Review Article

Transfusion-transmitted infections

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Abstract: Blood transfusion is remarkably safe in high-income countries (HICs), where safeguards have long protected the blood supply against the major transfusion transmissible infections (TTIs). Globally, surprisingly few pathogens have been implicated in transfusion transmitted infection and most pathogens do not merit specific intervention. Nonetheless, pathogens are emerging much more frequently than is often appreciated, thus necessitating constant vigilance and individual assessment of transfusion-associated risk. Factors that inform the need for intervention include the ramifications (i.e., severity) of infection with a given pathogen, the likelihood of detection in the absence of a defined intervention, tolerance of standard processing and storage conditions (e.g., refrigeration), transfusion transmissibility and clinical penetrance (i.e., development of symptoms following transfusion transmission). Different approaches that have been used to protect the blood supply include donor selection and risk-based deferral, laboratory screening (i.e., using highly sensitive and specific serological and/or molecular assays), bacterial culture (platelets) and pathogen reduction (PR). Each approach has both strengths as well as limitations, whereby strategies are devised to meet national or regional risk, while balancing available resources. TTIs, as a direct reflection of blood transfusion safety, highlight a World divided. In HICs, hypervigilance is increasingly disproportionate to risk; this has contributed to policies and interventions that have been wasteful, incurring enormous cost at marginal—if any—clinical gain. By contrast, many of the routine measures regarded as effective in HICs are conspicuously deficient or even absent in low- and middle-income countries (LMICs) where blood transfusion thus remains a major mode of disease transmission.

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Introduction

Blood transfusion in high income countries (HICs) is safe. The tragedy of human immunodeficiency virus (HIV) in the early 1980s highlighted multiple systemic deficiencies spanning blood donor selection, testing and post-transfusion surveillance (1,2). Almost 4 decades later, the enterprise of blood collection, processing and transfusion is vastly different. Consequently the risks of the major transfusion transmissible infections (TTIs) [i.e., HIV, Hepatitis B and C viruses (HBV and HCV respectively) and *T. pallidum*] is low (1,3). Such a transformation has allowed for focusing of efforts toward historically neglected transfusion associated infectious risks (e.g., bacteria, *Babesia*) while developing pathogen reduction technologies to contend with infectious risk proactively. The massive investment in blood safety to restore confidence in the blood supply, has contributed to a different problem: one of imbalance where the public health yield is often vanishingly low, whereby resources may arguably be better directed elsewhere (4,5). Blood safety at any cost is not without its own risk, impacting sustainability and capacity to contend with challenges as they arise (6).

Nonetheless blood transfusion offers another glaring example of health disparity. Specifically, blood transfusion safety and infectious risk is divided between HICs and low- and middle-income countries (LMICs). Every element of the blood safety continuum from donor selection through to post-transfusion surveillance is either lacking or absent

in low-income countries (7). TTIs are the metric of associated dysfunction, that to date still lacks for durable investment or public attention, despite broad impact on public health (7,8). This is not a unique problem, but rather one that falls under the purview of inattention to pathology and laboratory services in general (9). Demand for blood transfusion remains high in LMICs, forcing continued reliance on suboptimal practices (e.g., replacement and paid donation, rapid testing, etc.) (10). Further, post-transfusion surveillance is lacking, where a demonstration of transmission and clinical sequela might help to motivate for change (11).

The following offers an overview of transfusion associated infectious risk. Description of the major TTIs is used to illustrate some of the lessons learned and how history has informed current practice. Where possible, examples have also been used to illustrate the differences in risk and mitigation between HICs and LMICs.

Prevention strategies

The overwhelming majority of pathogens do not indeed require any intervention and pose little to no risk to transfusion recipients. There are multiple factors that inform the decision to intervene (12,13). Emergence of novel as well as re-emergence of established pathogens is occurring with far greater frequency than might be appreciated. Each agent requires careful evaluation of risk to the blood supply. Foremost among those factors is the association with a clinically important outcome. Given the resources required for assay development, it is not feasible to address all—or even most—pathogens. Agents that are short lived in the blood generally do not pose risk. By contrast, agents with protracted, asymptomatic phase (e.g., HIV, HBV and HCV) are particularly dangerous as donors are likely to be unaware of their infectious status at time of donation. Individuals who are infected with pathogens that confer acute symptom onset are likely to self-defer or be detected during pre-donation screening (e.g., fever, anemia). Second are considerations surrounding tolerance of storage and processing, transfusion transmissibility and clinical penetrance. Agents that do not survive prolonged refrigeration, are unlikely to transmit. Laboratory evidence of transmission alone is insufficient evidence of recipient risk. Rather, there should be evidence of symptomatic disease in recipients. Third is the epidemiology of the agent, including the geographic distribution, seasonal incidence and prevalence in the blood donor population. Fourth is detectability. Specifically, one needs to weigh up each of the available approaches and the associated advantages and disadvantages of each. Fifth, are the financial ramifications. Ideally, this is guided by formal economic analysis to quantify the cost per quality adjusted life year ($/QALY). Finally, there are other variables that impact decision making. These are more difficult to quantify but often carry undue influence over the science. Politics, funding and culture all affect decision making.

When intervention is decided, the different approaches include donor selection and risk-based deferral, laboratory-based testing and pathogen reduction (PR).

Risk based deferral

Risk-based decision making (RBDM) is used to identify low-risk donors. RBDM is typically accomplished using a donor history questionnaire. The latter is designed specifically to exclude those with medical history and/or socio-behavioral risk factors for TTIs.

Laboratory-based blood donor testing

Serological testing

Some pathogens are not easily detected through RBDM and require a laboratory-based strategy, using serological-(detection of antibodies with or without antigens) and/or nucleic acid testing (NAT). There are advantages and disadvantages of each strategy. Serological testing is undertaken using a variety of different technologies [e.g., Enzyme linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA), etc.]. The presence of antibodies generally reflects exposure rather than active infection. With some pathogens (notably chronic viruses e.g., HIV), it may reflect active infection. Serological assays are lower cost than NAT, readily available and have a variety of formats, spanning rapid/point of care, semi-automated and fully automated. Rapid tests are typically not validated for blood donor screening; consequently, they lack comparable sensitivity and specificity of automated assays (14,15). They are most commonly used in low resource settings given the low cost and ease of use (15).

NAT

NAT offers a better correlate of active infection than serology. The key advantage of NAT is its ability to shorten the window to detection of a given pathogen. As

way of example, the pre-seroconversion window period of HCV is 1–3 months (16,17). By contrast, HCV RNA becomes detectable within 5–8 days of infection. For HIV, NAT has shortened the time to detection by ~10–15 days (18-20). Nonetheless, NAT is relatively high cost, and requires both greater technical expertise and infrastructure than serological testing. Consequently, use of donor NAT remains rare in upper middle-income countries (e.g., South Africa, Namibia) and non-existent in low-income countries (10).

Many of the NAT assays are able to be performed on individual donor samples (ID-NAT) or in mini-pools (MP-NAT). Mini-pools improve the efficiency and cost-effectiveness of screening. The size of the pools is informed by the background incidence of the targeted pathogen in the donor population. As way of example, multiplex NAT is undertaken routinely for HIV, HBV and HCV in pools of 6 to 16 donor samples. In the event of a positive result, the pools are "deconstructed" and the individual donor samples are subjected to multiplex NAT. Larger pools may be used in populations with a low incidence of infection for the individual agents. By contrast, MP-NAT is not appropriate in cases with a high background incidence of any of the targeted pathogens i.e. it would defeat the purpose given the need for frequent need to investigate reactive pooled samples.

Testing algorithms

The testing algorithms in use impact infectious risk. In high-income countries (HICs) testing algorithms typically combine screening tests, repeat testing in the event of a reactive result (i.e., use of the same assay on additional aliquots from the index sample), confirmatory testing (i.e., use of a different assay) with or without supplementary testing (2). The latter is used to facilitate donor counseling and management. For example, a non-treponemal assay such as the Venereal Disease Research Laboratory (VDRL) assay might be used to understand whether a donor has active syphilis, even though this information would not be necessary for blood product management given that the screening results would have already led to disposal of the blood and deferral of the donor. Given the high costs of reagents and challenges surrounding procurement, testing approaches in LMICs typically lack repeat and/or confirmatory testing.

PR

PR offers a departure from the traditional paradigm of targeted testing (21). There are a variety of technologies (e.g., photochemical inactivation (PI), solvent detergent treatment, nanofiltration) that allow for global treatment of blood products, rendering them safe from infection (22). PR has long been in routine use for plasma derivatives (e.g., albumin, and immunoglobulins) (23). PI is increasingly being used to contend with bacterial contamination of platelets. Addition of a psoralen or riboflavin to the blood product followed by exposure to UV light, leads to irreversible cross-linkage of DNA or RNA in the case of amotosalen/UVA or oxidation of the guanine bases with strand breakage in the case of Riboflavin/UVB light, thus rendering a broad range of pathogens incapable of replication (22,24). Other approaches include methylene blue treatment, solvent-detergent treatment or glutathione treatment (22). Key advantages include the ability to address different classes of pathogen simultaneously using a single intervention. These include those pathogens that are well established (e.g., HIV, HBV, HCV), those that may be emerging and those that are entirely novel. Function is not significantly different from untreated products. Independent of infectious risk, PI is a very effective measure to prevent transfusion associated graft vs host disease. While the individual technologies vary, the key limitations of PR in general, is the absence of a licensed technology for red cells and whole blood, which remain the major blood products. Further, cost is a formidable barrier, particularly in low resource settings where PR would confer greatest benefit (25,26).

Categorization of TTIs (*Tables 1-3*)

TTIs can be categorized broadly based on the evidence for transfusion transmissibility, the extent of risk (i.e., whether global or regional) and intervention. For the purpose of this review, Category I pathogens (i.e., HIV, HBV, HCV and *T. pallidum*) are those for which transfusion transmissibility is well established, risk is global and donor screening is near universal (*Table 1*). Category II and III both include pathogens for which transfusion transmissibility has been well established and mitigation measures have been implemented albeit in selected countries (*Table 2*). They differ with respect to extent of risk whereby Category II

Table 1 Category I: risk and intervention for the major TTIs in HICs

	Pathogen	Disease association	Transfusion transmissible	Risk-based deferral	Donor serology	Donor NAT	Pathogen reduction*	Other	Contextualized residual risk
Category I	HIV	AIDS	+++	√	√	√	√		Rare; 1 in 2.3 million donations (3)
	HBV	Chronic hepatitis; cirrhosis; hepatocellular carcinoma	+++	√	√	√	√		Rare; 1 in 1.5 million donations (3)
	HCV	Chronic hepatitis; cirrhosis; hepatocellular carcinoma	+++	√	√	√	√		Rare; 1:2.6 million donations (3)
	T. pallidum	Syphilis	++	√	√	–	√	Refrigeration	Rare/absent; e.g., no reported cases in US since 1960s

+ to +++ grading of risk (+ is lowest and +++ is highest risk). √, in routine use (note: interventions may be applied alone or in combination). *, platelets and plasma; –, not available or not routinely performed as blood donor intervention. HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; AIDS, acquired immunodeficiency syndrome.

pathogens pose global risk and Category III pathogens are regional, acknowledging that the distinction is somewhat arbitrary. Category IV includes pathogens that have been implicated—albeit rarely—in cases of transfusion transmitted disease. Risk is considered low independent of the prevalence in the general population (*Table 3*). Finally, Category V includes pathogens for which there is no clinical evidence for transfusion transmitted infectious disease.

Viruses

HIV

No other infectious agent has impacted blood transfusion safety like HIV. A link between HIV and blood transfusion was first raised following development of immune dysfunction in three patients with hemophilia (51). Similarly, a neonate who was transfused developed opportunistic infections at 14 months of age (52). A lookback study revealed that one of the 3 blood donors had died from AIDS related complications, offering supporting evidence of transfusion transmissibility. Delayed recognition of transfusion as a mode of transmission had devastating consequences, most notably for patients with hemophilia who depended on plasma-derived clotting factor concentrates for treatment. One study that employed retrospective modeling of transfusion associated risk of HIV in the San Francisco Bay area from January 1978 to March 1985 offered important insights into the scale of the early epidemic and the then hazard of blood transfusion (53). From 1980 to 1982, there was a 50% increase in cases of contamination, peaking in 1982, when 3.3% of all donations were HIV contaminated. Measures that were introduced in 1982 to 1983 included self-deferral of high-risk donors (e.g., MSM) and confidential exclusion of donated units. Beginning in May 1984, exclusion of anti-HBc positive donations further reduced the by 40–50%. In March 1985, the first highly sensitive and specific antibody test was implemented for HIV-1. In 1992, implementation of a third generation enzyme immunoassay, enabled detection of HIV-2 (54). In 1999 minipool-NAT for HIV was introduced as a multiplex test with HCV. Nearly four decades since first recognition, transfusion transmitted HIV is rare in HICs. For example, the estimated risk in the US is less than 1 in 2 million, a figure based on a modeled—rather than an observed incidence (2,3). Unfortunately, this is not the case in LMICs where transfusion transmitted HIV remains a significant public health challenge, given the high background incidence of HIV coupled with suboptimal blood donor selection and testing (7,11).

Hepatitis B and hepatitis C virus (HBV and HCV)

Prior to the HIV era, HBV and *T. pallidum* were the only agents screened in blood donors. Studies in the 1950s and

Table 2 Category II (global) and III (regional) TTIs

	Pathogen	Disease association	Transfusion transmissible	Risk-based deferral	Donor serology	Donor NAT	Pathogen reduction*	Other	Contextualized residual risk
Category II	Conventional bacteria	Transfusion-associated sepsis	++	–	√	±*	√	Diversion pouches; bacterial culture; point of care testing	High risk (27,28). Depends on: product type (highest for platelets); safeguards in place to prevent contamination (low to absent risk with PR); the contaminating organism; collection technology; active *vs.* passive surveillance; definition i.e., risk of culture positivity (1 in 2,500–4,000) *vs.* septic transfusion reaction (1 in 60,000–220,000) *vs.* fatality (rare) (29)
	Plasmodium	Malaria	+++	√	Selectively in some non-endemic countries	–	√		Rare in HICs (30): 1–2 cases per year. High risk in LMICs (31)
Category III	HEV	Acute fulminant hepatitis	+++	√	–	√	±		Rare (32,33)
	HTLV-I/II	Adult T-cell leukemia/ lymphoma HAM/TSP	+++	√	√	–	√	Leukoreduction	Rare but… Difficult to quantify given long latency and variable penetrance; most countries do not test
	WNV	Meningoencephalitis	+++	–	–	√	√		Rare
	T. cruzi	Chagas disease	++	√	√		√		Rare
	Babesia	Babesiosis	+++	√	–	√	√		Rare/absent. Since adoption of molecular screening in US (34)
	CMV	Retinitis, enteritis, disseminated infection, interstitial pneumonitis	+	–	√	–	√	Leukoreduction	Rare in HICs. Highly variable (35,36) depends on: serostatus of donor and recipient; risk factors in recipient; number of units transfused and product type; leukoreduction

√, in routine use (note: interventions may be applied alone or in combination). + to +++ grading of risk (+ is lowest and +++ is highest risk). *, platelets and plasma; – not available or not routinely performed as blood donor intervention. HTLV, human T-cell lymphotropic virus; HEV, hepatitis E virus; HAM/TSP, HTLV associated myelopathy/ tropical spastic paraparesis.

Table 3 Pathogens that have rarely been implicated as TTIs (Category IV) or have prompted intervention (Category V) without definite cases of transfusion transmission

	Pathogen	Disease association	Transfusion transmissible	Risk-based deferral	Donor serology	Donor NAT	Pathogen reduction	Other	Contextualized residual risk
Category IV	vCJD	Spongiform encephalopathy	+	√	–	–	√	Leukoreduction	Rare/theoretical. A total of 4 transfusion transmitted cases in the literature
	Dengue	Dengue hemorrhagic fever	+	√	√	√	√		Rare (37-40). Some HICs conduct selective test in travelers returning from endemic areas; despite high rates of detectable RNA in recipients following transfusion from Dengue RNA+ donors (41), clinical cases of transfusion transmitted dengue are rare despite high background incidence, globally
	Hepatitis A virus	Acute hepatitis	+	–	–	–	√**		Rare/ historical (42,43)
	Leishmania	Leishmaniasis	+	√	–	–	–		Rare/theoretical (44,45)
	Anaplasma	Anaplasmosis	+	–	–	–	–		Rare (46-48)
	Toxoplasma	Toxoplasmosis	+; historical cases from granulocytes	–	–	–	–		Rare/historical (49,50)
Category V	Zika virus	Congenital Zika syndrome: severe teratogenic effect with microcephaly, intracranial calcifications intrauterine growth retardation, abortion and fetal demise; Guillain Barre in adults	±; no clinical cases of transfusion transmitted infection	√†	–	√	√		Theoretical. No clinical cases of transfusion transmitted Zika have been confirmed
	Chikungunya	Arthritis	±	√	–	–	√		Theoretical. No clinical cases of transfusion transmitted Chikungunya have been confirmed

±, theoretically possible/no clinical cases have been described. √, in routine use (note: interventions may be applied alone or in combination). + to +++ grading of risk (+ is lowest and +++ is highest risk). –, not available or not routinely performed as blood donor intervention. *, platelets and plasma; **, fractionated plasma products (not in use for community blood donation); †, travel based deferral used early in Zika pandemic. vCJD, Variant Creutzfeldt-Jakob disease.

1960s first highlighted the risk of post-transfusion hepatitis in recipients of blood transfusion from paid donors (up to 4-fold higher than that from voluntary donors) (55,56). In one study of patients who underwent open heart surgery, 51% of those who received blood from commercial donors developed post-transfusion hepatitis *vs.* 0% from voluntary donors (57). Testing for Hepatitis B surface antigen (HbsAg) began in the 1970s. However, a high proportion of patients with transfusion-associated hepatitis did not have evidence of HBV or other viruses that were commonly associated with hepatitis [e.g., hepatitis A virus or cytomegalovirus (CMV)], earning the designation as non-A non-B hepatitis (NANBH) (58). Hepatitis B core antibody (HBcAb) was later found to be a surrogate marker of NANBH; in one study 12% of recipients of HBcAb positive blood went on to develop NANBH (59). Alanine transaminase (ALT) was also recognized as a surrogate measure of NANBH; one study suggested that its measurement in donors would prevent 29% of cases of post-transfusion hepatitis (60). Consequently, ALT and HBcAb were integrated into donor screening (61).

HCV was ultimately implicated as the cause of NANBH; this led to the implementation of anti-HCV testing (e.g., in the US) in 1990 (62). Anti-HCV screening was estimated to prevent half of all cases of transfusion-associated hepatitis (63,64). Of those infected with HCV, 50–60% will develop chronic hepatitis (65). Nonetheless, the long pre-seroconversion period remained a significant limitation of a serology-based strategy alone. Consequently, HCV NAT was adopted in the US in 1999; HBV NAT was added in 2009 (2). Testing for HBV and HCV has had a major impact on blood safety, whereby the estimated residual risk of acquisition of HBV (1 in 1.5 million donations) and HCV (1 in 2.6 million donations) from blood transfusion, at least in HICs, is extremely low (3). NAT also confers the ability to detect occult hepatitis B infection (OBI), particularly in settings where HBcAb is not routinely performed (7,66,67).

Hepatitis E virus (HEV)

HEV is a non-enveloped, positive-sense, single-stranded RNA virus. There are 4 Genotypes (G1-4), which differ with respect to their primary mode of spread and epidemiology. Specifically, G1 and G2 are spread by the fecal-oral route, accounting for epidemics in low-income countries (LICs) through water-borne spread. G3 and G4 are food-borne zoonosis (porcine viruses) whereby human spread follows consumption of infected meat (68,69). HEV is a major cause of acute hepatitis globally. Largely neglected (compared to HBV and HCV), it has drawn attention given a progressive increase in HEV in parts of Western Europe. While it causes mild self-limiting infection in the immunocompetent, it may result in severe or even fatal disease (i.e., acute fulminant hepatitis) in pregnancy and the immunocompromised. Persistent infection and chronic hepatitis are also well described with rapid development of cirrhosis.

Surveillance studies suggest high rates of background exposure in parts of the world, as reflected by observed seroprevalence estimates in Nepal (47%), Bangladesh (50%), France (53%) and Netherlands (27%) (70,71). Cases of transfusion-transmitted HEV G3 have been reported in France, UK and Germany. Risk of transfusion transmitted HEV pertains to RBCs, platelets, granulocytes and plasma. The lowest infecting viral dose 2×10^4 IU and 55% of components transmit the virus conferring a 40–50% risk of infection in recipients (72). Molecular surveillance in donor population suggests variable rates of G3 viremia e.g., 1 in 762 (The Netherlands), 1 in 9,500 (USA); 0 of 13,993 (Canada), 1 in 4,997 (Ireland) and 1 in 3,830 (England) (73-76). Surveillance has likely informed donor screening policy: HEV NAT is routinely performed in donors in Japan, Netherlands, France, Germany, UK and Ireland (77). Of note, PR (e.g., Intercept, Mirasol) is relatively ineffective against non-enveloped viruses, including HEV.

Human T-cell lymphotropic virus (HTLV)

HTLV-I and HTLV-II were the first described retroviruses in humans. HTLV-I is the cause of adult T-cell leukemia/lymphoma (ATCL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). While less well defined, HTLV-II produces similar neurological disease to that observed in HAM/TSP (78,79). Most HTLV-I and HTLV-II infections are asymptomatic. HTLV "hot spots" (i.e., areas with high endemicity) include Southwest Japan, Central Africa, Melanesia, Caribbean basin and Brazil (80). While HTLV-1 is prevalent in Europe and Japan, a high proportion of HTLV infected donors in the US have HTLV-II (81). Both HTLV-1 and II are transfusion transmissible (82). In one study, 63% of recipients who were transfused with—relatively fresh—cellular blood components (whole blood, red blood cells, and/or platelets) from HTLV-I antigen or antibody positive blood donors, seroconverted (83). Transfusion-transmitted HTLV can lead to persistent infection in transfusion recipients (84). Many of the risk

factors for HTLV (notably intravenous drug use) are enquired specifically on the donor history questionnaire. Leukoreduction also helps to prevent transmission (85). Donor screening is not universal; rather it is largely confined to HICs (81). Most countries have elected to forgo testing for HTLV given low regional prevalence and/or clinical penetrance where most infections are asymptomatic and the incidence of HAM/TSP and ATCL in HTLV-1 infected individual is ~1% and 2–4% respectively) (86). Given the high cost of averting serious HTLV-associated morbidity or death, testing of first-time donors only has been proposed as a more cost-effective approach (87). Countries that do screen blood donors do so using antibody-based testing. For example, donor screening in the US has been effect since 1988 using an EIA against a whole blood HTLV lysate. Supplementary tests have been used to interpret the findings (86). In general, the high homology (60%) between HTLV-1 and HTLV-II, enables detection of both viruses using assays that target HTLV-I (88). Over time, adoption of refined algorithms has reduced reliance on supplementary testing for interpretation or results (89,90).

CMV

Blood transfusion has long been cited as a risk of CMV, notably in the immunocompromised (e.g., organ transplant recipients) and hospitalized neonates and infants (91-93). In one study, 67% of neonates who received CMV seropositive blood went on to show laboratory evidence of infection vs none in the group who received blood from seronegative donors (35). Nonetheless, the risk of transfusion transmitted CMV remains contentious given that a high proportion of the general population is already CMV seropositive and most infections are asymptomatic (35). Further, the risk estimates have been highly variable. For example, one study found only 1 of 126 (0.8%) seronegative neonates became infected following transfusion of seropositive blood (36). A landmark clinical trial showed that the risk of transfusion-transmitted CMV was not significantly different between leukocyte filtered blood and blood collected from CMV seronegative donors (94). This led to the gradual transition away from selective inventories where blood was reserved for high-risk patient populations (e.g., pregnant women, the immunocompromised, neonates), instead favoring leukoreduced blood. Leukoreduction is now routine in many if not most HICs. This is not the case in LMICs where leukoreduction is the exception.

West Nile virus (WNV)

WNV is a mosquito-borne *flavivirus* within the Japanese encephalitis (JE) antigenic Complex (95,96). The majority (80%) of infections are subclinical; however, ~1% of those infected will develop neuro-invasive disease, including meningoencephalitis. Historically, there were sporadic outbreaks of WNV in Africa, Middle East and Western Asia (95). Its sporadic nature changed with the emergence of WNV in New York City in August 1999 (97); within 5 years, WNV was widely distributed throughout the continental US (95,98). At the outset of the US epidemic, transfusion associated risk was estimated to be low (2.7 per 10,000 donations) (99). Multiple cases of transfusion transmitted WNV were subsequently described (100); one of the initial reports described 23 cases of transfusion-transmitted WNV, representing 16 blood donors (101). NAT for WNV was developed rapidly and implemented in 2003 (102,103). A strategy was devised whereby mini-pool NAT is performed year-round with reflex to ID-NAT following detection of a positive donor in a given area code (102,104,105). ID-NAT is continued for a minimum period (e.g., seven consecutive days) in the geographic region in which the infectious donor originated. This approach is used to optimize probability of identifying donors with low level viremia that might otherwise escape detection using MP-NAT (102,106). MP-NAT is resumed thereafter assuming that no additional positive donors are detected. The period of ID-NAT may be extended based on regional surveillance and seasonal activity. For example, one might include overlapping geographic regions (107). WNV positive donors are deferred for a period of 120 days after donation. Lauded as one of the successes of modern blood banking, the current testing approach has proved to be very effective having successfully interdicted thousands of potentially infectious blood products (103,108).

Protozoa

Trypanosoma cruzi (T. cruzi)

T. cruzi is the protozoan parasite that is responsible for the eponymous Chagas disease. While most *T. cruzi* infections are asymptomatic, up 40% of those who are infected either have or will develop complications that include cardiomyopathy and gastrointestinal disease (e.g., megaesophagus, megacolon) through destruction of intramural autonomic ganglia (109). *T. cruzi* is widely endemic in Central and South America, extending as far

North as the Southern US where autochthonous cases have been reported (109,110). Global travel, trade and migration have blurred historical boundaries of endemicity extending risk to non-endemic countries (111,112). *T. cruzi* is primarily transmitted by triatomine insects (aka assassin or kissing bugs), accounting for its association with poverty i.e., triatomine insects inhabit adobe, mud, straw and thatch (113). Vertical transmission (i.e., congenital *T. cruzi* infection) and blood transfusion are also well described routes of transmission. Blood donor antibody-based screening, has long been in use in the Americas to prevent transfusion-transmitted *T. cruzi*. Individuals with a history of either a positive test for *T. cruzi* or clinical (Chagas) disease are permanently deferred from blood donation. RBDM (e.g., inquiry regarding birth or residence in an endemic country) may also be effective in non-endemic countries (114).

Babesia

Babesia is a genus of tick-borne intraerythrocytic protozoan parasite and the causative agent of the clinical infection babesiosis. The major species that infect humans are *B. microti*, *B. divergens*, *B. duncani* and *B. venatorum*, each of which differs with respect to its geographic distribution (115). *Babesia* are readily transfusion transmissible from any red blood cell (RBC) product, with as few as 10–100 parasites needed to establish competent infection (116). The overwhelming majority of cases of transfusion-transmitted babesiosis (TTB) are ascribed to *B. microti*, rare cases have been caused by *B. duncani* and other variant species (117-119). *B. microti* is widely endemic in the Northeastern and upper Midwestern United States: over 200 cases of TTB have been reported (117). Infection in immunocompetent adults is often subclinical or mild; by contrast, selected patient subsets—notably the extremes of age, the asplenic and immunocompromised—are at risk of severe infection accounting for the high fatality rate (~20%) in TTB (115). Further, persistent, symptomatic infection is not uncommon, such that donors are unaware of infection status at time of donation (120,121). This recognition led to development of antibody and molecular assays for blood donor screening in the US (121-125). In 2018, the US FDA published their recommendations, favoring regional molecular screening for Babesia in the highest risk states (126). The approved molecular assays are highly sensitive and specific and are capable of detecting the 4 major species of clinical concern. Where available, PR is also permissible as an alternative to molecular testing. The few blood donor studies that have been undertaken outside of the US (i.e., in Canada, China, Australia and Austria) suggest that risk of TTB remains low (127-130).

Plasmodium

Plasmodium (the cause of Malaria) is a leading, unaddressed risk to global blood transfusion safety (31). Malaria poses very different challenges for blood safety in endemic and non-endemic countries. In endemic countries, the optimal mitigation strategy is still uncertain. Approaches in use for clinical diagnosis, such as microscopic examination of peripheral blood smears, are not amenable to high throughput donor testing given the low sensitivity of microscopy, coupled with the labor required for slide preparation and screening (131,132). Serological testing is not feasible given the high seroprevalence whereby residents in endemic countries often develop semi-immunity (antibodies with low grade, subclinical parasitemia) early in childhood (133). Therefore, antibody testing would incur very high rates of deferral in areas where blood supply is already inadequate (134). By contrast, molecular testing is exquisitely sensitive but is high cost and technically demanding, accounting for its rare adoption in LMICs even for the major TTIS (HIV, HBV and HCV). Further, optimal management of donors with positive molecular results (i.e., DNA- or RNAemia) is uncertain given that a high proportion of donors would be expected to be parasitemic, there is already unmet need for blood and many of the recipient population are also infected with *Plasmodium* (135). Alternative strategies that have been proposed to prevent transfusion-transmitted malaria (TTM) include PR of whole blood (i.e., using a PI system), prophylactic administration of antimalarial to transfusion recipients and/or addition of antimalarials to blood products (136,137).

Malaria also poses a problem for non-endemic countries, where deferral of donors for malaria risk is often out of proportion to the actual risk of TTM (138). Specifically, most non-endemic countries enquire regarding travel to or residency in an endemic country. An affirmative response results in temporary deferral ranging from 3 months to several years. While risk-based deferral is generally effective (i.e., cases of TTM are rare in non-endemic countries), a high proportion of those who are deferred will never return (30). Novel molecular assays

have been proposed to screen donors either universally or selectively (e.g., those with history of malaria, travel or residency in endemic countries) in non-endemic countries.

Bacteria

Globally, bacterial contamination of blood products and associated septic transfusion reactions remains another major neglected transfusion associated risk. Platelet products are disproportionately at risk given their storage at high temperatures (20 to 24 ℃), in gas permeable bags. Bacteria that are most commonly implicated include Gram positive commensal, skin and mucosal flora (e.g., coagulase negative *Staphylococcus spp*., *Staphylococcus aureus*) that are thought to be introduced at time of collection (27,139). The most commonly implicated organisms display attributes that favor growth in blood products (e.g., adherence to plastics and formation of biofilms) as well as ways of evading host immune system (140,141). Gram negative flora are more commonly implicated in contamination of red blood cells. In the US and other HICs, a number of measures were adopted almost 20 years to limit contamination, including standardized phlebotomy site cleaning, use of diversion pouches during collection and bacterial culture (142,143). Collectively, these measures reduced the incidence of bacterial contamination by ~70%. Nonetheless, recognition of residual risk of bacterial contamination has led to development and now adoption of other safeguards, including large volume delayed sampling, secondary bacterial culture, point of care testing and PR (143-147). In LMICs, even primary bacterial culture is the exception (148). Post-transfusion surveillance and reporting is suboptimal, likely accounting for the low rates of reported septic transfusion reactions.

T. pallidum

Syphilis, caused by the spirochete, *T. pallidum*, was the first recognized TTI. First described in 1915, by 1941 138 cases of transfusion-transmitted syphilis had been reported (149). Mandatory antibody-based testing for *T. pallidum* began in the 1950s. This proved highly effective: no cases of transfusion-transmitted syphilis have been reported in the US since the 1960s (1,150). Current testing in the US employs an inverse testing algorithm using a treponemal specific assay, reserving non-treponemal specific assays for supplementary testing to guide counseling. Primary screening with treponemal specific assays avoids the problem of false positivity and unnecessary deferral of donors. Testing notwithstanding, other factors likely have contributed to the absence of reported cases. Survival studies have showed that *T. pallidum* only remains infectious for 72 to 120 h of refrigerated storage (151). The prevalence of active syphilis in blood donors is low and risk-based deferral likely serves to exclude syphilis positive donors given shared socio-behavioral risk factors for other TTIs (152,153). The low risk of transfusion-transmitted syphilis has led to intermittent calls to abandon testing given high cost with limited yield. A cost effectiveness study in Australia estimated that the cost utility of universal testing was $538.5 million per disability adjusted life year averted (154). The counterargument that *T. pallidum* serves as a surrogate marker for other TTIs, has not been substantiated (155). By contrast, screening in LMICs remains important given a larger reservoir of syphilis, transfusion of fresh whole blood and suboptimal donor selection (156).

Other

A relatively low number of pathogens pose credible risk to the blood supply. Yet an ever-expanding list of pathogens has been described. Many of those "other" pathogens have largely been confined to isolated case reports (e.g., hepatitis A virus, Dengue) and case series (*Leishmania*, *Toxoplasma*, *Anaplasma*), without prompting a change in policy and/or leading to adoption of a defined intervention (37,46-49,157). Unfortunately, there are also pathogens that have been targeted for intervention (e.g., Zika virus, vCJD), incurring enormous cost with questionable gain (4,12,158-160). Hypervigilance is not without risk: in one extreme example, a reported association between chronic fatigue syndrome (CFS), and xenotropic murine leukemia virus-related virus by a laboratory in Nevada, prompted concerns of a novel transfusion-associated risk (161). This led to deferral of patients with CFS from blood donation pending evaluation while a series of studies were launched to investigate the link, none of which were able to conform the finding. Rather it was late established that XMRV was a rumor virus, ascribed to contaminating reagents and adherent laboratory practices (162). The unfortunate saga of XMRV ended with a retraction of the original article and ultimately closure of the reporting laboratory amidst demonstrated scientific misconduct (163). A few prominent examples where interventions were adopted merit description for the lessons that they offer.

Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD)

are prion diseases that are included among transmissible spongiform encephalopathies (TSEs), a group of untreatable, progressively debilitating and ultimately fatal neurodegenerative diseases, characterized by accumulation of misfolded, proteinaceous infectious particles, or prions in the brain and lymphoreticular tissues (164). To date, no cases of CJD have been attributed to blood transfusion. However, 3 cases of transfusion-associated vCJD have been described (165). A fourth, pre-clinical case of transfusion-associated vCJD was identified on autopsy material (158). The 4 cases are the culmination of exhaustive donor recipient tracing studies and mining of registries in the United Kingdom (UK) (166). The UK was the focus of the outbreak of bovine spongiform encephalopathy (BSE) (i.e., "mad cow disease") in the 1990s; vCJD in humans has been ascribed to ingestion of beef that had been contaminated with the BSE protein (167). Of note, both BSE and scrapie, another prion disease, have been shown to be transfusion transmissible (168-170). vCJD merits description as a TTI for the scale of the response by the blood banking community. Permanent donor deferral has long been in place for those with a risk factor for CJD (e.g., family history, transplantation of dura mater) or vCJD (e.g., residence or time spent in the UK and parts of Western Europe around time when the incidence of BSE and vCJD were highest [1980–1996] (171). The blood banking community's response to vCJD offers an example of application of the precautionary principle: when data are lacking, one is compelled to do everything possible to guard against a public health threat (172). Nonetheless, that is not without its own negative consequences whereby the donor loss and impact to blood supply arguably far exceeded that of the risk of vCJD. Likely spurred by the response to COVID-19, the deferral policy for vCJD was revised in 2020, to focus on deferral of those who spent time UK, France and Ireland (i.e., the highest risk countries) (173,174).

Zika virus, a formerly obscure mosquito-borne flavivirus (*Flaviviruses* include Dengue, Yellow Fever Virus and WNV), drew attention in 2007 with the first sizable outbreak in Yap, Micronesia (175). Following subsequent outbreaks in the Pacific, including a large epidemic in French Polynesia, Zika emerged in Brazil in 2014, thus heralding rapid, pandemic spread (176). Although the overwhelming majority of infections are either asymptomatic (~50–80%) or mild (i.e., self-limiting, flu-like illness) when contracted during pregnancy, Zika has the propensity toward severe teratogenic effect (176). Complications include microcephaly, abortion and intrauterine death (177-179). Risk to the blood supply was uncertain at the outset, forcing reliance on scant data to guide blood transfusion policy (180). In 2016, the US became the only country to mandate blood donor testing, using NAT. During the outbreak in French Polynesia a surveillance study found that 42/1,505 (2.8%) of asymptomatic blood donors were ZIKA RNA+, 11 of whom developed symptoms post-donation (181). Another study in Martinique (i.e., which had not been published at time of implementation of the US policy) reported that between January and June 2016, 76/4,129 (1.84%; 3% at peak) blood donations were Zika RNA+; over half (54.7%) of the associated blood donors developed symptoms (182). Four cases of possible transfusion transmission were reported in Brazil, none of which resulted in clinical sequelae in the recipients (183-185). The US policy was criticized given continued testing despite a waning epidemic, coupled with the absence of clinical cases of transfusion-transmitted Zika. The policy, abandoned in 2021, came at enormous cost ($US137 million per year and $US341 million per QALY) with no discernible benefit to blood safety (4,5,186). The lessons of Zika pertain less to how best to respond to an emerging infectious disease, and more about how to modify practice as new data become available (12,13).

Summary

Decades of investment in blood transfusion safety has largely restored confidence in the blood supply in HICs. Risk of TTIs is low given the collective strategies spanning refined donor selection and testing. Further, innovative strategies such as PR, could prove transformative by addressing infectious risk proactively. However, the pendulum has swung from one extreme to another: from relative neglect in the pre-HIV era to a growing litany of indiscriminate and disproportionate responses to known or emerging pathogens. This is reflected in the economics of blood transfusion safety, where interventions routinely exceed $US1million per quality adjusted life year, questioning sustainability and counter-intuitively, straining the ability to respond to emerging infectious threats (6,187). By contrast, LMICs contend with the opposite problem whereby transfusion-associated infectious risk remains pervasive, largely unaddressed and poorly characterized given a myriad of challenges and competing priorities (8). There is need and opportunity to do better.

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