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REVIEW

Payment, compensation and replacement – the ethics and motivation of blood and plasma donation

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The supply of blood and plasma to produce haemotherapies varies around the world, but all environments need donors to furnish the raw material. Many countries still lack adequate supply, and the question of what amounts of blood and plasma are required for optimal treatment is still unresolved. The issue of compensating donors has been a controversial and emotive one in blood transfusion for many decades. Donors are conventionally classified as paid, voluntary or replacement, and a level of stigma, based on safety and ethical considerations, has been attached to paid donation. This review points to evidence which renders many of these concerns redundant. Purist arguments against compensated donation have little basis in evidence and would lead to many of today's voluntary donors being designated as paid, because of the large range of incentives used to recruit and retain them. Misplaced application of 'Titmussian' volunteerism has precipitated its own safety and supply problems. Current systems of compensation and replacement are needed to maintain supplies of essential products and lead to safe products in controlled environments. We propose that a plurality of routes towards donation is an appropriate paradigm in the heterogeneous landscape of blood and plasma product supply.

Key words: altruism, donors, motivation, safety.

Introduction

The provision of blood and blood-derived therapeutics has evolved along diverse paths in different areas of the world. As a result of this evolution, three main sources of blood and aphaeresis/source components (plasma for transfusion, plasma for manufacture, platelets and red cells), have been established:

(1) Voluntary, non-remunerated: These donors are considered to have received no compensation for their donation, on the basis of definitions to be discussed later.
(2) Paid, compensated: These donors are openly compensated monetarily for their donation.
(3) Replacement, family: These donors donate with the intent of replacing or directly contributing to blood used by a specific patient.

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The developed first world economies have, on the whole, phased out the collection of whole unmodified blood through the compensated and replacement routes. Compensated and replacement donors are still a significant and sometimes predominant part of the blood supply in developing countries [1]. Apheresed components such as platelets are still harvested from compensated donors in many countries, such as Austria and Germany, where this is excluded for whole-blood donation. Source (apheresed) plasma for fractionation is still procured from compensated donors in many countries. The United States source plasma industry, comprising some one million donors and 17 million collections yearly, is responsible for 55% of the world's supply of plasma derivatives [2].

In the USA, the practice of paying whole-blood donors was established until the 1970s. The American Blood Commission established in 1973 developed a National Blood Policy [3], which advocated, amongst other measures, the phasing out of compensated blood donation. The pressure for this measure had been mounting since the demonstration that such donors transmitted high rates of hepatitis [4].

Reportedly, the Commission was strongly influenced by the classic sociological text on blood of Richard Titmuss. This book – The Gift Relationship (TGR) – become a bedrock for the case against paid donation. Allegedly, the then Nixon administration consulted Titmuss on the need for reform in the US blood system [5, p. 6].

TGR is essentially a manifesto for the classical welfare state vision of public goods and services and exemplifies these concepts primarily through a comparison of the US and UK blood systems in the late 1960s. Titmuss' arguments are still reflective of the case against compensated donation:

(1) Commercial supply of paid blood discourages altruistic, voluntary donation, hence leading to supply shortfalls – the so-called 'crowding out' effect [6] – and increasing costs.
(2) Paid blood is inherently unsafe as the financial motive makes people in high-risk groups for certain diseases lie about their status to get money.
(3) Paying donors invariably draws the most economically challenged part of a community into an exploitative relationship because of an economic as opposed to a gift-based negotiation with the collection agency.

In advocating for a gift rather than market-driven relationship for blood donation, Titmuss invokes classic sociological concepts of the gift as exemplified by the work of Mauss [7] in primitive cultures. Such gift-giving is much more structured and much more based on presumptions of reciprocity than the spontaneous, totally unilateral character which Titmuss attributes to the voluntary blood donor. Analysis of the raw data from which Titmuss drew his conclusions indicates methodological problems which lead Rapport and Maggs [8] to conclude that the motivations of voluntary blood donors cannot be drawn from TGR. It is likely that Titmuss' influence, despite the accolades heaped on TGR, has been exaggerated and that moves to phase out paid donation in the developed work occurred independently of this work. The principal legal measure used to put pressure on paid donation was the introduction by the FDA in 1975, and its mandating in 1978, of a requirement to label blood as 'paid' if it is from monetarily compensated donors [9]. By the late 1970s, the proportion of blood establishments compensating whole-blood donors had shrunk to 5% of the total.

Internationally, the main influence in generating an ethos against compensated blood donation has been the World Health Organization (WHO). In 1975, the World Health Assembly (WHA) passed resolution WHA 28.72 [10] urging member states to develop blood systems based on voluntary non-remunerated donation of blood. This resolution is prefaced by the concern that the operation of commercial plasmapheresis firms in developing countries was impeding efforts to develop national blood systems through 'crowding out' donors from the blood collection sector. WHA 28.72 has proven to be the ideological basis for a range of blood policies worldwide, and was endorsed by all the WHO member states, including countries that continue to sanction the compensation of some donors in their blood systems, particularly source plasma donors, to this day.

Current perspectives on the blood supply worldwide

Blood and blood components

The amount of blood needed for mainstream transfusion and fresh component purposes obviously depends on the socio-economic status of the particular country. WHO recommendations in the 1980s specified a donation rate of 50 per 1000 population [11] but do not seem to be based on evidence. Current Council of Europe data show a wide range of donation rates between countries of an apparently similar health care delivery status [12]. Currently, the WHO specifies 10 donations per 1000 population as the minimum [1] and cites a wide range in the donation rates between countries broadly classified as developed, transitional and developing. One would expect similar clinical practices and transfusion regimens in, e.g. Australia and Canada, but the blood donation rates are significantly lower in Canada which collects 35 units per 1000 population compared to Australia's 48·5 [13–15]. The two countries' capacity to generate plasma for fractionation is also very different, with 6·1 and 18·7 ml per inhabitant for Canada and Australia respectively. This demonstrates deep differences in the way the two countries manage the delivery of blood-derived therapies while achieving similar outcomes in comparable socio-economic health systems.

The optimal number of blood collections required relates to variations in clinical practice which are hard to discern superficially. For example, in the mid 1980s, Canada's blood system was operated by the Red Cross and collected a peak of 45 donations per 1000 population. It collapsed to a nadir of 23 per 1000 population, 10 years later in the wake of the 'blood scandal' [16] before coming back to the present 35 per 1000 population. There is little evidence that clinical outcomes in blood-demanding interventions were affected by this. Similarly, a significant drop in red cell issues of 26·4% as a result of safety-related deferrals over 1998–2008 by the United Kingdom's blood services was absorbed without reported adverse clinical outcomes [17]. It seems that developed blood systems cope with donor loss when the circumstances dictate no other option, probably because of an economic capacity to pursue alternatives to transfusion. It is noteworthy that contingency blood supply plans indicate that up to half the average national collection rates can absorb the medical needs of

an emergency precipitous drop in the blood supply [18], while day-to-day fluctuations of up to 10% in the main supply occur in developed countries without affecting clinical outcomes [19].

The red cell usage rate is the historical driver of whole-blood collection for the purpose of making transfusable fresh components and collection above this rate for, e.g. generating plasma for fractionation will lead to red cell expiry and unnecessarily expose donors to risks such as iron deficiency. Given Canada and the UK's experience in adjusting to a shrinking donor base, it appears that a supply rate of 35 units of red cells per 1000 population may be sufficient for a developed health system. Increasing awareness of the modest evidence base for red cell transfusion and dosage [20], which is detached from any regulatory requirements to demonstrate efficacy, may be shaping clinical policy in the face of supply levels lower than historically thought to be desirable. Emerging indications of the possible adverse events of stored red cell transfusion [21] may be expected to moderate red cell usage further. It is noteworthy that both Canada and the UK, in contrast to Australia, have detached their blood systems from the need to collect plasma for fractionation as the main supply driver.

Clearly, many emerging countries are not achieving rates comparable to those of developed countries, [1] (Fig. 1) and are not even achieving the WHO's minimal target of 10 red cell units per 1000 population. Many of these countries are dependent on achieving even these modest rates on replacement donors. While an opportunity may exist to shape blood supply policies in these countries to reflect optimal usage and evidence rather than historically driven figures, there is little doubt that donation rates in many countries are desperately inadequate, e.g. 26% of in-hospital maternal deaths in sub-Saharan Africa (SSA) are from lack of blood [22]. This is a reflection of the blood supply's conformance to global inequality, with 82% of the world's population is in developing countries accessing only 39% of the donated blood supply [23]. In many such countries, the development of a first-world type centralized blood service is too expensive and at odds with overall public health policies which promote decentralization [24]. The blood supply in much of SSA is dependent on hospital-based services drawing on replacement donors [25]. The main reason is cost, with uncompensated units continuing to be at least double the cost of replacement units [24], partly because of an infrastructure for rewarding and acknowledging uncompensated donors [26]. Costs for replacement donors, however, may be hidden and result in significant burdens on the patients' families [22]. Studies have shown that the relative safety of uncompensated and replacement donors in these environments is a feature of the particular demographic [26,27]; regular replacement donors are safer than first-time donors, irrespective of whether these are uncompensated or replacement donors. Repeat donation and not donor type is what determines blood safety.

Plasma protein derivatives

Unlike blood components, approval to market these drugs depends on the demonstration of efficacy for the medical

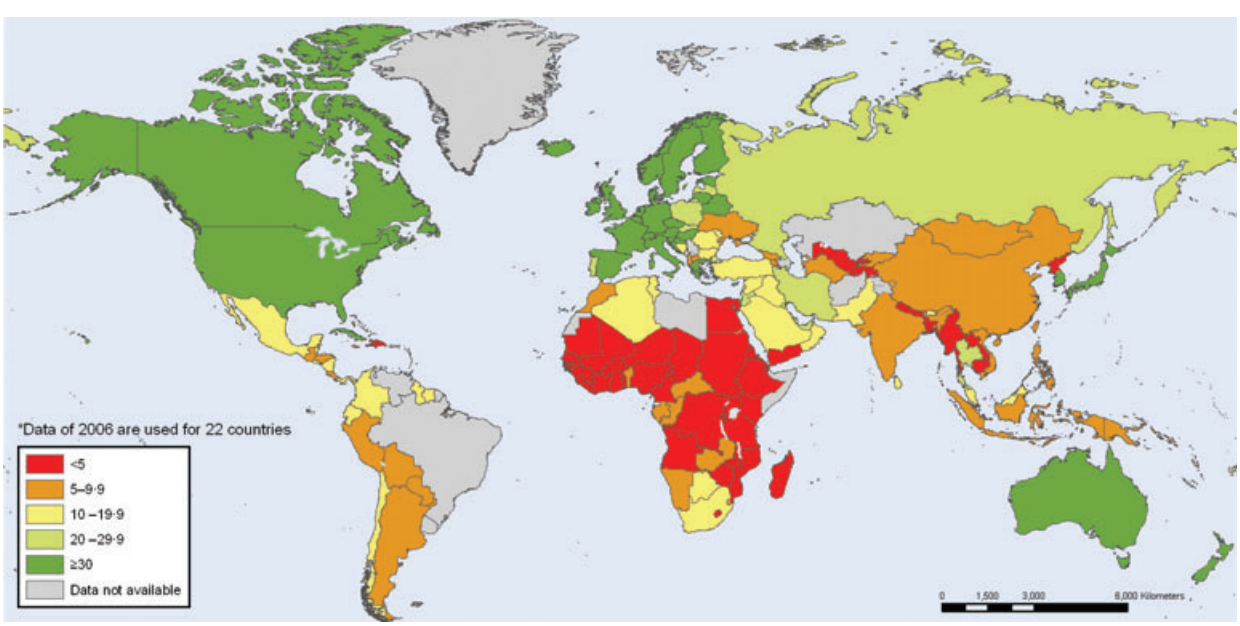

Fig. 1 Blood donation rates per thousand population. From http://www.who.int/mediacentre/factsheets/donations_per1000_population_20091110.pdf.

indications sought. The historical development of plasma protein therapies has been reviewed [2] and has progressed through a series of product drivers, each of which has determined the amount of plasma required for the manufacture of the therapies. Thus, the industry has progressed from albumin to coagulation Factor VIII to concentrated immunoglobulin as the product drivers. The demonstration of efficacy of immunoglobulin solutions in a large number of immunodeficiency and autoimmune states led to immunoglobulin (Ig) assuming its current dominant role in the 1990s [28]. As more indications become supported by evidence, the clinical use of Ig continues to grow [29] and supplies are constantly under pressure. A usage of around 100 g per 1000 population in Australia is allocated by a single government funder on the basis of strict evidence-based criteria [30] and constant monitoring, and is reflective of usage in most developed countries, including the USA, outside the European Union which supplies 41·5 g per 1000 population [2]. These relative disparities are a reflection of different capacities to generate plasma for fractionation and the presence or absence of protectionist policies for national fractionators. The USA generates 32·5 ml per inhabitant of plasma compared to 10·3 ml per inhabitant in the European Union, while Australia generates 18·7 ml per inhabitant. In many EU countries, plasma product imports are curtailed, e.g. in France, imported products are restricted through shorter licence periods than domestic products.

Continuing pressures in the supply of Ig, fuelled by an increasing range of indications and increasing dosages [31], make the supply of plasma for fractionation a crucial factor in assuring access to patients. The world supply of plasma derivatives is still strongly dependent on the US source plasma industry which compensates donors and is exempt from the FDA's labelling requirement [9]. In 2010, 51% of the world's supply of plasma for fractionation will be generated by the US source plasma sector [2]. The global dependence on the United States is worrisome and should spur efforts to access other plasma sources. This high capacity to generate source plasma is because of the plasmapheresis regimens approved by the FDA which are more liberal than those of the EU. The US legal limit of 104 collections annually is unreflective of the reality of a 14–17 collections per donor per year [32], but is still higher than the five collections per donor yearly achieved by a typical European national fractionator [33]. The realities of clinical need clearly moderate the political drive for uncompensated donation and self-sufficiency in the European Commission's directives.

Generating sufficient amounts of aphaeresis plasma without compensating donors is considered unfeasible [34]. In Germany, compensated plasma donation results in 12 units per donor yearly, similar to the rate in the USA, collected from a different demographic to whole-blood donors [35], suggesting that apprehensions of 'crowding out' through plasma donor compensation are unfounded.

What is payment?

Over the years that this sensitive issue has occupied the minds of transfusionists, ethicists and policy makers various attempts have been made to define payment in the blood/plasma donor context. Two such definitions are embedded in statutory or semi-statutory statements. The FDA's labelling rule [9] specifies payment as cash or items directly convertible to cash, and defines which benefits constitute or do not constitute payment (Fig. 2). In the EU, the European Commission [36] encourages, but does not mandate, voluntary non-remunerated donation through the Council of Europe's definition [37]. The definition, in contrast to the FDA's form of words, specifies time off work (other than that required for the donation and travel) as a substitute for money.

This raises the issue of incentives for blood donation in lieu of direct monetary compensation. Such incentives abound in the European Union. While some jurisdictions, such as France and the Netherlands, strictly allow time off work as that needed to donate and associated travel, in Italy, a paid day off work has been shown to increase the average blood donation rate by one unit yearly [38]. Such incentives are also considered to be very important by Greek donors [39], and Greek investigators have urged for their expansion [40].

Incentives in the United States appear to occasionally skirt around the FDA's regulations, such as legitimate questions regarding, for example is a car won through a

"Paid" incentives	Items that qualify as "non-payment"
Cash payment or cash equivalent	Tokens or prizes of nominal value (cups,t-shirts etc)
Tickets to events where markets for resale exists	Paid time off
Music media where market for resale exits	Raffle tickets where prize may not be directly convertible to cash
Transferable discounts/coupons convertible to cash	Gift cards/certificates not transferable, not redeemable, in donor's name
Vouchers for free medical tests	Medical tests performed at time of donation
Scholarships paid directly to students	Scholarships paid to academic institution
	Membership in blood assurance programs

Fig. 2 Summary of status of incentives as assessed by the Food and Drug Administration under the authority of the Code of Federal Regulations (CFR).

blood-drive promotion not 'convertible to cash'? [41]. The FDA's exemption of time off work also appears incongruous, given the undeniable monetary value of such a measure.

In the United States, the labelling requirement has effectively excluded payment for whole-blood collection, although some residual cytaphaeresis programmes continued into the 1990s [42]. In Europe, paid whole-blood collection is still a feature of some of the recently admitted countries of the European Union, such as Lithuania [43]. In addition, legislation specifying that all forms of blood and plasma donation is unpaid in Germany and Austria is interpreted by the authorities as compatible with reimbursement for expenses incurred in whole blood, plasma and platelet donation. This regularly exceeds the amounts given to compensated plasma donors in the United States [44]. Such ambiguity is also visible in China where payment for blood donation is illegal, but cash payments which exceed the costs of most mainstream everyday necessities are still made to donors [45]. In most countries, a tacit acceptance of the need to compensate donors in various ways appears to be established, while continued adherence to the 'voluntary, non-remunerated principle' is maintained.

Does payment render blood unsafe?

Recent statements from the WHO reiterate the belief that uncompensated donation contributes to safety from transfusion transmitted disease [46,47]. This paradigm is incomplete at best. Blood-borne infections cannot be automatically and causally linked to the composition of donor populations on the basis of socio-economic or compensation status. In localized, controlled environments, viral marker rates for paid and unpaid donors were shown to be similar for the established transfusion-transmitted infections, [42,48], while in others they were not [49]. The paid donor system in the EU state of Lithuania [43] is comprised mostly of regular donors with a better safety profile than first-time donors, irrespective of their compensation status [50]. Improvements in safety in these environments can be attempted through the use of nucleic acid testing and excluding the use of first time donations, a policy which is operated in tandem in South Africa.

The scenarios around the most recently emerging infections transmitted by blood [51] were unlinked to any aspect of socio-economic status or donor compensation. The initial entry of HIV in the US blood supply was primarily through highly motivated, voluntary male gay donors, committed to the type of social engagement advocated by Titmuss. Healy [52] has discussed how organizational and cultural allegiances influenced the measures taken by different parts of the blood and plasma sector. HIV's contamination of the plasma pools used to manufacture plasma therapies was irrespective of whether it originated from compensated or uncompensated donors. This is shown by the examples of countries like Australia and France, whose dependence on a voluntary plasma pool did not protect haemophiliacs from HIV infection rates similar to those in the USA [53,54]. Variant Creutzfeldt-Jakob disease (vCJD transmission) has only occurred in recipients of the UK's voluntary donor system, which has had to import commercially purchased compensated donor plasma to supply its plasma product users. In a globalized world, the challenge of emerging infections entering the blood supply can only be countered by pathogen elimination technologies such as have now been established by the plasma industry for the past 20 years. The introduction of such techniques for components would be a highly desirable consequence of the current precautionary paradigm. The dangerous and unpredictable environment underlying blood procurement [55] is unlikely to be sensitive to ethical principles, irrespective of their validity.

Ethics and altruism

The ethics of paying donors is confronting with the image of poverty-stricken individuals compelled to sell their blood. The demographics of plasma donors in the United States is more complex than this image [56]. In the absence of respect for the donor, and imposition of a social stigma [57], an exploitative situation can occur. The plasma industry has made efforts to negate these images [58]. Unquestionably, some individuals donate because of economic circumstances, but the ethical question of how to respond to the fact that some activities are taken up more by those with fewer financial means is not specific to the blood donation context. It is one of the biggest, and so far unsolved, challenges to modern political philosophy and social policy. Income inequalities leading to the donation process may be viewed as unethical and unjust, but this does not render the payment itself in this light [34]. Banning payment would simply lessen the visibility of the underlying social problem and precipitate another injustice on the recipients of plasma therapies affected by the consequent effect on supply.

Altruism may be defined as behaviour that benefits an unrelated individual(s) while being detrimental to the actor in the short term. Titmuss recognized that blood donors are still fulfilling an 'act of self-love', in which he claimed that the self is realized with the help of anonymous others, thus allowing the biological need to express itself [5, p. 279]. This has been characterized as a special form of self-interest, shared with others in a beneficent society [59]. Modern sociological theory defines this pattern, in which both the donor and the recipient gain, as benevolence rather than

altruism [60]. This concept is also designated as 'impure altruism' [61] and is associated with an emotional benefit when doing good – a 'warm glow', as well as with financial and status-based benefits [62]. Experimental simulations lend support to this concept [63]. Such reciprocity in gift-giving is resonant of Mauss' findings in primitive cultures, suggesting that it embedded in human behaviour. Reviewing a range of behaviours, some of them analogous to blood donation campaigns, Moore [64] proposes a model of, essentially, self-centered behaviour based on the generation of status and group dominance through the interaction. Behaviour of this kind has been shown to be neurologically and cognitively established in humans [65,66]. It appears to be embedded evolutionarily as both primate and human infants exhibit it without training [67], although increasing age leads to selective help towards reciprocal and group inclusion. Hauser *et al.* [68] show that such behaviour is shown among unrelated primates though preferential giving is exhibited towards those who reciprocate.

In analysing these concepts, in the context of blood donation, Ferguson *et al.* [69] have studied blood donation in the United Kingdom and concluded that blood donation is partly selfish and better specified through benevolence rather than altruism. They point out that incorporating these concepts in donation campaigns may result in benefits in blood donation rates. This does seem to be recognized through slogans such as 'Feel good about yourself – Give blood'. A scrutiny of, for example, the American Red Cross' 'Top 10 reasons for giving blood' [70] (Fig. 3) is a fascinating example of 'impure altruism'.

Does payment crowd out altruism?

The basis for WHA 28.72 in 1975 was an apprehension that paying plasma donors in developing countries was obstructing the development of blood donor services for essential medical support. Studies on crowding out in blood donation are infrequent and yield inconsistent findings, probably because the phenomenon is strongly context dependant. A Swedish study found that payment crowded out female, but not male, donors, who returned to full donation rates when given the option of donating the money to a charity [71]. Swedish donors are still compensated routinely [72]. Png [6] analysed WHO data for a number of countries and concluded that, independently of economic, cultural or institutional differences, collection incentivized through payment or replacement led to a drop in voluntary donation; however, a net increase in the blood supply was the overall result.

In a theoretical analysis of crowding out, Seabright [73] suggests that individuals may reject monetary payments for actions they would perform freely because of a desire to signal their social type to their peer group. Such signals elicit rewards in the form of an increased likelihood of subsequent interaction with people of a similar ilk. One can easily envisage this occurring through, e.g. blood donor organizations. Such an interaction would be of high value, as individuals seek to associate with like-minded peers. Seabright proposes that these individuals are the type who benefit through recognition of civic actions. Milinski *et al.* [62] show that donors, through signaling their social reliability to their target peer group, benefit both materially and through reputation in scenarios which are superficially perceivable as altruistic. The possible significance of this for blood donation has been pointed out by Ariely *et al.* [74], who suggest that crowding out is more likely to occur in publicly visible donation environments, e.g. blood drives where such type signaling behaviour would be important. Status, which varies strongly across culture and sex, has been shown to be worth a positive amount of material gain in an experimental utility calculation [75]. Public recognition is seen as a strong incentive to donate in an Italian study [76], but only when accompanied by visible awards and public visibility of the blood donors' names. Such status seeking is recognizable in blood donation situations [77].

Titmuss himself gave little evidence of crowding out in TGR, but Holland has provided an example [49] and the phenomenon has been claimed to be evident in the European Union [77] and the United States [78] as a result of the current economic problems. There is a paucity of data supporting these claims. In Germany, concurrent whole-blood donation and plasma donation is common practice within the compensated system. In the USA and other countries, the demographics of blood and plasma donors are different, and there is no evidence that source plasma donors would be more likely to donate blood if plasma compensation did not exist, always keeping in mind that nothing precludes this in the current system.

A plea for plurality

Healy [79] has shown how donation rates, rather than being a reflection of national differences in some nebulous concept of altruism, are more a function of how blood systems are organized through different agencies which stamp their own cultural message on the donation experience. Thus, donor population composition varies between government-based, Red Cross and community blood bank systems, and is affected by, for example, the presence of donor organizations and other entities. In turn, blood collection is organized through centralized blood services mostly detached from the clinical interface, as is the case in most developed countries, or hospital-based services where the collection, processing and transfusion activities all occur in the same

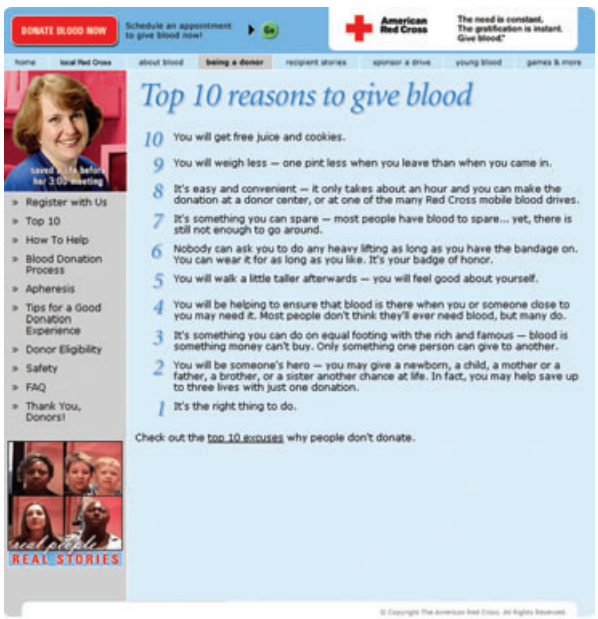

Fig. 3 Impure altruism – the American Red Cross' reasons for giving blood. Nine of these 10 reasons are not selfless.

location. This is the situation in many emerging countries including the SSA area discussed above [80]. Plasma products are also manufactured by different organizations – commercial entities utilizing mostly source plasma from compensated donors and state based entities fractionating mostly recovered plasma form their national blood systems. While the profit-not for profit divide is used to describe this system, both types of agencies compete for the same global plasma product market.

In concordance with a recent consensus meeting involving blood collectors, manufacturers, patient groups and government agencies [81], we propose that this plurality of routes to safe and sufficient haemotherapies is best achieved through the plurality which has evolved in the donor systems which supply the raw material. A political and societal consensus has evolved in the developed world that whole-blood donation is best achieved through the uncompensated route. This has led to sufficiency for all the transfusable components in most situations. Growing scrutiny on the optimal use of transfusion products, including evidence that historical dosage regimens may be moderated without deleterious clinical outcomes [82,83], may further optimal blood use and balance the demographically challenged donor base. In the developing world, continuing dependence on replacement donors is best addressed through appropriate management and evidence-based use of this source, as discussed by Bates [22], rather than through the imposition of unsustainable centralized systems modelled on the western paradigm. It may be anticipated that, as happened in the developed world, evolution to a voluntary system may occur in tandem with the development of improved public health care.

The provision of plasma products has evolved primarily through the manufacture of source plasma from compensated donors, and the volumes of plasma needed for current clinical needs are only attainable through this route. The not for profit sector has increased its output of source plasma but is still dependant on recovered plasma as a raw material for fractionation or for sale to the commercial fractionators. All these sources of plasma are contributing to the global supply of essential plasma products.

A recent US study reiterates the role of factors other than altruism, such as benefits, in maintaining donation frequency in the current United States system [84]. Buyx proposes the recognition and formal integration of such incentives as a 'middle way' between altruism and payment [85]. Are such incentives any better, or worse, than direct monetary compensation? One man's meat may be another man's poison, and the kind of social recognition accruable by visibly volunteer blood donors is certainly a benefit to those involved [86]. Social recognition, peer-signalling, days off work, cash are all incentives, possibly appealing to different demographic groups. Accepting this plurality will do more to secure the supply and safety of haemotherapies than adherence to dogma. In the rich and diverse landscape of the global blood supply, a diverse route to ensuring patients are appropriately treated should moderate the passion evoked by the continuing debate on donor compensation, and 'Let a thousand flowers bloom'.

Authors' contribution

Albert Farrugia wrote the paper and compiled the bibliography. Joshua Penrod researched donor incentives, sourced literature, contributed to the development of the paper and engaged in the discussion. Jan M Bult provided information and resources on plasma industry logisitics and management, contributed to the development of the paper and engaged in the discussion.

Conflict of interest

The authors provide services to the plasma protein therapeutics industry which manufactures plasma protein therapies from the plasma of compensated and non-compensated individuals worldwide.

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