



FROM DEFICIT TO CONTRIBUTION: THE CASE FOR VOLUNTARY COMPENSATED PLASMA COLLECTIONS IN SPAIN

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1. INTRODUCTION

Spain has been the world leader (Gobierno de España, 2020), "by some considerable margin", in organ donation for over 28 years. With 49.6 donors per million population, and 117.4 transplants per million population, Spain accounted for a remarkable 20% of all organs transplanted in the European Union, and 6% of all transplants around the world. Other countries, including Australia and Canada, look to copy the "Spanish Model."

Similarly, Spain is a world leader in the production of plasma-derived medicinal products. Grifols, headquartered in Barcelona, is one of the largest plasma companies in the world. In 2016 through 2017, for example, the Grifols share (Mikulic, 2019) of the U.S. immunoglobulin market was right around 30%, or nearly a third.

Founded in 1909, Grifols operated 295 plasma collection centers around the world in 2019, making it the largest network of plasma collection centers in the world. While making its home in Spain, it does not operate any plasma collection centers there. Instead, 41 of their collection centres were located in China, 43 in Germany, and 252 in the United States (Grifols 2019, pps. 27-28) 73% of their more-than 24,000 employees are in the United States (17% in Spain).

Despite being home to Grifols, a world leader in plasma therapies, and despite the innovative approach that characterizes the Spanish Model in organ donation and transplantation, Spain uses an antiquated, inefficient, and ineffective model for plasma collection. This needs to change.

To ensure security of supply for patients in a more efficient manner than at present, Spain should adopt the commercial model of plasma collections. Spain already relies on this model to supply more than 60% (Ministerio de Sanidad, 2019) of the plasma therapies Spanish patients depend upon.

The commercial plasma collection model has been effective in every country where it has been adopted, while the other approaches, including the one used by Spain, have failed to meet demand in every country where they are the standard. The handful of countries that permit commercial plasma collection make up for the growing shortfall in plasma collections in every country. While being home to approximately five per cent of the world's population, the countries that have a commercial plasma collection

sector contribute more than 90 per cent of the plasma used to manufacture plasma therapies.

Spain is falling further and further behind, threatening current and future patients who depend upon lifesaving plasma therapies. To keep up with demand for plasma therapies and to avoid potential shortages as is likely to happen given the current pandemic, Spain needs to change policies. We argue that the path forward is for Spain to learn from and mimic the significantly superior Czech Model of plasma collections.

2. PANDEMIC EXPOSES THREATS TO PLASMA SUPPLY

While increasing demand for human blood plasma, the pandemic has also exposed the threat to security of supply that national blood operators have been warning about for years.

The pandemic resulted in a decline in plasma donations in the United States, with estimates suggesting a 20-25% reduction in plasma donations. Since the United States provides 75% of the world's supply of plasma for the manufacture of plasma therapies, such a decline represents a threat to patients all over the world.

Patients in Spain are amongst the first to feel the effects. Already a shortage in immune globulin is being reported, with hospitals rationing the therapy. Marta Ortiz, a nurse at the Hospital Clinico San Carlos in Madrid was quoted in La Razon as saying:

"It is a problem throughout the country and worldwide. It was known that there was going to be a reduction in immunoglobulins because donations during the first year of the pandemic were almost nil. Now we are low."

Italy, France, and Belgium are also reporting tensions in supply, which are likely to persist and so harm patients for a long time.

This is what Dr. Lluís Puig, Care Director at the Blood and Tissues Bank of Catalonia, warned about when he wrote about plasma self-sufficiency in Catalonia in 2018. He recognized a number of safety concerns when it came to the supply of plasma. Amongst them he listed the "possibility of restrictions on the export of plasma and plasma products from the United States to other countries" for reasons like "an increase in demand as a consequence of new indications or the introduction of protocols requiring increased doses of plasma-derived products."

But he also insisted that we recognize "the risk of epidemic events, which could prevent the export of plasma or plasma products." (p.39).

We are now in the midst of one of these epidemics. This may lead the United States to adjust policies if the shortage is severe enough to affect access to supply by American patients.

WHAT IS PLASMA AND WHAT IS IT USED FOR?

Plasma is the aqueous part of blood containing proteins and salt in which red and white blood cells and platelets are suspended. It constitutes approximately 55 per cent of total blood volume. Important elements in plasma include albumin, coagulation factors, fibrinolytic proteins, immunoglobulin and other proteins.

Plasma donations arose out of the health system's needs for sufficient quantities of raw material to produce medicines that are essential to treat a number of chronic diseases including immune deficiencies, hereditary emphysema and angio-edema, coagulation disorders, neuromuscular and cognitive disorders and hepatic disease. Additionally, they have proven essential in managing acute injuries and exposure to infectious agents. Moreover, to the known benefits of therapies derived from human plasma, exciting research into the development of new proteins and the expansion of indications for existing therapies is opening the door to a new age of medicine

Plasma can be obtained in two primary forms: recovered plasma (obtained from the "by-product" of whole blood collection) and source plasma (obtained through dedicated plasmapheresis). Collecting plasma from whole blood is subject to limited yields (a maximum of one litre of plasma per year, per donor). In addition, technical progress means that the need for red blood cell transfusions and thus for blood donations is declining. As a consequence, the primary source of plasma utilized in processing plasma protein therapies is from plasma centers (80% from the United States) and is fractionated primarily by private companies.

Through the process of plasmapheresis, plasma is removed, and the blood cells, platelets and other blood components are returned to the donor. This process can take as long as two hours to complete and the plasma obtained can be used only for the further manufacture of plasma protein therapies. Unlike blood cells from whole blood donations, the proteins in plasma lost through donation can be regenerated by the body in less than 24 hours.

3. COOKIES-AND-MILK DOES NOT WORK

Whereas Spain leads the world in organ donation, it trails countries like the Czech Republic, Hungary, Germany, and Austria, by some considerable margin when it comes to plasma collections. To give just one example, the Czech Republic, with about a quarter of the population of Spain, manages to collect nearly twice as much plasma – 726,859 in the Czech Republic, compared with 389,379 litres in Spain in 2019. It trails the United States by a margin that can only be described as insurmountable (the United States contributed (Penrod, 2020) more than 53 million litres to the global supply of plasma in 2019).

Unlike patients who require an organ transplant and can rely on fellow Spaniards to provide the organs, patients who depend on PDMPs, immunoglobulin in particular, rely mostly on the United States to supply the life-saving medicine they require. As Victoria Camps, prominent bioethicist and Emeritus Professor of Moral Philosophy at the Autonomous University of Barcelona, put it, “[n]either Catalonia nor Spain nor Europe are self-sufficient in plasma; if the pharmaceutical industry is able to attend to current demand for plasma products, it is thanks to the plasma collected in the United States, where donation is remunerated.” (Fundació Víctor Grífols i Lucas, 2018)

The model of cookies-and-milk-for-plasma has failed to meet demand everywhere in the world since 2014. In 2014, New Zealand was the only country in the world that was fully self-sufficient in plasma for plasma therapies without compensating donors. By 2015, however, New Zealand started importing and, according to their latest annual report, imported 12.5% of needed immunoglobulin plasma therapies in 2019.

The model recommended by the World Health Organization, the European Blood Alliance, and the government of Spain has resulted in insufficient plasma collections at a much higher cost than the alternative. The World Health Organization did not look at the evidence and adjust their recommendation. Instead, in 2012, they issued the Rome Declaration which urged countries to move to adopt policies of reaching national self-sufficiency through 100% non-compensated plasma donations by 2020.

When they issued the Declaration, only New Zealand was 100% self-sufficient in plasma therapies using non-compensated plasma donations. Today, no country is. Non-compensated plasma donations is a smaller and smaller proportion of the donations used to make plasma therapies, now representing merely a tenth (less than 11%) of the world's plasma therapies. Every country that approved the Rome Declaration and adopted the WHO standard has come to rely more and more, not less and less, on plasma from donors who are compensated for their time by commercial companies in the handful of countries that allow it. Especially the United States. This includes Spain.

4. THE SPANISH TREND

In 2012, more than half (57.2%) of Spain's immunoglobulin plasma therapies were made using Spanish unpaid plasma, with the remainder coming from paid donors at mainly Grifols-owned collection centres in the United States. By 2019, the latest publicly-available data, only a third (33.6%) of Spain's supply is made using Spanish unpaid plasma, with two-thirds (66.4%) being plasma collected from paid American donors.

Use of immunoglobulin has increased every year since 2012, when Spain was using 2,363,147 grams of immunoglobulin representing a rate of 51.36 grams per 1,000. By 2019, use had doubled to 4,718,967 grams, or 101.78 grams per 1,000.

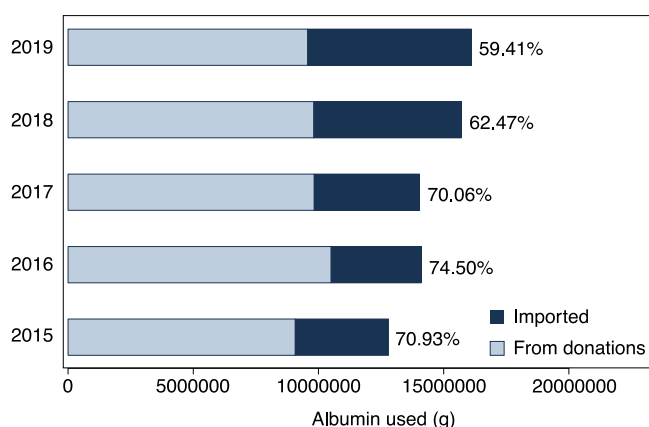
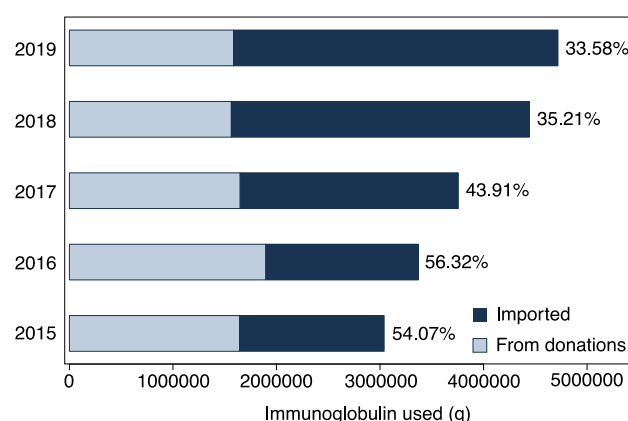


Figure 1. Immunoglobulin and albumin supply imported and obtained from voluntary non-remunerated blood donations (VNRBD) over 2015-2019. The percentage of immunoglobulin and albumin from non-remunerated blood donations is provided, respectively.

5. THE SPANISH REGULATION

European-continental legal systems are based on altruism and voluntarism as a rule regarding biological extractions from one's own body, excluding any compensation in exchange for these. There is a trend, still incipient though at the European level, to include exceptions to this general rule: the most relevant one is in relation to the donation of ova. In Germany or the Czech Republic, plasma collection has already been incorporated into the list of exceptions in which compensation is permitted.

In particular, the prohibition of economic compensation in exchange for the extraction of plasma in Spain was explicitly introduced in its current form in 1985 with the approval of the National Plan for Hemotherapy, which is based on "self-sufficiency in blood and blood products through altruistic donations". In the same year Royal Decree 1945/1985 was passed, which explicitly prohibited the compensation for the donation of blood or any of its components. In its Article 3.1 it established the following:

"The donation of blood or one of its components is the act of submitting to its extraction for the purpose of transfusion or obtaining therapeutic derivatives. It is always voluntary and unpaid and, consequently, there shall be no economic remuneration for the donor, nor shall any price be charged to the recipient for the blood donated. It must be carried out under medical control or supervision and in compliance with the requirements, minimum conditions and guarantees indicated in this Royal Decree and its regulations".

The text of the referred article is almost exactly the same as Article 2 of the Royal Decree 1574/1975, approved in the last years of the Francoist Regime, that for the first time in Spain explicitly prohibited the economic remuneration for the extraction of plasma.

Article 4 of Royal Decree 1088/2005, still in force and which replaced Royal Decree 1945/1985, which establishes the technical requirements and minimum conditions for haemodonation and transfusion centres and services, establishes the "principle of altruism":

1. The donation of blood and blood components is voluntary and altruistic. For these purposes, a voluntary and altruistic donation is defined as one in which a person willingly donates blood, plasma or cellular components and receives no payment for it, be it in cash or in any form that could be considered a substitute for money. Small

gifts in appreciation or reimbursement of direct travel costs are compatible with a voluntary unpaid donation.

2. The time required for a blood donation shall be regarded for all purposes as the fulfilment of a public and personal duty

It is worth noting two elements of the Royal Decree 1088/2005 in addition to the "principle of altruism": first, that the Royal Decree establishes in its preamble that "altruism and the voluntary nature of blood donation are the best guarantee of quality and safety for the donor and the recipient"; and second, that despite the fact that the aim of the Royal Decree is the incorporation into Spanish law of two European directives, 2002/98/EC and 2004/33/EC, relating to standards of quality, safety and technical requirements for human blood collection, neither of the two directives establish the principle of altruism as an obligation of Member States. The "principle of altruism" is thus a legislative innovation strictly of the Spanish legislator, and not an obligation under European law.

Likewise, it is pertinent to recall that the Royal Decree mentioned above establishes in its article 13.3 that "*imports of blood and blood components from third countries, including those used as raw material for the manufacture of medicinal products derived from human blood and plasma, shall comply with the quality and safety standards established in this Royal Decree*". As a result, Spanish legislation allows for the procurement of the plasma that may be needed without distinguishing whether the plasma has been obtained from paid or unpaid donors.

In addition, there are regional regulations, promoted by each of the Regional Ministries of Health of the Autonomous Communities, which reinforce the principle of altruism - any regional provision that modifies the content of Royal Decree 1088/2005 so as to allow financial compensation of plasma extractions would be illegal. As an example, the Catalan legislation (the Decree 298/2006, that regulates the Haemotherapy Network and creates the Haemovigilance System in Catalonia) establishes in its preamble and in its article 4.3, letter i), that any program of non-therapeutic plasmapheresis and cytophoresis must be "based in an altruistic donation" – the Catalan decree, in short, is in line with the Spanish Royal Decree and foresees the duty of the health administration to promote altruistic blood donations.

6. WHY VNRBD BECAME THE STANDARD

In the late 1990s, demand for immune globulin was flattening and there was hope that we might see only moderate growth in demand for this product in the future. At the same time, use of plasma-based Factor VIII was rapidly declining as a consequence of recombinant DNA technology making it possible to create a Factor VIII product without the use of human blood plasma. Meanwhile, improvements in the fractionation process meant that we could extract a larger number of proteins from each liter of plasma. Such innovations hinted at the possibility of seeing demand growth moderate, and possibly decline. In the late 1990s, then, the pressure to improve systems and increase plasma collection was low.

Simultaneously, many countries around the world were just beginning to see the full consequences of the tragedy of the global tainted blood scandal in the 1980s and early 1990s (European Commission, 2019). In Canada alone, a country with a population of around 25 million at the time, 30,000 individuals were infected with Hepatitis C and HIV, a then-novel virus, from blood transfusions and, mostly, use of plasma-based Factor VIII. Canada had imported blood for transfusions, as well as plasma therapies from the United States. Many countries, including Spain, relied on the same source for their plasma-based Factor VIII therapies. It was a near-certainty that patients with hemophilia who used Factor VIII would end up being infected with hepatitis.

Only later did we discover that the blood and plasma was collected in large part from prisoners in the United States penal system. This was a high-risk population. The prisoners were also paid for their plasma, which made the program very popular. In subsequent years, even to this day, people have overly focused on the fact that the plasma therapies were made from compensated donors, rather than from the fact that the plasma was sourced from prisoners, and other high-risk populations.

The combination of the possibility that demand for plasma therapies would moderate, coupled with the consequences of the tainted blood scandal and the over-emphasis on payment pushed more and more countries to adopt the Voluntary Non-Remunerated Blood Donation (VNRBD) standard. It also pushed plasma companies into significantly increasing their safety standards, including more restrictive deferral policies, and the

widespread use of not only heat treatment, but solvents/detergents, and other viral inactivation techniques. Along with improvements in testing for the presence of viruses, plasma therapies have had an unparalleled safety record. There has not been a transmission of an infection through plasma therapies meeting these high safety standards in over 30 years. And the vast, overwhelming majority of these plasma therapies were made using the plasma of donors who were compensated.

So while it was not unreasonable to believe that we could meet demand using the cookies-and-milk model of plasma collections in the late 1990s, it has been an unreasonable view ever since. We have discovered many additional applications for immunoglobulin that we did not anticipate 30 years ago. Today, a wide range of ailments, are treated with immunoglobulin. These continue to be rare diseases — immune deficiencies, autoimmune diseases, neurological disorders like multifocal motor neuropathy, hematological disorders like von Willebrand disease, and others — but it is now more likely that we will continue to find new indications (Novaretti & Dinardo, 2011).

7. CONTINUED GROWTH IN DEMAND

Spain will continue to see the portion of plasma therapies made from non-compensated Spanish donors decline for the foreseeable future. Continued rising demand, the prospect of new indications for currently existing plasma therapies, and improved diagnosis of ailments treated by plasma therapies will combine to make this a near certainty. The current pandemic may also result in a significant increase in demand, as might the prospect of new indications for more common diseases, like Alzheimer's and dementia. The continuing increase in demand comes just as the pandemic has revealed the precarious nature of the current supply chain for plasma therapies, exposing a potentially significant threat to security of supply for patients (Stanworth *et al.*, 2020).

From 1986 to 2014, the compounded annual growth rate in demand for immunoglobulin was 10.7 (Farrugia *et al.*, 2019). This demand is expected to continue to grow at 6-10% through at least 2025. In Spain, demand has increased 11.7 per cent per year on average between 2015 and 2019.

Such growth rates have been sustained as a consequence of the discovery of new indications for immunoglobulin, and the development of targeted diagnostic methods for patients who would benefit from immunoglobulin treatment. For example, immunoglobulin has been discovered to be effective against the Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathies (CIDP) (van Doorn, 2005) and just last year a publication (Díez-Porras *et al.*, 2020) described it may prevent myasthenia gravis exacerbations. While these are rare ailments, they are part of a pattern of expanded indications for this plasma therapy. The continuing increase in demand comes just as the pandemic has revealed the precarious nature of the current supply chain for plasma therapies, exposing a potentially significant threat to security of supply for patients.

Some continue to hold out hope that demand for immunoglobulin will flatten or is higher than it should be. It is a fact, for example, that we continue to see off-label uses of immunoglobulin, with some doctors prescribing the expensive treatment for ailments that do not have sufficient evidence. It may also be true that the volume of immunoglobulin prescribed is sometimes more than what is appropriate.

Such hopes are, unfortunately, misplaced. The population of patients using immunoglobulin in off-label or non-indicated cases is much smaller than the population of people who would benefit from immunoglobulin but are currently not using it. Looking exclusively at primary immune deficiencies and neurological conditions for which immunoglobulin is the first-line therapy or one of the primary recommended treatments, Albert Farrugia *et al.* have estimated the latent therapeutic demand at 250 grams per 1,000, more than twice Spain's current use at 101.78 grams per 1,000. With one of the strictest systems for prescribing immunoglobulin, Australia, for example, uses approximately 240 grams per 1,000 (Farrugia *et al.*, 2019).

The estimate provided does not foresee the possibility that we might find additional indications for immunoglobulin in common diseases, which would dramatically change this earliest forecast. Beginning in 2004, Grifols has dedicated significant resources on an albumin replacement therapy (Grifols, 2020) for Alzheimer's, a form of dementia expected to affect 82 million people by 2030 according to the World Health Organization. In 2011, Grifols began a clinical trial called AMBAR (Alzheimer Management by Albumin Replacement). Published on July 27, 2020, the results of the trial were promising: "This trial suggests that Plasma Exchange with albumin replacement could slow cognitive and functional decline in Alzheimer's Disease, although further studies are warranted." (Boada *et al.*, 2020).

In line with this, a novel anti-SARS-CoV-2 hyperimmune globulin product is undergoing trials. Obtained from convalescent plasma, hyperimmune globulin is highly purified and concentrates the specific antibodies to largely neutralize coronavirus, which makes it likely to be superior to the transfusion of non-purified and non-concentrated convalescent plasma. According to Peter Vandeberg and co-authors, "Processing convalescent plasma into hVIG resulted in a highly purified IgG product with more concentrated neutralizing antibody activity. hVIG will allow for the administration of greater antibody activity per unit of volume with decreased potential for several adverse events associated with plasma administration. IgG concentration and IgG antibody specific to SARS-CoV-2 were increased over 10-fold from convalescent plasma to the final product" (Vandeberg *et al.*, 2020).

Taken together, a decrease in demand for plasma therapies is highly unlikely, while similar or higher growth rates than at present are likely.

The insecurity in current and future supply represents one of the most significant threats to national health-care systems that needs to be immediately addressed. As Ll. Puig Rovira recently wrote: "If forecasts for the increase in world use of IVIG are met, it is highly unlikely that the USA and other countries in which plasma donations can be remunerated will be able to respond to this increase in demand." (Ll. Puig Rovira, 2020)

8. COMPENSATION WORKS

Unlike countries that adopted the World Health Organization standard that have seen domestic plasma collections fail to keep up with growing demand, the few countries that permit commercial plasma collections which use a compensation model are now not only 100% self-sufficient in plasma for their plasma therapies, they are also the only reason why patients in other countries get the lifesaving therapies they need. Germany, Austria, Hungary, and the Czech Republic are not only self-sufficient in safe and effective plasma therapies, but they are also net exporters.

However, as noted by a European Commission Evaluation of the Union legislation on blood, tissues and cells, there are not enough private plasma collection centres in the EU to keep up with demand: "While the number of private plasma collection centres in the EU has increased in recent years, *this is far from sufficient to keep up with increasing demand for plasma derived medicines*. This has led to high dependency on import of plasma from the US." (European Commission, 2019)

Commercial, compensated plasma collection is safe, efficient, and effective in every country it has been permitted. Apart from its obvious effectiveness in the United States, which alone supplies nearly three-quarters of the world's plasma for plasma therapies, the Czech Republic is an illustrative example.

When compensation is ruled out, potential donors are often offered non-monetary benefits in exchange for blood. But non-cash benefits are not automatically bereft of economic value; someone covers the costs of the blood donated, albeit indirectly. For example, Spanish law specifies that "*time spent donating blood is for all purposes considered to be fulfilling a public and personal duty*". This means that workers can leave their jobs to give blood and that management must absorb the cost either of lower productivity or of temporarily replacing employees. That is to say, the employer effectively transfers resources to the blood-supply system.

Assuming that an all-volunteer system requires at least 50 donors per 1,000 people to give whole blood twice annually (and plasma much more frequently), the transfer of resources becomes considerable. A program to compensate employers for employees' lost time seems an unsatisfactory solution on two counts. First, it would solve neither lower production levels nor reduced

productivity, particularly in small, extremely specialized firms which depend on highly trained personnel. Second, such a program would open the door to abuse and fraud. From an ethical standpoint, it is difficult to justify why one sector should bear the financial burden of the blood-supply system, which is ostensibly the responsibility of the entire community.

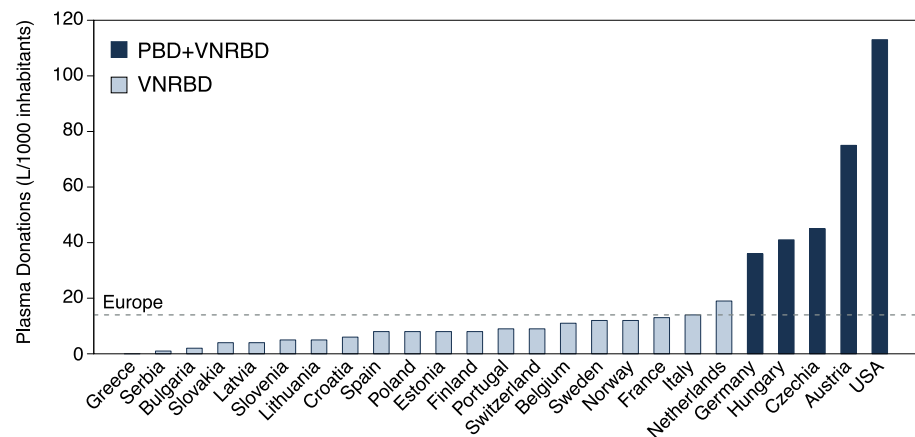


Figure 2. Plasma donation per capita in European countries and USA (litres per 1,000 inhabitants) in 2017. Countries allowing paid blood donors (PBD) along with voluntary non-remunerated blood donors (VNRBD) are shown in dark blue. Those with plasma collections derived only from VNRBD are shown in light blue. The European average of collected plasma is represented as a dashed grey line (Marketing Research Bureau: Reports 2017. <https://marketingresearchbureau.com>).

9. THE CZECH MODEL

The Czech Republic saw its first commercial, compensated plasma collection centre open in late 2007, with a significant increase in these centres in 2008. Like Spain, the Czech Republic was reliant on imports of plasma therapies made from compensated donors in 2007. That year, the Czech Republic sent 116,601 litres of plasma for further manufacture into plasma therapies, representing 11.29 litres per 1,000 population. 2007 represented a significant increase over the prior year's volume of plasma sent to fractionation, which was 82,900 litres, or 8.05 litres per 1,000.

Over the next three years, plasma collections for fractionation increased nearly five-fold from 116,601 litres in 2007 to 541,072 litres in 2010; from 11.29 litres per 1,000, to 52.38 litres per 1,000. Over just three years, the Czech Republic went from importing the majority of their plasma therapies to collecting more plasma than needed by Czech patients, and so joining Germany, Austria, and the United States in helping to ensure that patients in countries like Spain get the life-saving medicine they need. This was a remarkable achievement.

To compare the performance of the Czech Republic to Spain, consider that in 2006, Spain had sent 302,105 litres of plasma to fractionation, representing a rate of 6.88 litres per 1,000 to the Czech Republic's 8.05 litres. Despite a population nearly four times smaller than Spain's, the Czech Republic was sending more litres of plasma for further manufacture into plasma therapies by 2010 -- 541,072 litres to Spain's 380,560 litres. By 2016, the Czech Republic was sending nearly twice the volume of plasma for fractionation as Spain was -- 613,600 litres representing 58 litres per 1,000 to Spain's 373,376 litres representing 8 litres per 1,000.

This remarkable achievement is all-the-more remarkable when we consider the fact that the increase in plasma collections did not come exclusively from the commercial sector. Plasma donations to the not-for-profit, non-compensated sector also increased. Again, in 2007, the Czech Republic collected 90,285 litres from non-compensated source plasma donors. While the 2008 data set combined the commercial and non-commercial sectors (so we cannot disentangle which came from which), the 2009 data tells us that 92,067 litres of plasma came from non-commercial, non-compensated source plasma donors, rising to 103,258 litres of source plasma in 2010 (meanwhile, the commercial sector contributed 309,249 litres in 2009, and 408,574 litres in 2010).

We have more comprehensive data when we look at the total volume of plasma sent for fractionation from non-compensated source plasma collections and recovered plasma taken from non-compensated whole blood donations. In 2006, the total volume of non-compensated plasma sent for fractionation was 70,130 litres. It rose to 84,076 litres in 2007. In the year that compensated source plasma donation started, the volume of non-compensated plasma sent for fractionation increased to 104,815 litres, then to 122,364 litres in 2009, and to 164,681 litres in 2010. From 2007, the year prior to the introduction of commercial, compensated plasma collections, to 2010, the volume of non-compensated plasma sent for fractionation by the non-commercial sector increased by 95.87%.

Did this increase in commercial and non-commercial plasma collections come at the expense of whole blood donations? Not at all. In 2007, the Czech Republic collected 407,993 units of whole blood from 396,732 whole blood donations. 2008 saw an increase in whole blood collections and donations, with 419,154 units of whole blood collected from 410,594 whole blood donations. In 2009, 426,824 units of whole blood were collected from 425,350 donations. 2010 saw essentially no change with 421,467 units collected from 425,234 donations.

The pattern has continued. By 2012, the Czech Republic had 40.9 whole blood collections per 1,000 population, while Spain had 37; they had 1.7 platelet apheresis donations per 1,000, while Spain had 0.2 (Creative Ceutical, 2015). And while Spain had 0.5 source plasma donations per 1,000, the Czech Republic had 58.8. (Creative Ceutical, 2015)

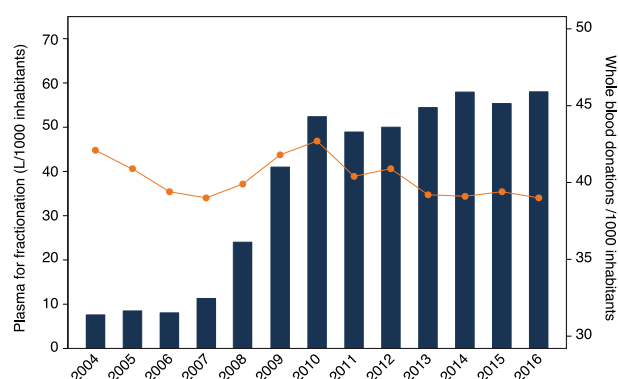


Figure 3. Plasma collections and whole blood donations in Czech Republic from 2004 to 2016. Bar plots show plasma for fraction as L per 1000 inhabitants and orange dots represent whole blood donations per 1000 inhabitants.

The Czech success with commercial plasma collections did not come at the expense of non-commercial, non-compensated blood or plasma collections. The two sectors appear to complement one another, rather than be rivalrous.

It also did not come as a result of higher donation frequencies. While the United States and Canada permit twice weekly, with 48 hours in-between, plasma donations up to 104 times per year, the Czech Republic permits a donation frequency of once every 14 days, for a maximum of 33 times per year.

Instead of "crowding out" or "encroaching" on non-commercial source plasma, whole blood, and platelet donations, they each saw an increase despite the introduction of the commercial, compensated plasma donation model in 2008.

10. OBJECTIONS TO THE CZECH MODEL

The Czech Model is significantly better than the Spanish approach to plasma collections, and so Spain should look to the Czech Republic to ensure safe and sufficient therapies for Spanish patients. What stands in the way?

A number of practical as well as ethical concerns have been raised. These include concerns about:

- i.The safety of the final product when processed from the plasma of compensated donors;
- ii.The safety of frequent plasma donations to donors;
- iii.The worry that compensated collections will undermine non-compensated blood collections;
- iv.The possible erosion of "solidarity" or altruism as a consequence of permitting compensated donations;
- v.And the concern that the commercial, compensated plasma collection model exploits low-income populations.

Already we have seen that considerations about the safety of plasma therapies made from remunerated plasma are flawed. If it were an actual concern, Spain would not be largely relying on plasma therapies obtained from this source.

Concerns over the safety of too-frequent plasma donations to donors are a result of failing to see that the United States and Canada are not the only possible models for commercial, compensated plasma collections. Such concerns are not applicable to, for example, the Czech model nor similar models found in Austria or Germany where the maximum number of donations are 50 and 60 times per year, respectively.

Thus, self-sufficiency does not depend on permitting twice-weekly plasma collections, as each of these three countries collect sufficient plasma not only to meet the needs of Czech, Austrian, and German patients, but also enough for export.

11. CROWDING OR "ENCROACHMENT"

This self-sufficiency need not come at the expense of non-compensated blood donations. It is common, however, for blood organizations to express concerns about the impact of compensated plasma on non-compensated blood donations. The Belgian Red Cross, for example, wrote in 2018, "Where payment for plasmapheresis is introduced, the pool of people willing to donate for free evaporates fast." The European Blood Alliance said in 2016, "Payments to blood and plasma donors by commercial suppliers erode the current community-based, non-compensated, donor population, which is the key element to secure a sustainable blood supply."

And it continues to be the position of the European Blood Alliance that compensated plasma has a negative effect on non-compensated blood donations ("In some Member States, the development of commercial plasma collection centers, using compensated donors, is eroding the voluntary donor base for labile blood products and jeopardizes the sustainability of the supply of the full range of blood products." Page 2). Such sentiment is echoed by the European Commission as well ("The blood supply might also be threatened when potential blood donors are attracted away from blood donation by compensation given for plasma donation in the commercial sector." Page 35)

The evidence in favor of this negative impact is, however, anecdotal and based on surveys. In actual practice, there is as yet no support for this negative impact hypothesis. The experience of the Czech Republic, which saw increases in non-compensated blood and plasma collections after the introduction of opportunities to sell one's plasma, is not unique. A similar result was found in Canada and the United States, when looking at cities that saw the introduction of compensated plasma opportunities in the presence of long-standing non-compensated blood collections. In those cases, as in the Czech Republic, there was a small but positive effect. Meanwhile, in the case of Germany, Dr. Franz Weinauer, the former medical director of the blood donation service for the Bavarian Red Cross, has explained that there was no impact on blood collections in Bavaria from compensated plasma collection centres.

Such results have a few possible explanations. The most likely explanation is that different populations are attracted to these opportunities. Some donors are not interested in the financial incentive, and so will donate blood or plasma but won't do it in the presence of compensation. Others are not interested in giving either blood or plasma, but might be persuaded given a sufficient financial incentive. A third type might be interested in either, and would be willing to either donate blood or plasma, or do it with compensation.

This hypothesis suggests that "encroachment" will come not from the introduction of compensated plasma opportunities, but from the introduction of more significant efforts to collect non-compensated plasma. National blood operators will be asking the very same population to shift from donating blood to donating plasma. It is unlikely that they will attract many new donors but will, instead, turn repeat blood donors into plasma donors instead.

12. MORAL CONCERNS (SOLIDARITY AND EXPLOITATION)

Concerns regarding the safety of the finished product, safety to donors, and the possible negative effect on non-compensated blood donations should therefore not delay a move to compensating for plasma collections. That leaves us with two important moral concerns -- one regarding solidarity and altruism, and another having to do with the exploitation of the vulnerable groups.

Before we address those concerns, however, it is worth pausing to remark on Spain's current policy. Spain is significantly reliant on plasma therapies made from the plasma of American donors who have been compensated. The money spent by the Spanish government to purchase plasma therapies is used by companies like Grifols to, in part, pay those donors. Following this rationale, Spain already compensated plasma donors, it just chooses to pay Americans for their plasma, rather than Spaniards for theirs. As Victoria Camps put it, "It is hard to describe this situation as anything other than hypocritical." (Fundació Víctor Grífols i Lucas, 2018)

She continued:

"In general, in Spain, with a few exceptions, the principle of non-compensated blood and plasma donation has been maintained without distinction. At the same time, nobody objects to the use of plasma from compensated donors to attend to the therapeutic needs of our patients. The question is this. Which is ethically more acceptable: maintaining the altruistic principle of non-compensated donation along with the attendant hypocrisy, or accepting reasonable reward for plasma donation so that countries are able to supply their own needs?" (Fundació Víctor Grífols i Lucas, 2018)

There are also open questions about whether or not compensating plasma donations will, of necessity, come at the expense of altruism and solidarity. We pay nurses and medical doctors, for example, but recognize the possibility that there are nurses and doctors who do not pursue their profession exclusively for the money. It is an assumption, not an established fact, that people who are compensated for their plasma are indifferent to the life-saving

benefits of that plasma. Until there are enough studies of the motives of compensated donors, we need to leave open the possibility that some will do it for the money, and because it will help save lives.

13. CONCLUSION

Despite being home to Grifols, a world leader in plasma therapies, and despite the innovative approach that characterizes its organ donation and transplantation system, Spain uses an antiquated, inefficient, and ineffective model for plasma collection. This needs to change.

Relying entirely on non-compensated donors may lead to shortages, and undermines security of supply for patients, as well as negatively impacting research and development projects which rely heavily on plasma. And moral decisions that affect patients and other individuals should be evaluated by also taking into account the effects and consequences of policy. Thus, the most economically viable and socially constructive approach is to reverse the ban on compensated plasma collections.

The current regulation of plasma collection in Spain is unequivocal: under no circumstances is compensation to a plasma donor legal. However, there is no apparent impediment for the reform of the Royal Decree 1088/2005, given that there are no European Directives or Regulations that prohibit compensation for plasma collections; there are also no Constitutional references or Organic Laws –hierarchically superior to Royal Decrees – that could be considered an obstacle for permitting a compensated plasma collection model.

As this area is not considered of constitutional relevance, and so not subject to the special regime of the Organic Laws, a reform of Royal Decree 1088/2005 could be approved by the Council of Ministers. However, it should be noted that the new regulation should consider that some Autonomous Communities have regional laws that prohibit compensation, so special attention should be given to the implementation of the new regulation. Following the same example given above, the Catalan Decree 298/2006, that currently prohibits compensation for plasma collections, should be modified to comply with the eventual Spanish regulation –permitting compensation for plasma collections– by virtue of the latter being hierarchically superior in a functional sense. In short: it is just as true that currently no regional law could contravene the principle of altruism of the Royal Decree, as it is that if a new national law were to permit compensation for plasma collections, a regional law could not prohibit it.

The Czech Republic was perhaps Europe's most significant achievement in blood and plasma collections and services this past decade. There are also no reasonable prospects for the cookies-and-milk-for-plasma model to succeed. Demand for immune globulin is projected to continue growing at 6-10 per cent well into the future.

To become and remain self-sufficient, Spain not only has to increase plasma collections seven-fold (as the Czech Republic did), but it would also have to continue to increase collections at 6-10 per cent each year. And if Spain, a wealthy, healthy, and generous nation, wants to contribute to the global supply of plasma, as every wealthy and healthy nation should, it has no choice but to adopt a model that permits compensation. It should be clear that accepting reasonable reward for plasma donation -- following the Czech Model -- is ethically more acceptable.

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