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

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In this issue

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 both 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 Heath 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*"

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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 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].

TABLE I

Safety means used to secure blood inventory and blood components for transfusion purposes

Predonation	Securement of the inventory (prevents the decrease of vigilance when inventory has to be replenished in emergency)
	Ethics (widely considered as a guarantee against infectious risks)
	Education to self-deferral
Donation	Medical selection
	Epidemiological surveillance (update the geographic risks)
Collection	Hygiene and asepsis; clean venopuncture
	Derivation of the first 30 mL of drawn blood into a separate bag
Testing	Conventional testing for the most frequent infectious agents (antigens and antibodies)
	NAT: detects genetic materiel of certain viruses
	Epidemiological surveillance of newly acknowledged infectious risks
Processing	Prestorage: often considered to allow best phagocytosis of bacteria
	Leukoreduction: widely admitted to reduce considerably the risk of transmitting viruses, but also bacteria
	Pathogen reduction (inactivation) technologies: widely admitted to reduce considerably or even eradicate most viruses, bacteria and parasites
Storage	Temperature control (limits the infectious pathogen growth in most microbe species)
	Quarantine: allows for delayed testing or re-testing
	Observation: the swirling test yet allows to discard bacterium contaminated platelet components
Distribution, delivery	Bacterial testing of platelet components
	Hygiene at all steps of blood component handling, with special mention to thawing steps of frozen plasma
Bedside	Control of temperature and time to transfuse
	Enforced patient observation
General	Education of personnel (all steps)

It must be noticed, however, that measures taken for to 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-benefice 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 II
Comparison of the most commonly acknowledged transfusion transmitted agents in three countries: France, Brazil, and Cameroon

Infectious agent	France [103]	Brazil [104–106]	Cameroon
	Residual risk	Residual risk	Prevalence in blood donations
HIV		11×10^{-6}	1.6×10^{-2}
HIV with NAT	0.33×10^{-6}	4.2×10^{-6}	–
HCV		5×10^{-6}	1.8×10^{-2}
HCV with NAT	0.03×10^{-6}	0.6×10^{-6}	–
HBV		NA (prevalence: 2.89×10^{-3})	NA (incidence: 10.6×10^{-2})
HBV with NAT	0.16×10^{-6}	–	–
HTLV	0.11×10^{-6}	5×10^{-6}	NA (incidence: 1.2×10^{-2})
Plasmodium spp.	Exceptional	Incidental	NA (incidence: 6.5×10^{-2}) [107]

HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HTLV: human T leukemia virus; NA: not available.

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 (Mirasol^{TM}), 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 commutations. 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, H5N5. . .) 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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References

[1] Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood 2008;112:2617–26.
[2] Lefrère JJ, Berche P. Arnault Tzanck (1886–1954), founder of the first blood centre worldwide. J Med Biogr 2013;21:211–9.
[3] Kleinman SH, Lelie N, Busch MP. Infectivity of human immunodeficiency virus-1, hepatitis C virus, and hepatitis B virus and risk of transmission by transfusion. Transfusion 2009;49:2454–89.
[4] Garraud O. Transfusion-transmitted parasitic diseases or transfusion-transmitted parasites? Not just a matter of semantics. Vox Sang 2006;91:349.
[5] Mahanty S, Prigent A, Garraud O. Immunogenicity of infectious pathogens and vaccine antigens. BMC Immunol 2015;16:e31.
[6] Pirofski LA, Casadevall A. What is infectiveness and how is it involved in infection and immunity? BMC Immunol 2015;16:e13.
[7] Pirofski LA, Casadevall A. Q and A: what is a pathogen? A question that begs the point. BMC Biol 2012;10:e6.
[8] Siblini L, Lafeuillade B, Ros A, Le Petit JC, Pozzetto B. Reduction of Yersinia enterocolitica load in deliberately inoculated blood: the

effects of blood prestorage temperature and WBC filtration. Transfusion 2002;42:422–7.
[9] Choudhury N, Murthy PK, Chatterjee RK, Khan MA, Ayyagari A. Transmission of filarial infection through blood transfusion. Indian J Pathol Microbiol 2003;46:367–70.
[10] Altfeld M, Gale Jr M. Innate immunity against HIV-1 infection. Nat Immunol 2015;16:554–62.
[11] Garraud O. Mechanisms of transfusion-linked parasite infection. Transfus Clin Biol 2006;13: 290–7.
[12] Bolton-Maggs PH, Cohen H. Serious hazards of transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol 2013;163:303–14.
[13] Zimring JC, Spitalnik SL. Pathobiology of transfusion reactions. Annu Rev Pathol 2015; 10:83–110.
[14] Benjamin RJ, McDonald CP, ISBT transfusion transmitted infectious disease bacterial workgroup. The international experience of bacterial screen testing of platelet components with an automated microbial detection system: a need for consensus testing and reporting guidelines. Transfus Med Rev 2014;28:61–7.
[15] Tagny CT, Diarra A, Yahaya R, Hakizimana M, Nguessan A, Mbensa G, et al. Characteristics of blood donors and donated blood in sub-Saharan Francophone Africa. Transfusion 2009;49:1592–9.
[16] Tagny CT, Mbanya D, Tapko JB, Lefrère JJ. Blood safety in Sub-Saharan Africa: a multifactorial problem. Transfusion 2008;48:1256–66.
[17] Bloch EM, Vermeulen M, Murphy E. Blood transfusion safety in Africa: a literature review of infectious disease and organizational challenges. Transfus Med Rev 2012;26:164–80.
[18] Laperche S, Pillonel J. [Relevance of safety measures to avoid HTLV transmission by transfusion in 2014]. Transfus Clin Biol 2014; 21:167–72.
[19] Laperche S, Lefrère JJ, Morel P, Pouchol E, Pozzetto B. [Blood transfusion: control of infectious risks]. Presse Med 2015;44:189–99.
[20] Dodd RY, Foster GA, Stramer SL. Keeping blood transfusion safe from West Nile virus: American Red Cross experience, 2003 to 2012. Transfus Med Rev 2015;29:153–61.
[21] Pozzetto B, Memmi M, Garraud O. Is transfusion-transmitted dengue fever a potential public health threat? World J Virol 2015;4: 113–23.
[22] Fredericks AC, Fernandez-Sesma A. The burden of dengue and chikungunya worldwide: implications for the southern United States and California. Ann Global Health 2014;80: 466–75.
[23] Yoon IK, Alera MT, Lago CB, Tac-An IA, Villa D, Fernandez S, et al. High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. Plos Negl Trop Dis 2015;9:e0003764.
[24] Fuller T, Bensch S, Müller I, Novembre J, Pérez-Tris J, Ricklefs RE, et al. The ecology of emerging infectious diseases in migratory birds: an assessment of the role of climate change and priorities for future research. Ecohealth 2012;9:80–8.
[25] Mackenzie JS, Williams DT. The zoonotic flaviviruses of southern, south-eastern and eastern Asia, and Australasia: the potential for emergent viruses. Zoonoses Public Health 2009;56:338–56.
[26] Salvador FS, Fujita DM. Entry routes for Zika virus in Brazil after 2014 World Cup: new possibilities. Travel Med Infect Dis 2015 [pii: S1477-8939(15)00173-8].
[27] De Kort W, Mayr W, Jungbauer C, Vuk T, Kullaste R, Seifried E, et al. Blood donor selection in European Union directives: room for improvement. Blood Transfus 2015;1–8.
[28] Barlet V. [Technological evolutions in blood donation screening and their impact on the residual risk]. Transfus Clin Biol 2011;18:292–301.
[29] Tayou Tagny C, Owusu-Ofori S, Mbanya D, Deneys D. The blood donor in Sub-Saharan Africa: a review. Transfus Med 2010;20:1–10.
[30] Cable R, Lelie N, Bird A. Reduction of the risk of transfusion-transmitted viral infection by nucleic acid amplification testing in the Western Cape of South Africa: a 5-year review. Vox Sang 2013;104:93–9.
[31] de Sousa G, Seghatchian J. Highlights of PBTI Coimbra conference on PRT of plasma & current opinions on pathogen reduction treatment of blood components. Transfus Apher Sci 2015;52:228–32.
[32] Kaiser-Guignard J, Canellini G, Lion N, Abonnenc M, Osselaer JC, Tissot JD. The clinical and biological impact of new pathogen inactivation technologies on platelet concentrates. Blood Rev 2014;28:235–41.
[33] Liumbruno GM, Marano G, Grazzini G, Capuzzo E, Franchini M. Solvent/detergent-treated plasma: a tale of 30 years of experience. Expert Rev Hematol 2015;8: 367–74.
[34] Seltsam A, Müller TH. Update on the use of pathogen-reduced human plasma and platelet concentrates. Br J Haematol 2013;162:442–54.
[35] Prudent M, D'Alessandro A, Cazenave JP, Devine DV, Gachet C, Greinacher A, et al. Proteome changes in platelets after pathogen inactivation – an interlaboratory consensus. Transfus Med Rev 2014;28:72–83.
[36] Salunkhe V, van der Meer PF, de Korte D, Seghatchian J, Gutiérrez L. Development of blood transfusion product pathogen reduction treatments: a review of methods, current applications and demands. Transfus Apher Sci 2015;52:19–34.
[37] Heddle NM, Lane SJ, Sholapur N, Arnold E, Newbold B, Eyles J, et al. Implementation and public acceptability: lessons from food irradiation and how they might apply to pathogen reduction in blood products. Vox Sang 2014;107:50–9.
[38] Swissmedic. Rapport d'hémovigilance 2014. http://Swissmedic_Haemo_F.pdf [accessed on December 4th, 2015].
[39] ANSM. Rapport d'activité d'hémovigilance 2014. http://ansm.sante.fr/var/ansm_site/storage/original/application/4ee5a6-f35365ab8b2ab1ad5eaccb5bd6.pdf [accessed on December 4th, 2015].
[40] Knutson F, Osselaer J, Pierelli L, Lozano M, Cid J, Tardivel R, et al. A prospective, active haemovigilance study with combined cohort analysis of 19,175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. Vox Sang 2015;109:343–52.
[41] Bost V, Chavarin P, Boussoulade F, Fabrigli P, Chabre C, Benamara H, et al. Independent evaluation of tolerance of therapeutic plasma inactivated by amotosalen-HCl-UVA (Intercept [TM]) over a 5-year period of extensive delivery. Vox Sang 2015;109:414–6.
[42] Tissot JD, Danic B, Schneider T. [Blood transfusion – safety of the inventory]. Presse Med 2015;44:178–88.
[43] Dasararaju R, Marques MB. Adverse effects of transfusion. Cancer Control 2015;22:16–25.
[44] Garraud O, Hamzeh-Cognasse H, Laradi S, Pozzetto B, Cognasse F. [Blood transfusion and inflammation as of yesterday, today and tomorrow]. Transfus Clin Biol 2015;22:168–77.
[45] West FB, Silliman CC. Transfusion-related acute lung injury: advances in understanding the role of proinflammatory mediators in its genesis. Expert Rev Hematol 2013;6:265–76.
[46] Poles D, Watt A. Dawe M, Bolton-Maggs BHB. Haemovigilance reporting in the UK 2013: collaboration to reduce confusion. http://www.shotuk.org/wp-content/uploads/2014-BBTS-Poster-Haemovigilance-Reporting-in-the-UK-2013-collaboration-to-reduce-confusion.pdf [accessed on December 4th, 2015].
[47] Motayo BO, Faneye AO, Udo UA, Olusola BA, Ezeani I, Ogiogwa JI. Seroprevalence of transfusion transmissible infections (TTI), in first time blood donors in Abeokuta, Nigeria. Afr Health Sci 2015;15:19–24.
[48] Bloch EM, Crookes RL, Hull J, Fawcus S, Gangaram R, Anthony J, et al. The impact of human immunodeficiency virus infection on obstetric hemorrhage and blood transfusion in South Africa. Transfusion 2015;55:1675–84.
[49] Mutocheluh M, Owusu M, Kwofie TB, Akadigo T, Appau E, Narkwa PW. Risk factors associated with hepatitis B exposure and the reliability of five rapid kits commonly used for screening blood donors in Ghana. BMC Res Notes 2014;7:e873.
[50] Pruett CR, Vermeulen M, Zacharias P, Ingram C, Tayou Tagny C, Bloch EM. The use of rapid diagnostic tests for transfusion infectious screening in Africa: a literature review. Transfus Med Rev 2015;29:35–44.

[51] Orkuma JA, Egesie JO, Banwat EB, Ejele AO, Orkuma JH, Bako IA. HIV screening in blood donors: rapid diagnostic test versus enhanced ELISA. Niger J Med 2014;23:192–200.
[52] Apata IW, Averhoff F, Pitman J, Bjork A, Yu J, Amin NA, et al. Progress toward prevention of transfusion-transmitted hepatitis B and hepatitis C infection – sub-Saharan Africa, 2000-2011. MMWR Morb Mortal Wkly Rep 2014;63:613–9.
[53] Rufai T, Mutocheluh M, Kwarteng K, Dogbe E. The prevalence of hepatitis B virus E antigen among Ghanaian blood donors. Pan Afr Med J 2014;17:e53.
[54] Mavenyengwa RT, Mukesi M, Chipare I, Shoombe E. Prevalence of human immunodeficiency virus, syphilis, hepatitis B and C in blood donations in Namibia. BMC Public Health 2014;14:e424.
[55] Zeba MT, Sanou M, Bisseye C, Kiba A, Nagalo BM, Djigma FW, et al. Characterisation of hepatitis C virus genotype among blood donors at the regional blood transfusion centre of Ouagadougou, Burkina Faso. Blood Transfus 2014;12(Suppl. 1):s54–7.
[56] Kabinda JM, Michèle DW, Donnen P, Miyanga SA, Van den Ende J. Factors for viral infection in blood donors of South Kivu in the Democratic Republic of Congo. Pan Afr Med J 2014;19:e385.
[57] Allain JP, Cox L. Challenges in hepatitis B infection among blood donors. Curr Opin Hematol 2011;18:461–6.
[58] Mbanya DN, Tayou C. Blood safety begins with safe donations: update among blood donors in Yaoundé, Cameroon. Transfus Med 2005;5:395–9.
[59] Lefrère JJ, Dahourouh H, Dokekias DE, Kouao MD, Diarra A, Diop S, et al. Estimate of the residual risk of transfusion-transmitted human-immunodeficiency virus infection in sub-Saharan Africa: a multinational collaborative study. Transfusion 2011;51:486–92.
[60] WHO. Making safe blood available in Africa – statement by Dr Neelam Dhingra. http://www.who.int/bloodsafety/en/ [accessed on December 2nd, 2015].
[61] WHO. Universal access to safe blood transfusion. Scaling up the implementation of the WHO strategy for blood safety and availability for improving patient health and saving lives. http://www.who.int/bloodsafety/StrategicPlan2008-2015AccessSafeBloodTransfusion.pdf?ua=1 [accessed on December 2nd, 2015].
[62] WHO 2013: global consultation on hemovigilance, Dubai, November 2012. http://www.who.int/bloodsafety/haemovigilance/haemovigilance-report.pdf [accessed on December 4th, 2015].
[63] Weiss DJ, Mappin B, Dalrymple U, Bhatt S, Cameron E, Hay SI, et al. Re-examining environmental correlates of plasmodium falciparum malaria endemicity: a data-intensive variable selection approach. Malar J 2015;14:e68.
[64] Pitman JP, Wilkinson R, Liu Y, von Finckenstein B, Smit Sibinga CT, Lowrance DW, et al. Blood component use in a sub-Saharan African country: results of a 4-year evaluation of diagnoses associated with transfusion orders in Namibia. Transfus Med Rev 2015;29:45–51.
[65] Mufti NA, Erickson AC, North AK, Hanson D, Sawyer L, Corash LM, et al. Treatment of whole blood (WB) and red blood cells (RBC) with S-303 inactivates pathogens and retains in vitro quality of stored RBC. Biologicals 2010;38:14–9.
[66] Tagny CT, El Dusouqui S, Rigal E, Mbanya D. Whole blood pathogen reduction: which benefit for blood safety in Africa? Int J Hematol Res 2015;1:27–8.
[67] Owusu-Ofori S, Kusi J, Owusu-Ofori A, Freimanis G, Olver C, Martinez CR, et al. Treatment of whole blood with riboflavin and UV light: impact on malaria parasite viability and whole blood storage. Shock 2015;44(Suppl. 1):33–8.
[68] Pozzetto B, Garraud O. [Emergent viral threats in blood transfusion]. Transfus Clin Biol 2011;18:174–83.
[69] Pozzetto B, Garraud O. [New viral threats in transfusion medicine by 2016]. Transfus Clin Biol 2016 [in press].
[70] de Mendoza C, Altisent C, Aznar JA, Batlle J, Soriano V. Emerging viral infections – a potential threat for blood supply in the 21st century. AIDS Rev 2012;14:279–89.
[71] Appassakij H, Khuntikij P, Kemapunmanus M, Wutthanarungsan R, Silpapojakul K. Viremic profiles in asymptomatic and symptomatic chikungunya fever: a blood transfusion threat? Transfusion 2013;53:2567–74.
[72] Oei W, Janssen MP, van der Poel CL, van Steenbergen JE, Rehmet S, Kretzschmar ME. Modeling the transmission risk of emerging infectious diseases through blood transfusion. Transfusion 2013;53:1421–8.
[73] Valença-Barbosa C, Fernandes FA, Santos HL, Sarquis O, Harry M, Almeida CE, et al. Molecular identification of food sources in triatomines in the Brazilian Northeast: roles of goats and rodents in chagas disease epidemiology. Am J Trop Med Hyg 2015;93:994–7.
[74] Martins-Melo FR, Ramos Jr AN, Alencar CH, Heukelbach J. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. Acta Trop 2014;130:167–74.
[75] Angheben A, Boix L, Buonfrate D, Gobbi F, Bisoffi Z, Pupella S, et al. Chagas disease and transfusion medicine: a perspective from non-endemic countries. Blood Transfus 2015;13:540–50.
[76] Tseroni M, Baka A, Kapizioni C, Snounou G, Tsiodras S, Charvalakou M, et al. Prevention of malaria resurgence in Greece through the Association of mass drug administration (MDA) to immigrants from malaria-endemic regions and standard control measures. Plos Negl Trop Dis 2015;9:e0004215.
[77] Goodell AJ, Bloch EM, Krause PJ, Custer B. Costs, consequences, and cost-effectiveness of strategies for Babesia microti donor screening of the US blood supply. Transfusion 2014;54:2245–57.
[78] Karafin MS, Stramer SL. The scientific method at work: xenotropic murine leukemia virus-related virus is neither a cause of chronic fatigue syndrome nor a threat to the blood supply. Transfusion 2012;52:222–5.
[79] Burnouf T, Emmanuel J, Mbanya D, El-Ekiaby M, Murphy W, Field S, et al. Ebola: a call for blood transfusion strategy in sub-Saharan Africa. Lancet 2014;384:1347–8.
[80] Burnouf T, Seghatchian J. Ebola virus convalescent blood products: where we are now and where we may need to go. Transfus Apher Sci 2014;51:120–5.
[81] Garraud O, Heshmati F, Pozzetto B, Lefrère F, Girot R, Saillol A, et al. PLasmatherapy against infectious pathogens, as of yesterday, today and tomorrow. Transfus Clin Biol 2016 [in press].
[82] Millar CM, Makris M. Dealing with the uncertain risk of variant Creutzfeldt-Jakob disease transmission by coagulation replacement products. Br J Haematol 2012;158:442–52.
[83] Martin M, Trouvin JH. Risk of transmission of Creutzfeldt-Jakob disease via blood and blood products. The French risk-analysis over the last 15 years. Transfus Clin Biol 2013;20:398–404.
[84] Angelakis E, Raoult D. Methods for the discovery of emerging pathogens. Microb Pathog 2014;77:114–8.
[85] Beale MA, Tettmar K, Szypulska R, Tedder RS, Ijaz S. Is there evidence of recent hepatitis E virus infection in English and North Welsh blood donors? Vox Sang 2011;100:340–2.
[86] Cleland A, Smith L, Crossan C, et al. Hepatitis E virus in Scottish blood donors. Vox Sang 2013;105:283–9.
[87] Xu C, Wang RY, Schechterly CA, et al. An assessment of hepatitis E virus (HEV) in US blood donors and recipients: no detectable HEV RNA in 1939 donors tested and no evidence for HEV transmission to 362 prospectively followed recipients. Transfusion 2013;53:2505–11.
[88] Sauleda S, Ong E, Bes M, et al. Seroprevalence of hepatitis E virus (HEV) and detection of HEV RNA with a transcription-mediated amplification assay in blood donors from Catalonia (Spain). Transfusion 2015;55:972–9.
[89] Gallian P, Piquet Y, Assal A, et al. [Hepatitis E virus: blood transfusion implications]. Transfus Clin Biol 2014;21:173–7.
[90] Slot E, Hogema BM, Riezebos-Brilman A, Kok TM, Molier M, Zaaijer HL. Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012. Euro Surveill 2013;18. pii:20550.
[91] Guo QS, Yan Q, Xiong JH, Ge SX, Shih JW, Ng MH, et al. Prevalence of hepatitis E virus in

Chinese blood donors. J Clin Microbiol 2010;48:317–8.
[92] Lapa D, Capobianchi MR, Garbuglia AR. Epidemiology of hepatitis E virus in European Countries. Int J Mol Sci 2015;16:25711–43.
[93] Gallian P, Lhomme S, Piquet Y, Sauné K, Abravanel F, Assal A, et al. Hepatitis E virus infections in blood donors, France. Emerg Infect Dis 2014;20:1914–7.
[94] Smith DB, Ijaz S, Tedder RS, Hogema B, Zaaijer HL, Izopet J, et al. Variability and pathogenicity of hepatitis E virus genotype 3 variants. J Gen Virol 2015;96:3255–64.
[95] Izopet J, Labrique AB, Basnyat B, Dalton HR, Kmush B, Heaney CD, et al. Hepatitis E virus seroprevalence in three hyperendemic areas: Nepal, Bangladesh and southwest France. J Clin Virol 2015;70:39–42.
[96] Lhomme S, Abravanel F, Dubois M, Chapuy-Regaud S, Sandres-Saune K, Mansuy JM, et al. Temporal evolution of the distribution of hepatitis E virus genotypes in Southwestern France. Infect Genet Evol 2015;35:50–5.
[97] Colson P, Brunet P, Lano G, Moal V. Hepatitis E virus genotype 4 in Southeastern France: still around. Liver Int 2015. http://dx.doi.org/10.1111/liv.12924.
[98] Pillonel J, Gallian P, Sommen C, Couturier E, Piquet Y, Djoudi R, et al. [Assessment of a transfusion emergent risk: the case of HEV]. Transfus Clin Biol 2014;21:162–6.
[99] Gallian P, Piquet Y, Assal A, Djoudi R, Chiaroni J, Izopet J, et al. [Hepatitis E virus: Blood transfusion implications]. Transfus Clin Biol 2014;21:173–7.
[100] Hogema BM, Molier M, SJerps M, de Waal M, van Swieten P, van de Laar T, et al. Incidence and duration of hepatitis E virus infection in Dutch blood donors. Transfusion 2015 [Epub ahead of print].
[101] Andonov A, Rock G, Lin L, Borlang J, Hooper J, Grudeski E, et al. Serological and molecular evidence of a plausible transmission of hepatitis E virus through pooled plasma. Vox Sang 2014;107:213–9.
[102] Hauser L, Roque-Afonso AM, Beylouné A, Simonet M, Deau Fischer B, Burin des Roziers N, et al. Hepatitis E transmission by transfusion of Intercept blood system-treated plasma. Blood 2014;123:796–7.
[103] http://www.invs.sante.fr/Dossiers-thematiques/Populations-et-sante/Donneurs-de-sang/La-surveillance-epidemiologique-des- donneurs-de-sang-VIH-VHC-VHB-HTLV-syphilis.
[104] Sabino EC, Gonçalez TT, Carneiro-Proietti AB, Sarr M, Ferreira JE, Sampaio DA, et al. Human immunodeficiency virus prevalence, incidence, and residual risk of transmission by transfusions at Retrovirus epidemiology donor study-II blood centers in Brazil. Transfusion 2012;52:870–9.
[105] de Almeida-Neto C, Sabino EC, Liu J, Blatyta PF, Mendrone-Junior A, Salles NA, et al. Prevalence of serologic markers for hepatitis B and C viruses in Brazilian blood donors and incidence and residual risk of transfusion transmission of hepatitis C virus. Transfusion 2013;53:827–34.
[106] Carneiro-Proietti AB, Sabino EC, Leão S, Salles NA, Loureiro P, Sarr M, et al. Human T-lymphotropic virus type 1 and type 2 seroprevalence, incidence, and residual transfusion risk among blood donors in Brazil during 2007-2009. AIDS Res Hum Retroviruses 2012;28:1265–72.
[107] Noubouossie D, Tagny CT, Same-Ekolo A, Mbanya D. Asymptomatic carriage of malaria parasites in blood in Yaounde. Transfus Med 2012;22:63–7.