity and altruism is enduring unnecessary but foreseeable shortages of the lifesaving medicine that patients need. Shortages express the view that we don't care enough about our patient community to do what works, to do what we need to do to ensure that patients can have the medicine that they can't go without. Canada's policies are also hypocritical. They don't permit commercial compensated plasma collections within their borders, but every country relies on them. If it is immoral to pay Australians or Canadians, why is it moral to pay Americans?

The world did not reach anywhere near 100 percent reliance on non-compensated plasma collections in 2020. In fact, that goal is even further away today than it was when it was articulated in 2009. We will not reach this goal by 2030 or 2040. Instead, we are much more likely to approximate 100 percent reliance on commercial compensated plasma collections than we are to approximate 0 percent. With the facts as they are, it is time to steer away from the iceberg and to create a policy framework that permits rather than forbids commercial compensated plasma collections.

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