

Globalization and blood safety

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Globalization may be viewed as the growing interdependence of countries worldwide through the increasing volume and variety of cross-border transactions in goods and services, and also through the more rapid and widespread diffusion of technology. Globalization is not just an economic phenomenon, although it is frequently described as such, but includes commerce, disease and travel, and immigration, and as such it affects blood safety and supply in various ways. The relatively short travel times offered by modern aviation can result in the rapid spread of blood-borne pathogens before measures to counteract transmission can be put in place; this would have happened with SARS if the basic life cycle of the SARS virus did not include an asymptomatic viraemia. This risk can be amplified by ecological factors which effect the spread of these pathogens once they are transferred to a naïve ecosystem, as happened with West Nile virus (WNV) in North America. The rationalization and contraction of the plasma products industry may be viewed as one aspect of globalization imposed by the remorseless inevitability of the market; the effect of this development on the safety and supply of products has yet to be seen, but the oversight and assurance of a shrinking number of players will present particular challenges. Similarly, the monopolization of technology, through patent enforcement which puts access beyond the reach of developing countries, can have an effect on blood safety. The challenges presented to blood safety by globalization are heightening the tensions between the traditional focus on the product safety – zero-risk paradigm and the need to view the delivery of safe blood as an integrated process. As an illustration of this tension, donor deferral measures imposed by globalization-induced risks such as vCJD and WNV have resulted in the loss of the safest and most committed portion of the blood donor population in many Western countries, leading to an increased risk to safety and supply. It is only through an appreciation of the basic needs of transfusion medicine, including the enunciation of appropriate principles to manage, rather than eliminate, risks, that the challenges imposed by globalization may be overcome.

What is globalization?

Globalization may be defined as the transition from national and regional economies to global economies, and includes a nexus of economic and social process whereby local markets and cultures are increasingly dominated by global markets and culture [1,2]. It is a result of the growing interdependence of countries worldwide through the increasing volume and

variety of cross-border transactions in goods and services, and also through the more rapid and widespread diffusion of technology. Although globalization is not just an economic phenomenon, it is frequently described as such, ignoring the homogenization of language and cultural identity that accompanies this flux of material, ideas and money. The most controversial aspects of globalization, manifested in the sometimes violent demonstrations accompanying events designed to further it, centre around this aspect. With the free, if unequal, flow of raw materials, manufactured goods, intellectual property and financial transactions, supervision solely through an international trade authority overlooks the effects on identity, environment and culture.

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Table 1 Number of blood units screened for infectious disease markers, by HDI (Human Development Index) category. From Reference [8]

| Countries Blood units | Low HDI 2326354 | | | Medium HDI 29428212 | | | High HDI 49380110 | | |
|--------------------------|-----------------|------------|---------|---------------------|------------|---------|-------------------|------------|---------|
| | Screened | Unscreened | Unknown | Screened | Unscreened | Unknown | Screened | Unscreened | Unknown |
| HIV | 91.9% | 6.9% | 1.2% | 98.5% | 0.5% | 1.0% | 99.9% | 0.1% | n/a |
| HBV | 92.5% | 6.3% | 1.2% | 98.3% | 0.7% | 1.0% | 99.9% | 0.1% | n/a |
| HCV | 51.3% | 47.5% | 1.2% | 96.3% | 2.7% | 1.0% | 99.9% | 0.1% | n/a |
| Syphilis | 34.1% | 61.2% | 4.7% | 97.2% | 1.8% | 1.0% | 98.7% | 1.3% | n/a |

Some reflections on the global health environment

It is worth reflecting on the evidence of globalization in the delivery of health care, particularly in the therapeutics sector. It is clear that the bulk of the profits of the pharmaceutical sector occur as a result of the consumption of these products in the developed world [3]. High-mortality developing countries, representing 41.4% of the world's population, carry 82% of the world's communicable disease burden [4]. At the same time, tropical diseases and tuberculosis, accounting for 11.4% of the global disease burden, attracted only 1% of the new chemical entities marketed between 1975 and 1999 [5]. Furthermore, the capacity to develop therapeutics to counter these diseases is lacking in the very areas which are affected by them, with more than 90% of the worldwide pharmaceutical production by value, and 97% of research and development activities, occurring in developed countries in 1998 [6]. Furthermore, three-quarters of new therapeutic drugs approved by the FDA between 1989 and 2000 were 'me-too' medicines with no significant benefit over existing treatments [7], suggesting that pharmaceutical research has minimal orientation to diseases affecting the developing world. The needs of the developing world appear to be unaffected by globalization, at least to any favourable level.

The global blood safety and supply environment

The unequal distribution of pharmaceutical provision is reflected in the world's blood supply. Data gathered by the World Health Organization show that the donation rate [8] and extent of viral marker testing (Table 1) are dependant on economic status [9]. In an ideal and globalized environment, one would expect that the challenges facing the world's safety and supply of blood would be addressed through the free movement of blood-derived therapeutics across borders, by the free and rapid implementation of measures to counter safety threats and by investment into the major problems underlying safety and supply. Is this happening? The developed world's capacity to deal with established and emerging blood

safety threats, many of which are the result of globalization, is impressive and issues such as West Nile virus (WNV) and variant Creutzfeldt-Jakob disease (vCJD) will be discussed below. A similar capacity is clearly lacking in the developing world where a different set challenges exist. Malaria is probably the most common transfusion-transmitted infection worldwide [10], and may be introduced into developed blood systems via travellers in endemic areas; in this instance current deferral measures in these systems is considered to provide adequate protection. Its high prevalence in endemic areas makes deferral measures unrealistic, and a screening strategy based on a specific test is urgently needed. It is relevant that such a testing infrastructure is only just starting to emerge, with the Australian blood service introducing a strategy aimed at minimizing the donor losses incurred through travel-associated deferral [11]. It would be beneficial if this strategy could be 'globalized' into environments where it is desperately needed; the extent to which this may happen will depend on how much it can be supported by governments in these areas, and how issues such as patents (see below) can affect its delivery to the developing world. One can anticipate that other, currently restricted, infections such as Chaga's Disease will recruit the interest of developed blood systems and diagnostic manufacturers, with similar issues as to their introduction to the areas where they are most needed.

Is the world's blood supply globalized?

This question is intrinsically controversial as proponents of the so-called 'national self-sufficiency principle' would argue that the blood supply should be restricted to national borders. The publicly stated reason for self-sufficiency is frequently ascribed to the World Health Assembly's Resolution 28.72 of 1975, which urged member states to develop national blood systems to avoid the exploitation of blood donors in the developing world. This laudable principle was universally subscribed by the Assembly; its extension to the exclusion of blood and blood products from cross-border passage has been a regrettable incursion of nationalistic interests into blood management, frequently at the expense of patients. The use of surplus red cells from the Swiss Red Cross by thalassaemics

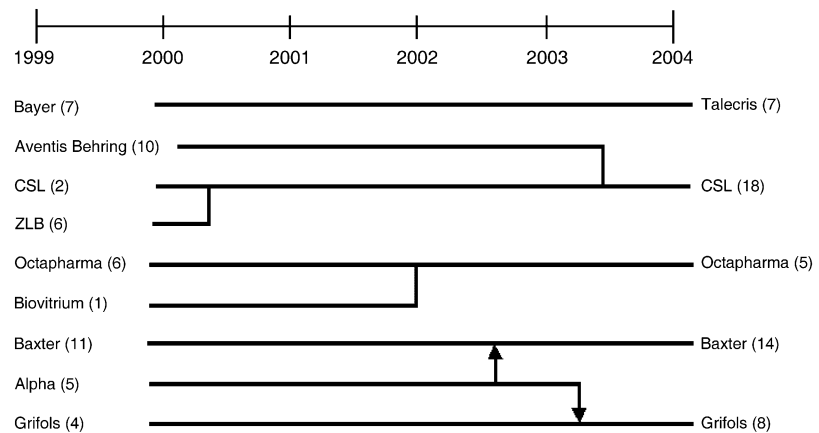


Fig. 1 Plasma Fractionators – Mergers and Acquisitions 1999–2004. Percent share of world capacity indicated in parenthesis.

in Greece and Cyprus in the 1960s and 1970s,¹ and more recently the 'Euroblood' programme which supplied 33% and 2% of the New York and US blood supply, respectively [12], are examples where blood has, successfully and beneficially, crossed borders. The image of Yasser Arafat donating blood for the victims of 9/11 [13] was a potent example of one aspect of globalization attempting to ameliorate the effects of another aspect.

Unfortunately, as will be discussed below, the continuing emergence of infectious agents is another aspect of globalization which is affecting the safety and supply of blood, and which makes such cross-border passage of blood more difficult than in previous times. Nevertheless, the global nature of the plasma industry, with previous demarcations between commercial and not-for-profit plasma suppliers eroding under the effect of market pressures, is an example where blood is still crossing borders. Where this is done with suitable controls for safety, benefits in the supply of products can accrue to communities which have, traditionally, lacked access to high quality plasma derivatives. The decline in the price of plasma-derived FVIII, as a result of competition with the recombinant product in the developed economies, has seen high-purity products become affordable for countries formerly unable to purchase them.²

In summary, when self-sufficiency levered increased government efforts and investment into the setting up of viable blood services it is a welcome manifestation to commitment to the public health. When it has been a thinly disguised manifestation of economic nationalism verging on racism through unscientific allegations of selective association of increased infectious risk in certain ethnic groups, it is to be deplored. A stark example is the Israeli ban on Ethiopian blood donors because of an (alleged) enhanced risk of HIV

transmission, a decision which resulted in mass protests leading to serious injuries. Subsequent assessment [14] concluded that 'the banning of Ethiopian donors reduced the annual number of HIV-1 infected donations from 0.34 to 0.24, an absolute reduction of only 0.1 infectious donations per year', and suggested that 'viewed simply from this perspective, was banning Ethiopian donors justified? The costs of treating those injured in protests might exceed the cost resulting from an additional infectious donation every 10 years.' In summary, if the mass movements in human population which have been a feature of globalization over the past 20 years are not reflected in an appropriate and scientifically based policy for the integration of these people in the blood supply, then detrimental effects on this supply will ensue, as happened in Israel [15].

'Blood is national, plasma is global' [16]

The plasma products industry has been traditionally stratified into the commercial, source plasma based sector and the not-for-profit (NFP) public agencies drawing on plasma recovered from whole blood donations for their raw material [17]. While the commercial sector has always sought to supply whichever market is able to support its products, the NFP agencies have historically supplied the national market, frequently as part of self-sufficiency policies. Over the past decade the sector has changed markedly [13] and many of the historical divides have eroded. Interestingly, globalization has played a significant role in these changes. These have included:

- The rationalization of the international commercial plasma industry, with a significant contraction in the number of players (Fig. 1). A number of pressures (discussed in reference [13]) have led to most of the pharmaceutical multinationals shedding their plasma fractionation businesses.
- Similar rationalization of the NFP sector has seen Canada, Finland and Denmark terminate their fractionation activities and France reduce the number of its plants from six to

¹Hassig A (deceased) (1985) Personal communication.

²Israngakura P (2005) Personal communication.

one. At the same time, the UK's policy of not using British plasma because of the vCJD risk (below) has seen the two plants in the UK abandon self-sufficiency to fractionate plasma sourced from outside the UK, in the most instance from compensated donors.

- Commercial fractionators are similarly accessing and processing plasma drawn from a number of NFP blood collection systems, as these generate surpluses to their needs for clinical plasma. At the same time the commercial sector is taking steps to securing their plasma supplies through owning their own commercial plasma collection sites.

The industry has responded to lowered margins and excess plasma and product inventory through rationalization. This is a salient feature of market pressures and the globalized nature of the sector is very evident through the multiple plants now owned by the major fractionators, with the capacity to collect plasma in one country, generate intermediate fractions in another and deliver final product in a third. While the flexibility generated through these developments makes product delivery more efficient, the need for a strong regulatory system to oversee this cross-border traffic of plasma and products was illustrated by the Albovina scandal in the late 1990s [18]. The shrinking number of players has the potential to decrease choice while the gradual elimination of non-profitable products from the portfolio of many fractionators is of concern, particularly to sufferers from rare disorders [19].

The pressure of market-driven globalization on national supply policies is exemplified by the evolution of self-sufficiency policies in the publicly funded blood systems of the European Union, where regional, rather than national self-sufficiency is promoted [20]. Concurrently some countries have wound down their national fractionation capacity to access the capacity of large agencies such as Sanquin in the Netherlands, or have elected to sell plasma to the commercial sector and purchase product independently, e.g. the Czech Republic. In the commercial sector, similar competitive pressures have seen the USA–Australia Free Trade Agreement include a commitment by the Australian government into conducting a review of its plasma fractionation arrangements [21] which have traditionally been the monopoly of a single national fractionation agency.³ It is intriguing that this process has already caused a change in Australia's national self-sufficiency policy, with a move away from previous criteria demanding clinical superiority in imported products before their acceptance by the national regulator [22]. Irrespective of the rationale of such national-centric policies, and this author's reservations are noted above, the pressure to alter

national policies in response to market-driven pressures articulated through political powers must be viewed with concern. In this instance, it is linked to the US government's introduction of national price negotiation mechanisms, such as Australia's Pharmaceutical Benefits Scheme [23], into free trade negotiations.

Is globalization enhancing blood safety?

Patents, innovation and blood safety

The trade related aspects of intellectual property rights agreement – TRIPS – mediated by the World Trade Organization patent rules have been globally implemented [24]. These will result in 20-year patents on pharmaceutical products also in countries that previously did not grant product patents, e.g. India. There will be no differentiation between lifesaving medicines and trivial goods. In November 2001, WTO members adopted the Doha Declaration on TRIPs and Public Health, which said the TRIPs Agreement 'can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all' [25]. This welcome declaration contrasts with some aspects of patent protection which have affected public health, including blood safety. As an example, the high royalty payment associated with HCV testing increases significantly the cost of the test for screening blood [26], and it is significant that HCV screening is the lowest in low HDI countries (Table 1). These patent-driven increased prices are claimed to be necessary to ensure recouping of R & D costs and reinvestment into R & D for new and innovative products. The sombre reality is that little pharmaceutical investment is being put into innovative treatments, with the bulk going into existing treatments [7] as 'me-too' products. There is a tendency for this in blood safety measures in developed systems, exemplified by the increased investment in further refining NAT for the 'known and loved' viruses through single donation testing platforms which do little to enhance safety with microscopic cost-effectiveness [27], while, as discussed above, pathogens of relevance in the developing world remain untested. There is scant evidence that patent protection, touted as essential to ensure continued development and globalization of health benefits, is enhancing blood safety. The patenting of technologies such as solvent-detergent and heat-treatment of plasma derivatives contributed to the delay in the widespread introduction of inactivation of the pathogenic transfusion transmitted enveloped viruses. The growing obsession with intellectual property shown by publicly funded utilities sits uneasily with their declarations of moral superiority over the 'commercial' sector and demands for protection from competition, a posture which frequently characterizes the 'self-sufficiency' proponents.

³CSL Ltd, which transitioned from a single country NFP manufacturer to the world's largest commercial plasma fractionator over the course of a 5-year privatization process.

No boundaries for bugs

Blood moves across national boundaries in two main forms:

- *as products*, especially plasma derivatives, bought and sold on the world market, as discussed above;
- *in people* – travelers and immigrants – who then plan to donate blood to their national or regional medical services, and who may not realize they may be subject to restrictions based on their place of origin or travel destinations [28].

We are living in an era when ‘trade-related infections’ are influencing strongly the safety and supply of blood [29]. The long incubation periods of many of the pathogens which have challenged blood safety over recent years permit their introduction into ‘globalized’ products such as plasma derivatives before safety measures can be effected. The introduction of HIV from the US risk groups into the haemophilic populations of other countries is an example; this occurred both as a result of the passage of products (e.g. US to Japan) and people (e.g. US to Australia⁴).

Even when the biology of agents is well understood, their introduction, as a result of globalization pressures, into a new environment, can take a blood system unawares, as happened with WNV in the USA. In this instance, the affected system had the resources to rapidly generate a capacity to address the problem; the sober reality is that WNV has clearly been a presence in less well-resourced blood systems closer to the agent’s geographical origin. It is worth noting that the virus’ susceptibility to the inactivation techniques used in modern plasma fractionation [30] is what prevented a similar incident to the HIV transmission described above.

‘We have seen the enemy ... and it is us’ [31]

Human behaviour, reacting to globalization pressures, is responsible for many of the current challenges posed by ‘trade-related infections’ [29] (Table 2). As mankind impacts more and more on the natural environment, mostly under the pressures introduced by globalization, risks emerge in fairly unpredictable fashions. As discussed by Murphy [32], assuming that an understanding of the causes of past problems in blood safety and supply will lead to an ability to address future problems, through a linear approach to predict threats,

⁴The prevalence of HIV in the severe haemophilia population in some areas of metropolitan Australia in the early 90s approached that of the USA (McGrath KM, Spelman D, Barnett M, Kellner S. Spectrum of HTLV-III infection in a hemophilic cohort treated with blood products from a single manufacturer. *Am J Hematol.* 1986; 23:239–45.), despite a policy of strict ‘self-sufficiency’ (non-importation), as infected Australians returned from high risk excursions in the USA and infected the domestic blood supply (Ballard J. HIV-contaminated blood and Australian policy – the limits of success. In *Blood Fueds: Aids, Blood and the politics of Medical Disaster* Feldman E & Bayer R pp. 243–272, Ch 8, Oxford Univ Press 1999).

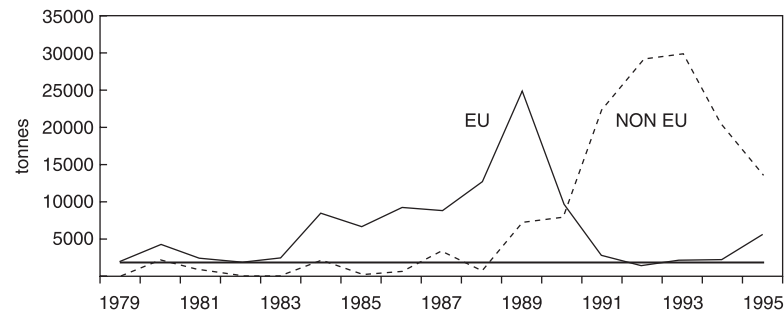
Table 2 Human behaviour and transfusion-transmitted infections (From Dodd ref)

| Agent | Presumed cause |
|------------------|--|
| HIV | Bush meat, sexual behaviour, travel |
| Malaria | Global climate change, travel |
| Chagas’s disease | Population migration |
| West Nile virus | Unknown (travel?), irrigation practices |
| SARS | Exotic diet, air travel |
| vCJD | Intensive agricultural practice and export of feed, travel |

is open to criticism. The effect of globalization pressures on these events is, however, undeniable. As a case study, the events surrounding the introduction of bovine spongiform encephalopathy (BSE) to cattle, the infection’s subsequent spread beyond its origin and its ultimate passage into humans as vCJD, with the current demonstration of its transmissibility through blood, bear reflection (Fig. 2). The presumed aetiology proposes that pathologic prion was introduced and amplified into the cattle food chain through modified rendering processes which had insufficient capacity to inactivate it.⁵ The need to maximize UK beef production as a result of the competitive global trade for beef presumably influenced this decision [27]. This demonstrates the danger of streamlining manufacturing processes when the outcome may be a biological product capable of transmitting disease. The passage of this infection into humans as vCJD was rapidly appreciated as a potential blood safety risk, as animal models had demonstrated infectivity in blood and the increased lymphoreticular involvement in vCJD compared to classical CJD suggested that the epidemiological indications that the latter was not transmitted through blood could not be extended to vCJD. These apprehensions were borne out by the small number of vCJD cases transmitted through blood. The UK government’s decision to stop using British plasma for the production of plasma derivatives represented a commendable attempt to avoid further spread of the infection through these products; subsequent restrictions by authorities worldwide on blood donors resident in the UK are thus understandable. The effect of these policies on overall blood safety and supply has been pointed out by O’Neill [26], who has commented on the shift in deferral policies from the exclusion of the indigent and the ill to that of the healthy and the wealthy, which are the class of the population which travel and are educated, two characteristics of blood donors in developed countries.

Many of these effects of the donor population occur whenever travel-related deferrals occur, but the example of SARS – another infection generated through unpredictable events and rapidly transmitted through global travel – also

⁵This is a clear example of an event unpredictable from a linear process.



Total Exports of MBM 1988–1993

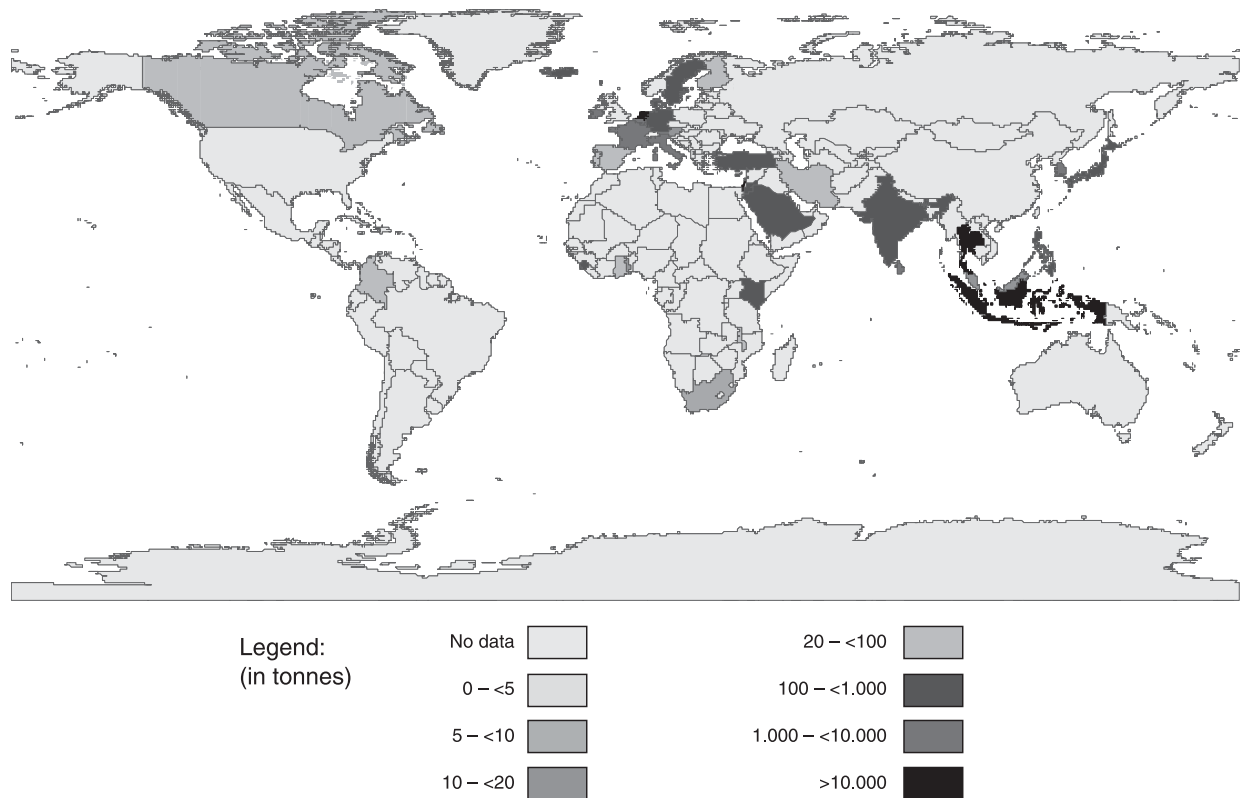


Fig. 2 The globalization of BSE – Export of British meat and bone meal. The accelerated export during the height of the BSE epidemic in the UK presumably led to the infection's incursion in other countries.

shows the potentially catastrophic effects on the blood supply in countries affected by SARS [33].

Anti-globalization – its effects on blood safety and supply

The blood system is in the forefront of the challenges posed by the era of global terror [34], which is partly driven through the tensions precipitated by globalization. The potential need for blood as a result of terrorist incidents is obvious; what is perhaps less predictable is the extent to which blood agencies

can manage these incidents in an optimal fashion. For example, the American Red Cross' decision to continue collecting blood in the aftermath of the 9/11 incident despite the clear indication that much of it was not needed, to be followed by the inevitable discarding of expired units [35], drew substantial criticism. Unplanned expansions in the blood supply also have the potential to affect safety through affecting the balance between new and regular donors in the blood supply [36]. Other effects can ensue from the introduction of bioterrorism agents into the blood supply, a scenario which is no longer as fanciful as may have been envisaged some years ago [29].

Conclusions

The increasing traffic in goods and people which characterizes the modern era of globalization has affected blood safety and supply in many ways. The increasing commoditization of blood, markedly but not exclusively in the plasma products sector, has eroded some of the historical barriers between different countries and has enhanced the supply of essential products for countries able to pay for them. The infectious disease threats posed by other globalization-driven changes have also been successfully addressed by the developed world – so far – and strengthening of the blood safety infrastructure through the development of new tests and pathogen elimination has ensued. Many of these benefits have followed the trend set by other developments in pharmaceutical manufacture and health care in general, in that they have been restricted and focused in rich countries. The WHO's efforts to increase the potential benefit to developing countries through the Global Collaboration for Blood Safety is therefore timely and commendable in the era of globalization [37]. The increasing rationalization of the pharmaceutical entities supply of blood products and their attendant materials such as test kits is a worrying development, but no more than can be expected if profit and the free-market are to be the sole arbiters of blood safety and supply policy. 'A framework that relies upon private marketing monopolies is morally repugnant, economically inefficient and corrupt. We can and should do better' [21].

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