The infectious risks in blood transfusion as of today – A no black and white situation

Olivier Garraud¹,², Luiz Amorim Filho³, Syria Laperche², Claude Tayou-Tagny⁴, Bruno Pozzetto¹,⁵

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Summary

Transfusion has been tainted with the risk of contracting an infection – often severe – and fears about this risk are still prevailing, in sharp contrast with the actual risk in Western countries. Those actual risks are rather immunological, technical (overload) or metabolic. Meanwhile, in developing countries and particularly in Africa, transfusion transmitted infections (TTIs) are still frequent, because of the scarcity of volunteer blood donors and resources and the high incidence and prevalence of infections. Global safety of blood components has been declared as a goal to be attained everywhere by the World Health Organization (WHO). However, this challenge is difficult to meet because of several intricate factors, of which the emergence of infectious agents, low income and breaches in sanitation and hygiene. This review aims at encompassing the situation of TTIs in different settings and means that can be deployed to improve the situation where this can possibly be.

What are transfusion transmitted-infectious pathogens and infections?

The transmission of infection in a naïve recipient by transfused blood appears to be as old as conventional transfusion itself, as the first reported cases date back from years 1910s. The first infectious pathogens reported were the malaria parasites and the syphilis spirochetes (though ascribed to be just bacteria at that time) [1]. The history of transfusion associated-infections (TTIs) has evolved with the development of transfusion, as it was extremely difficult if not impossible to test for a risk as far as donors presented as apparently healthy individuals. Back to the years 1928, Arnault Tzank – when founding the “Œuvre de la Transfusion Sanguine d’Urgence”...
in hôpital Saint-Antoine in Paris – made a statement in the Volunteer donor chart that donors on duty had to maintain themselves in good health and follow some hygienic rules [2]. Many cases of infections in relation with transfusion were thus reported, but transfusion was initially intended only for patients suffering immediate life threatening conditions. Transfusion indications evolved over time, along with blood preservation techniques and industrial plasma fractionation, and the case of TTIs culminated with the large dissemination of the human deficiency virus (HIV) and then the hepatitis C virus (HCV), the so-called black period or the scandal of blood transfusion. HIV infection rarely aborts in exposed individuals unless they present genetic advantage to non-infection or non-progression; otherwise, HIV is considered extremely contagious (HCV), the so-called black period or the scandal of blood transfusion. HIV infection rarely aborts in exposed individuals unless they present genetic advantage to non-infection or non-progression; otherwise, HIV is considered extremely contagious even with a small inoculum, as far as it is viable [3]. Since this time, the wording of transfusion-associated disease became common (and still is). We strongly disagree with this wording, not because of puritanism, but because it does not help understanding what the pathophysiology of TTI is [4–7].

To make a long story short, we propose to summarize conditions of TTI as follows:

- an infectious pathogen must be present in the circulation of a blood donor, presenting healthy enough to be eligible or qualified for donation; further, the blood donor candidate is in general or in principle unaware of his/her infectious carriage;
- this pathogen must be present in cell or plasma circulation at a minimal infectious dose to generate an infection;
- it must resist conditions of blood collection and pre-storage (for example, some bacteria can be eliminated by phagocytosis in the pre-storage prior to the leukoreduction and processing) [8];
- it must resist processing steps, filtration for leukoreduction when available, and temperature change (sustained exposure to 4 °C in the majority of cases apart from platelets); several infectious pathogens do not resist freezing for plasma when applied, but many others do including HIV, hepatitis B virus (HBV), and HCV;
- it must resist storage until the component is delivered to patient;
- it must resist innate immunity tools displayed in the recipient’s blood (plasma molecules such as antibodies and polyreactive immunoglobulins, complement factors), and resist phagocytosis and or targeting by natural and other killer cells such as γδ T (lymphocytes); it must also resist neutralizing antibodies (Abs) when some have been raised against major epitopes after previous immunization;
- it must be viable and able to multiply, and not present as a dead end microbe (it is thought, as an example, that certain parasites such as microfilaria lose some parameters multiplying capacity when it is not transmitted by an arthropod) [9]. Thus, when viable and able to multiply, the microbe must find a port of entry in a target cell (a receptor or a ligand), and must not be opposed, so doing, by elements of immunity in the host;
- the infected patient must also receive no anti-infectious drugs that can hamper the microbe development and expression of its pathogenicity. This may be valuable for bacteria; it is less suitable for viruses and parasites.

In aggregate, TTI is achieved after a tedious process (from the microbes’ side) and this may limit the number of observed cases. However, several microbes have all the above-mentioned properties, which in the case of having the capacity to impair all steps of the innate immunity [10]. Some microbes, including malaria parasites, trespass the natural defenses because they are injected massively where the natural infection allows gradual defenses [11].

**How important TTIs are compared to other transfusion associated risks?**

Clearly, when focusing in most European and North American countries, the infectious risks of transfusions are largely inferior to the most commonly observed other two major risks, namely overload and immunological hazards, which predominate even over the most feared residual risk that is the bacterial infection [12–14]. When addressing the situation in developing countries, infection can even threaten the making of an inventory and it may affect several blood donations: up to 20% of blood donations are discarded in many African blood banks [15–17]. Even in developed countries benefiting from highly secured blood transfusion services, the infectious risks are unequal, as the infectious pathogens themselves may be different. One may consider two situations: first, TTIs that can be ascribed to as classical, or conventional, such as HIV, HBV, HCV and HTLV. These TTIs have been consistently decreased by use of batteries of safety measures, satisfactorily applied over the past 2 decades; for example, in France, HCV is considered to be present and not detected in one per 33 million donations, and HIV in one per 3.45 million donations [18,19]. It may be made clear that such numbers refer to a theoretical risk but not to declared infections, because quite many transfused recipients do not survive their causal disease and develop this double penalty infection. Second, TTIs can result from occasional epidemic outbreaks, as exemplified when the West Nile virus (WNV) spread and then vanished in the USA [20], while some other TTIs evolve from an epidemic to an endemic-epidemic state such as dengue virus (DENV) in the Caribbean and South American countries [21,22]. The TTI risk depends on the attack score of the infection and on the capacity of the targeted population to develop protective antibodies, as observed after Chikungunya virus (CHIKV) outbreaks [23]. Some TT-infectious pathogens tend to set up in novel areas because conditions become favorable (WNV, DENV, CHIKV, Zika virus . . .) or following migrating populations (malaria and Chagas parasite infections) [24–26].
It must be noticed, however, that measures taken for reducing or limiting some infectious risks can be consistently applied. Four sets of measures can be considered: first, means which are considered meeting generalized quality and safety requirements such as recommended e.g. by the Council of Europe, including donor education and the clinical selection of blood donation candidates [27], and are considered as an attainable target for developing countries [28]; second, screening donations for classic TT pathogens, such as HIV, HBV, HCV, HTLV, and syphilis by classical serologic techniques [29]; third, specific measures which are widely applied in high income-countries, despite a cost-benefit balance commonly regarded as inefficient: this is the case of Nucleic acid testing (NAT) [30]; and lastly, measures that do not apply to the testing but to the component, i.e. Pathogen reduction technologies (PRTs) [31].

PRTs have been applied for more than three decades with doubtless benefit for plasma derived-drugs. Later on, the Solvent-detergent (SD) technology has been successfully applied to therapeutic plasma – especially in pools (though individual SD-plasma has been made recently available), for quite a long time with general satisfaction [32]. More recently – but near a decade ago – either dyes or nucleic acid targeting technologies, complemented by light exposure, have been made available to secure therapeutic plasma and platelet components, with variable success depending on the targeted pathogens, but leading in general to a substantial level of infectious safety [33]. The limit of the latter process is the as-yet unavailability for red blood cell components.

Table I reports on the different safety means that target the infectious risks. Numerous reports have been made available concerning safety and efficacy of PRT-treated blood components (BCs) [32,34–36]. Basically, while PRTs – actually on exceptional occasions – associate with process induced-pathology (i.e. allergy), there is some consensus that they primarily reduced occurrences of major risks, as reported by focused reports of hemovigilance [37–41].

<table>
<thead>
<tr>
<th>Predonation</th>
<th>Securement of the inventory (prevents the decrease of vigilance when inventory has to be replenished in emergency)</th>
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<tr>
<td></td>
<td>Ethics (widely considered as a guarantee against infectious risks)</td>
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<td></td>
<td>Education to self-deferral</td>
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<td>Donation</td>
<td>Medical selection</td>
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<td>Collection</td>
<td>Epidemiological surveillance (update the geographic risks)</td>
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<td></td>
<td>Hygiene and asepsis; clean venopuncture</td>
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<td></td>
<td>Derivation of the first 30 mL of drawn blood into a separate bag</td>
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<td>Testing</td>
<td>Conventional testing for the most frequent infectious agents (antigens and antibodies)</td>
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<td></td>
<td>NAT: detects genetic materiel of certain viruses</td>
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<td></td>
<td>Epidemiological surveillance of newly acknowledged infectious risks</td>
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<tr>
<td>Processing</td>
<td>Prestorage: often considered to allow best phagocytosis of bacteria</td>
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<td></td>
<td>Leukoreduction: widely admitted to reduce considerably the risk of transmitting viruses, but also bacteria</td>
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<tr>
<td></td>
<td>Pathogen reduction (inactivation) technologies: widely admitted to reduce considerably or even eradicate most viruses, bacteria and parasites</td>
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<tr>
<td>Storage</td>
<td>Temperature control (limits the infectious pathogen growth in most microbe species)</td>
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<td>Quarantine: allows for delayed testing or re-testing</td>
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<td>Observation: the swirling test yet allows to discard bacterium contaminated platelet components</td>
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<td>Distribution, delivery</td>
<td>Bacterial testing of platelet components</td>
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<td>Bedside</td>
<td>Hygiene at all steps of blood component handling, with special mention to thawing steps of frozen plasma</td>
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<td>General</td>
<td>Control of temperature and time to transfuse</td>
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<td>Enforced patient observation</td>
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<td>Education of personnel (all steps)</td>
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In contrast, some countries or systems cannot yet reach the expected infectious safety to below one clinically relevant TTI-case in at least one million delivered BCs. This risk is however balanced with the one of weakening the inventory, if for example, exceedingly stringent policy of donor selection reduces the blood component availability to below the level of safety (to be determined site by site, according to the medical, surgical, and obstetrical activity) [42]. Countries that have undertaken for years to secure the infectious risks – which are also in general self-sufficient to meet the demand – tend to consider more insistently the non-infectious risks, and propose actions to limit overload, metabolic risks, immunological hazards and the supply chain associated risks [43]. Indeed, in high-income-countries, reports of hemovigilance mainly focus on immunological hazards [44]; however, because sets of safety measures have been applied differentially and because the components are not strictly the same in terms of manufacturing, those immunological hazard reports strikingly differ: FDA (in the USA) still reports elevated incidence of Transfusion related acute lung injury (TRALI) [45], while this risk – which was some time ago considered major – has now become very rare in many European countries. In contrast, allergy, Febrile non-hemolytic transfusion reactions (FNHTRs), and inflammatory hazards at large, now predominate in Europe, as reported by SHOT in the United Kingdom (UK) [46], Swissmedic in Switzerland [38], and ANSM in France [39].

**What are actual (residual) TTI risks in distinct settings?**

Again, information that can be made available depends on how the surveillance of the transfusion process has been planned in a defined health system within a country.

In certain areas including European and North American countries, information is being made available, and revised annually. **Table II** makes an attempt to collect the last available information disseminated by such countries. In Western/Northern European countries, the viral infectious occurrence risk – if one considers the major 4 TTI-viruses – is estimated at about one in 1.59 million transfused blood components. In developing countries and particularly in inter-tropical Africa, HIV, HCV and HBV infection range from 0.5 to 15% of donations (the HBV carriage is particularly high) [17,47-59].

Some developing countries make efforts to follow – as an indicator – the number of cases of serious infection hazards having occurred in patients, with the limit that it is sometime difficult to decipher between a pre-carriage in the recipient and a carriage in the donor (or both). Besides, other countries experience difficulties either in collecting or disseminating information, which makes difficult the appreciation of, on the one hand the actual risk, and on the other hand, the efforts to reduce those risks. The objective of the WHO program on Blood transfusion safety (BTS) is to ensure provision of universal access to safe, quality and efficacious blood and blood products for transfusion, their safe and appropriate use, and also ensuring blood donor and patient safety [60,61]. WHO/BTS has defined its strategic direction on hemovigilance as the settlement of strengthening systems for assessment, surveillance, vigilance and alert, monitoring and evaluation [62], with particular emphasis to the African situation. In addition to those canonical TTI risks, one notes also the carriage of plasmodial infections (from 0.1 to 2-3%, depending on the location and the rainy vs dry season) [63]. TTI linked to *Plasmodium* parasite is particularly severe as it superimposes risks in fragile populations such...
as pregnant women, delivering mothers, newborns and children under the age of 5; in children, *Plasmodium* infection can lead to severe malaria rendering transfusion necessary, which may even create a vicious loop [64]. Programs aimed at assisting the most at-risk blood establishments regarding infectious safety have been proposed, such as evaluation of PRT applied to whole blood [65–67]. To the best of our knowledge, two such technologies are presently upon investigation in Africa or in preclinical phases, the S-303 technology developed by Cerus, Concord, CA, and the technology developed by TerumoBCT Denver, CO, (Riboflavin (MirasolTM), both raising serious hopes from the exposed populations and transfusion communities.

**What about emergence of novel infectious risks?**

Emergence and related concepts have been described and discussed in several recent reviews contributed by some of this paper’s authors, to which readers are kindly referred [21,68,69]. Emergence and/re-emergence of infectious risks is under scrutiny by various agencies worldwide, and alerts are made on regular bases. It is striking that infectious pathogens can travel incredibly fast, principally along with airlines communications. It now takes no more than 24–36 h for an individual to fly all across the globe, and this period is often below the threshold for clinical symptom appearance, rendering measures such as quarantine vain. To what extent such emergent infections threaten blood collection and inventory supply, or transfusion – if the infectious individual has given blood and if the donation has been transformed into one or more therapeutic components delivered within a day or two (the case for platelet components and possibly for liquid plasma) – is questionable. Lessons from the recent past taught that this may well happen: TTI-cases were reported following WNV and DENV recent outbreaks (CHIKV-TT remains not reported), imposing restrictions to blood component use [70–72]. As soon as it could be made available, additional specific testing (still possible for red blood cell components and therapeutic plasma but barely affordable for platelet components if not subjected to PRT) is recommended. Alerts have been made year after year following the last discovered viruses, notably SarsCoV, influenza pandemic viruses (H1N1, HS5N5….) and Zika virus. Emergence/re-emergence however does not apply only to acute viral infections but also to bacteria (an issue that does not seem to affect transfusion at the moment) and to parasites, as well as to long-time silent viruses leading occasionally to chronic infection and severe pathology.

Regarding parasites, some authors consider that *Trypanosoma cruzi* – the agent causing Chagas disease – re-emerges as it reaches novel areas and especially urban ones, where populations are concentrated, of whom blood donor candidates. In countries like Brazil, where arthropod transmission of *T. cruzi* was declining year after year, outbreaks of oral transmitted (by sugar cane or acai juice) acute Chagas disease have been recently described [73,74]. *T. cruzi-Ti* is not uncommon but it cannot be ascribed to as frequent, and it seems that PCs are more exposed than other blood components, which may help to address safety measures more appropriately [75]. Malaria infection emerges as well because the parasite and the mosquito territories re-expands to areas that used to be infected but were cleared of this risk, especially in Southern Europe [76]. All blood components are concerned, with the likely exception of therapeutic plasma if frozen. *Babesia* spp infection is presently a serious threat for RBCs in Northwest America, causing dozens of lethal cases every year [77]; for as-yet not fully understood reasons – apart from exceptional occasions – this parasite is not well transmitted in Eastern Europe where occurrences should be predicted and Europe yet reports no case of *Babesia* spp-Ti.

Emergence is predictable and can be modeled but there are obvious limits. The health community sometimes overreacted, as was the case for the XMRV that – some time ago – was presented as a novel and serious danger for transfusion recipients; no case has been documented since [78]. On the contrary, one can agree that the recent Ebola outbreak in Western/Central Africa has been underscored by agencies and by the majority of medical and scientific community: it has not threaten the blood inventory in high income-countries, despite some exceedingly alarming papers were released by the non-specialized media, but it has seriously impaired the already fragile transfusion systems in affected countries [79]. Of important note, these epidemics allowed the raise of novel transfusion strategies to relieve affected populations, such as potentially PRT-secured convalescent plasma therapy [80,81]. What about the case of the variant of the Creutzfeldt-Jakob disease (vCJD)? There again, some recent reviews make the case. If vCJD was considered as an emergent infectious disease and even a potential threat, the epidemics now vanishes in the most affected country – the UK – and has apparently disappeared in the second most affected country – France –. Documented vCJD TTI cases were limited to 4 cases, all in the UK, despite highly exhaustive surveillance [82,83]. Is there thus any reason to tune down the alert level regarding emerging pathogens in transfusion medicine? Certainly not, as erratic behavior of humans still poses unpredictable risks: feral animal food consumption, unusual petting (snakes and lizards, monkeys, exotic birds and other feral animals), non-conventional travel and trekking, criminal attitudes such as feeding remnants with dead animal body broth, expose to the risk of an unexpected adaptation of an emergent pathogen to a new host with possible dramatic consequences. Some newly adapted germs may become pathogens and be transmissible by blood [84].
What about hepatitis E-transfusion transmission and associated morbidity?

HEV infection is very common worldwide as demonstrated by anti-HEV IgG seroprevalence, as described in particular in blood donors from developed countries in whom IgG seroprevalence ranged between 4.7% and 32.6% [85–93]. There are four HEV genotypes; types 1 and 2 are water-borne transmitted infections, in general confined to developing countries. Types 3 and 4, now called zoonotic HEV, are mainly transmitted by meat consumption of raw pork and other mammals. Those 3 and 4 genotypes are the ones involved in HEV TT [94–97].

Autochthonous HEV infection is usually an acute self-limiting disease resolving within 1 to 2 months but it can evolve to chronic infection in approximately 60% immunosuppressed patients. Several transmissions by blood transfusion have been reported worldwide including with plasma treated with pathogen inactivation process. However, none of them were related to plasma-derived products. Blood transmission events are in line with the high prevalence of HEV-RNA reported in blood donors in Europe ranging between 0.7 and 4.2 per 10,000 donations [98,99] – and a recent Dutch study reports 13 in 10,000 – [100], together with the high resistance of the agent to inactivating processes [101,102]. This high prevalence of viremic donations and the high proportion of blood recipients being immunocompromised and repeatedly transfused prompted some practitioners to advocate the systematic screening of blood donations for HEV-RNA in countries where hepatitis E is endemic. There are still no European recommendations regarding HEV-RNA testing in labile blood components. However, some initiatives have been taken in some developed countries (UK, France) to dispose of HEV-RNA free products that would be reserved to at-risk recipients.

Conclusions and perspectives

In high income-countries, TTIs are not any longer threatening transfusion as they used to be. Indeed, the major concern has been displaced from the recipients to the donors with two new questions. First, what to do when donors are found to be the carriers of an infectious pathogen (tested for to qualify the blood component)? Second, will the inventory be threatened in case of an epidemic outbreak? Otherwise, the infectious concerns of transfusion have been replaced by, on the one hand, good practice issues, that can be fixed by education programs, and on the other hand, by immunological hazards that are still largely unpredictable though progress is being consistently made. In developing countries, TTIs are part of the still difficulty: the infectious pathogen carriage is exceedingly high and their screening is still conducted in blood services with limited quality system. Taken this into consideration, safe donations are far from meeting the demand; stricter action to adjourn infected donor candidates will have for immediate consequence blood shortage and to expose the health community to accept that people dies for not being transfused. In the meantime, it is barely acceptable to expose recipients to the double penalty of their causal disease and a TTI leading further to another severe condition. It thus appears urgent to help such countries to design suitable solutions for enough safe and available blood based on cost affordable methods that are appropriate for low income countries. Many countries are intermediate: unfortunately, little information is in general available from them (contrary to the case of African countries that better report their situation) though it would be extremely valuable to know better about their efforts and progress, and how they can share experience. Last, there is still strong hope with universal PRTs for whole blood or for red blood cell concentrates, and we would like to urge decision makers for providing more sustained help in this matter.

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