blood® Review Series

TRANSFUSION MEDICINE

Prevention of transfusion-transmitted infections

Michael P. Busch,[1,2] Evan M. Bloch,[3] and Steven Kleinman[4]

[1]Vitalant Research Institute (formerly Blood Systems Reseach Institute), San Francisco, CA; [2]Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA; [3]Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, MD; and [4]Department of Pathology, University of British Columbia, Victoria, BC, Canada

Since the 1970s, introduction of serological assays targeting virus-specific antibodies and antigens has been effective in identifying blood donations infected with the classic transfusion-transmitted infectious agents (TTIs; hepatitis B virus [HBV], HIV, human T-cell lymphotropic virus types I and II, hepatitis C virus [HCV]). Subsequently, progressive implementation of nucleic acid–amplification technology (NAT) screening for HIV, HCV, and HBV has reduced the residual risk of infectious-window-period donations, such that per unit risks are <1 in 1 000 000 in the United States, other high-income countries, and in high-incidence regions performing NAT. NAT screening has emerged as the preferred option for detection of newer TTIs including West Nile virus, Zika virus (ZIKV), and *Babesia microti*. Although there is continual need to monitor current risks due to established TTI, ongoing challenges in blood safety relate primarily to surveillance for emerging agents coupled with development of rapid response mechanisms when such agents are identified. Recent progress in development and implementation of pathogen-reduction technologies (PRTs) provide the opportunity for proactive rather than reactive response to blood-safety threats. Risk-based decision-making tools and cost-effectiveness models have proved useful to quantify infectious risks and place new interventions in context. However, as evidenced by the 2015 to 2017 ZIKV pandemic, a level of tolerable risk has yet to be defined in such a way that conflicting factors (eg, theoretical recipient risk, blood availability, cost, and commercial interests) can be reconciled. A unified approach to TTIs is needed, whereby novel tests and PRTs replace, rather than add to, existing interventions, thereby ameliorating cost and logistical burden to blood centers and hospitals. (*Blood*. 2019;133(17):1854-1864)

Introduction

Blood-transfusion therapy is integral to management of diverse hematological and other diseases. Prevention of transfusion-transmitted (TT) infectious agents (TTIs) remains a key element of blood-transfusion safety. Attributes of TTIs that pose greatest risk to blood safety include an asymptomatic infectious phase in the donor and the ability to persist despite processing and storage[1-3]; furthermore, TTIs must be associated with clinically significant adverse outcomes to warrant intervention. The responses to potential TTIs (eg, donor deferral, testing, and pathogen-reduction technologies [PRTs]) have advanced remarkably in terms of speed of assessment and implementation and efficacy of interventions, yet continue to be constrained by the need to strike a balance between blood availability, cost, and safety.

Blood-donor screening began in the 1940s with testing for syphilis, followed in the early 1970s by testing for hepatitis B surface antigen (HBsAg). Data from initial HBsAg screening demonstrating higher rates of infection in paid donors led to conversion to an all-volunteer blood supply in the United States and many other countries in the mid-1970s.[4,5] The recognition of transfusion-associated AIDS in 1982 and 1983 (subsequently linked in 1984 to HIV) as a worldwide blood-safety threat resulted in a paradigm shift toward more rapid implementation of blood-safety interventions, not only for HIV but also for other known and potential TTIs, and for increased surveillance for new agents. This also led to transformation of blood-banking organizations, practices, and regulatory oversight in the United States and many other countries.[4,5]

Over the ensuing decades, donor deferral criteria have been implemented to exclude donors with infectious disease risk factors, testing for major TTIs has been enhanced,[4,5] and systematic approaches for surveillance and responses to potential emerging infectious diseases (EIDs) have been developed.[1-3,6,7] Also, it has been recognized that in addition to "classic" TTIs that cause chronic asymptomatic infections in donors, other agents that cause acute infections may be transmitted at significant rates if there are focal epidemics or ongoing vector-mediated or recurrent seasonal transmission. Salient examples where interventions were implemented in the United States include nationwide testing for interdiction of donations from donors with *Trypanosoma cruzi*, West Nile virus (WNV), and Zika virus (ZIKV) infections, as well as selective testing for *Babesia microti* infection in endemic regions. Furthermore, testing for bacterial

contamination of platelet components after collection/manufacture was instituted to prevent septic transfusion reactions. Donor deferrals were implemented to reduce the risk of variant Creutzfeldt-Jakob disease (vCJD) and several other agents during outbreaks. Research studies have also excluded several infectious agents as significant blood-safety threats, whereas development and implementation of PRTs enables a proactive rather than a reactive response to new infectious threats.

Overview of current risks and laboratory screening to reduce these risks in the United States

Laboratory screening of blood donors for the classic TTIs (HIV, hepatitis B virus [HBV], hepatitis C virus [HCV]) has evolved from performance of progressively more sensitive serological assays in the 1970s to 1990s to adoption of nucleic acid–amplification technologies (NATs) to detect acute window period (WP; when donor-screening markers are not yet detectable but a transfusion is still infectious) and occult infections. NAT screening has also been implemented for other acute infections transmitted by blood components (eg, WNV[8,9] and ZIKV in the United States,[10,11] and hepatitis E virus [HEV] in Japan and some European countries[12,13]). Table 1 includes interventions and estimates for risk of TTIs from single-unit transfusions; risk will be higher (ie, multiplied by the number of units) for patients who receive multiple units.[14,15]

Viruses

The development of the incidence-WP risk-estimation model in the 1990s highlighted that the largest contributor to residual risk posed by established TT viruses is the infectious WP that precedes development of host-response serological markers.[16,17] Extensive research to understand the dynamics and infectivity of acute and chronic viremia,[18-22] coupled with advances in molecular diagnostic technologies such as polymerase chain reaction (PCR) and transcription-mediated amplification (TMA), led to development and implementation of NAT assays for blood-donor screening in the late 1990s in the United States and globally.[23,24] Single-virus NAT assays targeting HCV and then HIV-1, which were performed on manual or semiautomated testing systems in the early 1990s, evolved into multiplexed NAT screening systems (HIV, HBV, and HCV in the same assay) capable of detecting diverse variants on highly automated, high-throughput platforms. Initial implementation that required testing of relatively large "minipools" (MPs; composed of 16-96 donor plasma samples) evolved to testing of smaller MPs (4-16 samples) and even individual donations (IDs).[24-26] These advances have reduced risk to <1 in 1 000 000 per unit (Figure 1). However, policy debates continue over the cost-effectiveness (CE) of NAT-testing strategies in different settings, particularly in resource-constrained countries.[27,28]

Two other classes of TT viral agents that establish chronic but latent infections in donors are human lymphotropic virus types I and II (HTLV-I/II) and cytomegalovirus (CMV), Epstein-Barr virus (EBV), and other human herpes viruses (HHVs; varicella zoster virus [VZV], HHV-6, HHV-7, HHV-8). Prevention of TT of HTLV-I/II was addressed by implementation of antibody assays in the United States in the late 1980s.[29-31] The TT risk of CMV[32,33] was first addressed by selective provision of CMV-seronegative components to immunosuppressed at-risk recipient populations (eg, transplant recipients, neonates). Although studies have identified viral nucleic acids in donor blood, the TT risk of other herpes viruses is controversial; these highly prevalent viruses have either not been demonstrated to be TT or to cause disease in recipients, many of whom already harbor latent HHV infections under immune control. Consequently, screening is not performed for EBV or other HHVs.[34-37] The cell-associated nature of these infections coupled with the adoption of universal leukocyte reduction (LR) in most developed countries has led to reconsideration of the need for serological screening for CMV, with LR considered equivalent to CMV antibody-negative blood products by some authorities.[38,39]

Arthropod-borne viruses (arboviruses), transmitted by a variety of mosquito and tick species, cause a wide spectrum of disease in humans spanning from asymptomatic infections and mild flu-like illness to severe and potentially fatal hemorrhagic and neurological syndromes.[40] Concern with regard to blood safety relates to infected individuals developing acute high-level viremia without symptoms for several weeks following infection. The epidemiology of arboviruses is highly variable and unpredictable, ranging from localized, isolated events, to recurrent seasonal outbreaks, to massive epidemics. Agents of recent TT concern include WNV, Dengue viruses (DENV), Chikungunya virus (CHIKV) and ZIKV.[40]

WNV entered the United States in the late 1990s. In 2002 and 2003, 23 TT cases were identified, with recipients developing severe and even fatal neuroinvasive disease.[41] Within 9 months of recognition, newly developed WNV NAT assays were implemented in MP format using existing NAT platforms.[8,9] Although over 1000 infected blood donations were interdicted in 2003, small numbers of TT cases continued to occur, resulting from donations with WNV RNA below detection levels of MP testing.[8,9] This led to a new testing strategy, termed targeted ID-NAT, in which detection of MP-NAT$^+$ donor(s) in a specific geographic area triggered a switch to ID-NAT testing. Progressive enhancement of the ID-NAT trigger (to the current trigger of a single MP-NAT yield case in a surveillance zone) has virtually eliminated WNV TT. Testing has proven highly effective in the United States, where there have been annual WNV outbreaks for the past 15 years with 300 to 1000 WNV RNA$^+$ donations interdicted each year.[42,43]

Although DENV and CHIKV are not prevalent in the continental United States, outbreaks in Asia-Pacific countries, south and Central America, and Caribbean islands prompted concern for TT in those locales and in returning US travelers. Rates of DENV and CHIKV RNA$^+$ donations in Puerto Rico and several Latin American countries were shown to exceed 1% during active mosquito-transmission seasons.[42,44-47] A study in Brazil during large DENV-4 outbreaks established the dynamics of donor viremia[46] and documented an ~33% rate of TT from DENV RNA$^+$ transfusions.[45] However, DENV-related symptom incidence in hospitalized patients infected by transfusion or other routes was similar to that in control noninfected patients,[45] which led to discontinuation of prospective DENV NAT screening in Puerto Rico and several other countries.

In 2015, the outbreak of ZIKV in Brazil showed associations with Guillain-Barré syndrome and fetal brain abnormalities including microcephaly in the offspring of infected pregnant women.[48] These severe clinical outcomes, the documentation of several

Table 1. Blood-safety interventions over time and current estimates of the rate of potentially infectious units entering the US blood supply despite safety interventions

Pathogen	Clinical syndromes	Blood-safety interventions (approximate year of implementation in US)	Current per unit risk estimate
HIV	• Acute seroconversion illness	• HIV-Ab (1985)	1 in 2 million
	• AIDS	• MP-NAT (1999)	
HCV	• Acute hepatitis	• HCV-Ab (1990)	1 in 2 million
	• Chronic hepatitis	• MP-NAT (1999)	
	• Cirrhosis		
HBV	• Acute hepatitis	• HBsAg (1971)	1 in 2 million
	• Chronic hepatitis	• HBcAb (1986)	
	• Cirrhosis	• MP-NAT (2009)	
	• Hepatocellular carcinoma		
HTLV-I/II	• Adult T-cell leukemia/lymphoma	• HTLVI/II-Ab (1988)	1 in 3 million
	• HTLV-associated myelopathy/tropical spastic paraparesis		
CMV	• Retinitis	• Selective CMV-Ab (1980s)	<1 in 3 million
	• Enteritis	• Leukoreduction (~2000)	
	• Disseminated infection		
WNV	• Neuroinvasive disease	• MP-NAT/seasonal ID-NAT (2003)	<1 in 3 million
ZIKV	• Congenital Zika syndrome (including microcephaly)	• ID-NAT (2016)	<1 in 3 million*
	• Guillain Barré	• MP-NAT (2018)	
T pallidum	• Syphilis	• *T pallidum* Ab (1948)	None but theoretical risk from RT-stored platelets
Bacteria	• Sepsis	• Arm disinfection (early)	STR from platelet: 1 in 100 000†
		• Inlet diversion pouches (early 2000s)	
		• Bacterial culture platelets (mid 2000s)	
		• Pathogen reduction (~2016)†	
		• Point-of-care testing (~2016)†	
Plasmodium spp.‡	• Malaria	• Risk factor based donor deferral (1970s or before)	<1 in 3 million
Babesia spp. (*B microti*)	• Babesiosis	• Selective testing (not mandated) in high-endemicity areas (~2014)	Not known§,‖
T cruzi	• Chagas disease	• *T cruzi* Ab (2007)	<1 in 3 million
vCJD	• Transmissible spongiform encephalopathy	• Risk factor–based donor deferral (2000)	None, but theoretical risk

As a worst-case scenario, it can be assumed that any unit containing a pathogen will transmit that infection to a recipient. The estimates for risk of TTIs are for single-unit transfusions; risk will be higher (ie, multiplied by the number of units) for patients who receive multiple units either in single exposures or over a treatment course. See Kleinman and Stassinopoulos[14] and Kleinman et al[15] for extrapolated risks for large transfusion exposure clinical events (platelets and RBCs) and various chronically transfused recipient populations.[14,15]

Ab, antibody testing; Ag, antigen testing; ID, individual donation; MP, minipool; RT, room temperature; STR, septic transfusion reaction.

*No cases reported in the United States and only 4 possible TT cases reported globally, all in Brazil during the large 2015 to 2016 outbreak.

†These interventions have been adopted only by some blood centers or hospitals.

‡This is the risk for a clinically septic event from a platelet transfusion. The actual rate of transfusing a bacterial contaminated platelet may be much higher (estimate of 1 in ~2000 U). The risk of an STR from a RBC transfusion is much lower (<1 in 1 million).

§These are RBC parasites and risk is from transfusion of packed RBCs.

‖Because *Babesia* testing is performed extensively but not universally in highly endemic areas of the United States, it is unclear how much residual risk still remains.

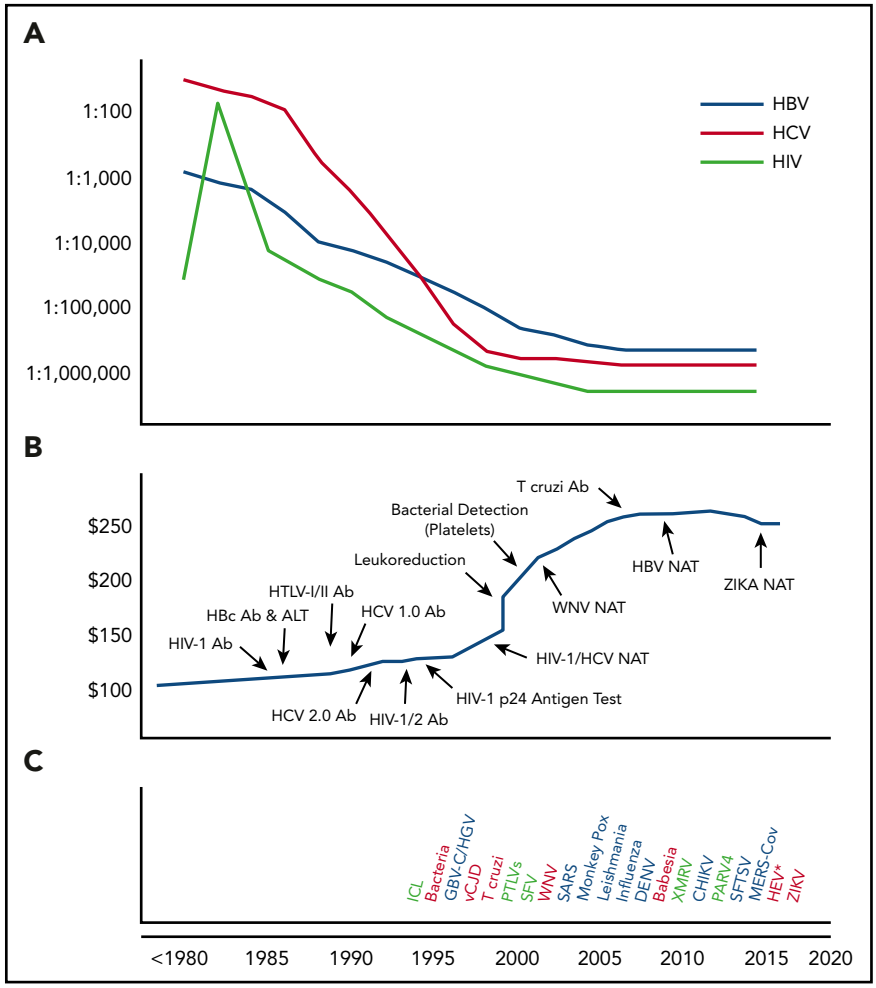

Figure 1. Risks of major TT viruses, progressive blood safety interventions and consequent costs, and EIDs that have been investigated for impact on blood safety over the past 4 decades. (A) Per unit infectious risk for HBV, HCV, and HIV from 1980 to 2018. (B) Temporal relationship of progressive interventions to reduce risks of TTIs to median service fee for acquisition of RBC components from blood-collection organizations in the United States (provided by Louis Katz, America's Blood Centers [these service fee costs do not reflect increases in the Consumer Price Index for medical care services, which increased fivefold to sevenfold from 1980 to 2018]). (C) Potential TT-emerging infection agents that were investigated over the past 25 years. Red indicates agents proven to be blood-safety threats for which interventions were implemented; blue, agents established to be legitimate infectious agents but not TT or associated with diseases; and green, alleged threats determined to not cause human infections or those due to artifacts. *No interventions in the United States, but interventions implemented in some countries where HEV incidence is higher. HGV, hepatitis G virus; ICL, idiopathic CD4$^+$ T-lymphocytopenia; MERS-Cov, Middle Eastern respiratory syndrome coronovirus; PARV-4, parvovirus type 4; PTLV, primate T-cell lymphotrophic viruses; SARS, severe acute respiratory syndrome; SFTSV, severe fever with thrombocytopenia virus; SFV, simian foamy virus. Modified from Perkins and Busch[4] with permission.

probable TT cases in Brazil, and ZIKV's spread to Puerto Rico led to the US Food and Drug Administration (FDA) requirement to screen blood collections in Puerto Rico using ID-NAT assays (developed and implemented within 3-6 months) beginning in April 2016.[49] ZIKV RNA was immediately detected and 339 infected donations were interdicted through 31 December 2016, likely preventing several hundred TT cases.[50] As mandated by the FDA,[51] ZIKV testing by ID-NAT was phased-in throughout the continental United States between June and December 2016. This resulted in detection of ~100 RNA$^+$ donations, most from recent travelers to ZIKV outbreak countries who were in the tail end of infection with very low RNA levels and high titers of neutralizing antibodies, and hence at very low risk for TT.[10,11,52] The epidemics in the Americas have since waned and very few cases of clinical disease or RNA$^+$ donations were detected in 2017 and 2018. This led to revision of the FDA guidance to allow for conversion to targeted ID-NAT, similar to the WNV-testing strategy.[51] There has been criticism over the FDA-mandated rapid implementation of ZIKV ID-NAT due to the observed low yield and low risk of TT to pregnant women, as well as very poor CE.[53-56] However, the public expectation of maintaining trust in the safety of the blood supply was deemed paramount in the face of uncertainty.

Parasites

Three parasitic diseases pose risk to the blood supply: malaria (*Plasmodium* spp.), Chagas disease (*T cruzi*), and babesiosis (*Babesia* spp.).[57] Reports of transfusion transmission of other parasitic infections (eg, toxoplasmosis and leishmaniasis) have been extraordinarily rare and often of questionable imputability.[57-59]

Babesia, a virulent intraerythrocytic parasite, is the agent of greatest concern in the United States. At least 225 cases of TT babesiosis (TTB) have been reported, almost all from packed red cells.[60] Naturally acquired infection via tick bite is frequently mild or even subclinical in immunocompetent hosts but can lead to an asymptomatic carrier state that can persist for years.[61] *B microti*, the predominant cause of human babeisosis[62] is widely endemic, particularly in the northeast and upper midwest,[63] whereas other *Babesia* species (eg, *Babesia duncani*)[64] are encountered in other parts of the United States, yet rarely result in TTB. Overrepresentation of high-risk clinical subsets (eg, extremes of age, asplenic, and/or immunocompromised) among transfusion recipients may explain a high fatality rate (~20%) in TTB. Serological[65,66] and molecular (DNA or RNA NAT) donor-screening assays[67] have been developed and clinical trials have documented reduced TTB in endemic areas. Although a combined antibody/PCR-based strategy attained FDA licensure in 2018, these assays are not commercially available.[68] Currently, donor screening is being performed by investigational NAT selectively in many US endemic regions. These NAT assays amplify highly repeated babesia RNA sequences in lysed donor whole blood, attaining detection of 2 to 3 parasites per milliliter

of blood, approximating the infectious dose by blood transfusion,[69] and potentially obviating the need for concomitant serological screening.[70]

T cruzi, which is transmitted by Triatomine vectors and causes Chagas disease, is widely endemic in Latin America where donor screening with multiple serological assays was successfully implemented decades ago. TT cases in the United States have occurred almost exclusively with platelet components.[71] Serological screening of all blood donations was initiated in the United States in 2007.[72] Based on subsequent information showing an extremely small risk of US residents contracting *T cruzi* through insect exposure and absence of incident infections in previously screened repeat blood donors in the United States,[73] the screening regimen has been modified to testing of only first-time donors, without the need for testing subsequent donations.[74]

There is no routine laboratory screening of donor blood for malarial agents. Questionnaire-based risk assessment and deferral (to detect potential chronic, asymptomatic carriers) is used in the United States. Donors are deferred for 1 to 3 years for either a history of malaria and/or travel in a malaria-endemic country.[75] Although this approach has proven effective, rare cases of TT malaria are still reported each year in the United States.[76] In some countries, but not the United States, testing for *Plasmodium* antibodies is used for accelerated reinstatement of deferred donors.

Bacteria

Bacterial contamination of blood products (notably platelets), and associated septic transfusion reactions (STRs) remains a major infectious risk to the US blood supply.[77] However, given a nonspecific clinical presentation, high rates of comorbid illness, antibiotic use in transfusion recipients that mask presentation, and lack of uniformity as to how cases are investigated, estimation of STR incidence is challenging.[78,79]

Risk-reduction strategies implemented in the 2000s included standardized, enhanced phlebotomy site disinfection, the use of diversion pouches integral to the blood collection set (in order to remove the first aliquot of donor blood, which may have higher concentrations of skin flora), and bacterial culture of platelet components.[80] The latter, performed at the blood collection center, typically involves sampling the platelet product ~24 hours following collection with inoculation into a single aerobic culture bottle. Units of platelets are quarantined for a further 12 to 24 hours prior to release to the transfusing facility. These measures have reduced STR incidence by ~70% with residual cases primarily due to gram-positive skin/mucosal or environmental flora that are present at low numbers during the initial testing procedure but which later multiply during room temperature (22-24°C) platelet storage.[81]

Despite these interventions, the residual risk of bacterial contamination has been measured as 1 in 1500 to 1 in 3000 based on passive surveillance data, whereas nonfatal and fatal STR are estimated to occur in 1 in 100 000 and 1 in 500 000 transfusions, respectively; however, active surveillance studies indicate that the nonfatal STR rate may be 10-fold greater.[82] Additional methods are being considered to further reduce residual risk; these include pathogen reduction, larger volume primary cultures including aerobic and anaerobic bottles, secondary bacterial culture[83] (ie, ~72 hours postcollection), delayed high-volume sampling (sample the platelet unit at 36-48 hours so as to allow bacteria to reach higher concentrations), and point-of-release testing using rapid detection assays.[84,85] Each has its own strengths and limitations.[77]

Since the 1940s, all donations have been routinely screened for *Treponemal pallidum* (*T pallidum*), the causative agent of syphilis. In most blood centers, treponemal-specific antibody tests are used as the initial screening assay to minimize false-positive results. These assays detect all seropositive donors including many with cleared remote infection. Supplemental testing is then undertaken using nonspecific assays (eg, rapid plasma reagin) to provide information to donors about current disease activity to guide counseling and treatment.

Prion diseases and other neurologic diseases of unknown etiology

Concern over potential TT of CJD was triggered in the 1990s by cases of iatrogenic CJD resulting from pituitary-derived growth factor concentrates and dura transplants. Subsequently, large prospective studies in the United States and United Kingdom that reviewed records from 1028 recipients of transfusions from 92 donors later diagnosed with CJD have failed to document any cases of TT CJD[86,87]; it seems reasonable to conclude that TT-CJD does not occur.

The UK outbreak of vCJD resulting from "mad cow disease" raised concerns of blood and plasma-derivative safety due to the explosive scale of the epidemic, oral route of acquisition, and systemic lymphoid dissemination of atypical vCJD prions.[88,89] Following quantitative risk analysis that attempted to strike a balance between risk reduction and tolerable decreases of the available blood supply, FDA mandated deferral of donors who had lived in the United Kingdom and other countries with vCJD for specified intervals.[90] Rigorous investigations of recipients of donors who later developed vCJD led to confirmation of 4 cases of TT-vCJD[91,92] in the United Kingdom and sparked efforts to develop prion-reduction filters and screening assays that could detect vCJD prions in blood in the presymptomatic stage.[93-95] Currently, the food-borne vCJD outbreak appears to be over with no cases reported in the United Kingdom in the past several years despite theoretical concern about a second-wave epidemic of long-incubation cases in persons who are heterozygous for a vCJD risk polymorphism in the prion protein.[96] Deferral policies in the United States have been slightly modified to reflect historical rather than current time spent in the United Kingdom/other at-risk countries, and expensive, marginally effective testing or filtration technologies are no longer under consideration.

Based on a broader understanding of the pathophysiology of prion diseases and documented parenteral transmission of Alzheimer and Parkinson diseases when large doses of infected material (brain homogenate) were infused into humanized donor mice followed by transfusions to recipient mice, concern has been raised over the potential TT of these diseases.[97,98] However, in a recent analysis using the large linked donor-recipient Swedish and Danish database (ScanDat) and national disease registries, no association was demonstrated between incidence of Alzheimers, Parkinson's or other neurological diseases in recipients of blood products from donors who later developed these diseases.[99]

Emerging infectious diseases, previous false alarms, and approaches to surveillance and response

The emergence and consequent risk to blood safety of EIDs has proven to be unpredictable.[1-3,6,7] The AABB Transfusion Transmitted Diseases committee in August 2009 published a *Supplement to Transfusion* that provided focused information on 68 EID agents that pose a real or theoretical threat to transfusion safety,[1] but for which existing effective interventions were lacking.[100] EIDs of concern span all pathogen classes, with well over 60% being from zoonotic sources. Updated individual agent "Fact Sheets"[101] provide information on: agent classification; background on the disease agent's importance; the clinical syndromes/diseases caused; modes of transmission (including vectors/reservoirs); likelihood of TT and information on known transmission cases; the feasibility and predicted success of interventions that could be used for donor qualification (questioning); tests available for diagnostics or that could be adapted for donor screening; and efficacy of PRT.[101]

In a similar effort, the European Centre for Disease Prevention and Control (ECDC) and blood-bank experts in Europe developed the European Up-Front Risk Assessment Tool (EUFRAT)[102] that estimates risk and prioritizes EID agents based on concerns that climate change is driving an increased threat to the blood supply. The agents considered of greatest concern were WNV, DENV, *Leishmania*, CHIKV, malaria, and *Borrelia burgdorferi*, the agent of Lyme disease. Two agents (CHIKV and *B burgdorferi*) were included even though TT of these agents has never been documented. The Asia Pacific Blood Network has also recently established the Asia Pacific Strategy for Emerging Diseases to proactively detect and address EID threats in this region.[103]

An unintended consequence of focusing on enhanced surveillance for potential blood-safety threats has been the identification of numerous agents (including many found through viral discovery programs using metagenomics technologies in which a virus is discovered with or without an associated disease) that can theoretically be transmitted by transfusion but which, upon subsequent investigation, prove not to be[104] (see Figure 1). The most striking example of this was xenotrophic murine leukemia-related virus (XMRV), which was reported to be associated with prostate cancer and later chronic fatigue syndrome and to be present in the blood of asymptomatic blood donors.[105,106] Intensive research consuming a huge amount of time and money subsequently determined that XMRV did not affect humans and was a laboratory contaminant from cell lines that contained this murine virus.[107-111]

These experiences led to the US National Heart, Lung, and Blood Institute (NHLBI) and FDA to convene workshops focused on proactive but rational and systematic responses to EIDs.[2,3] An AABB EID subgroup embarked on processes to make decision-making more transparent.[7] The Alliance of Blood Operators developed a "Risk Based Decision Making" (RBDM) process, which includes formalized methods for quantifying risk and evaluating interventions.[112] This process also includes obtaining stakeholder input.

Global blood safety

The high level of transfusion safety in high-income countries (HICs) has not been matched in most low- to middle-income countries (LMICs). Challenges in LMICs span the entire blood-safety chain from donor selection to posttransfusion surveillance.[113] LMICs are often situated in areas that are highly endemic for TTIs. Notable examples include HIV and malaria (sub-Saharan Africa), HBV (Asia), HCV (north and west Africa), and HTLV (Caribbean). Donor selection, the initial safeguard against TTIs, is often suboptimal given an unstable donor pool coupled with the high complexity and cost to recruit voluntary donors, which results in reliance on family replacement donors and/or paid donors and use of whole-blood transfusions.[114] In contrast to voluntary nonremunerated blood donors, replacement donors who are recruited in times of need (eg, after blood loss due to accidents or child birth) are widely considered to be higher risk for TTIs. In the context of quality control, collection in hot, humid conditions poses risk of bacterial contamination, which has been illustrated in studies in Africa, where rates of contamination up to 17.5% have been reported.[115]

TTI testing is also suboptimal. Systemic challenges such as lack of national regulatory oversight, lack of proficiency testing,[29,116,117] poor supply chains, high reagent costs, unreliable cold-chain management and electricity, and lack of skilled personnel contribute to reliance on rapid diagnostic tests (RDTs), particularly in remote settings. However, RDTs have not been validated for the blood-donor population and have repeatedly demonstrated low sensitivity and specificity to detect the major TTIs.[116-118] Exclusive use of serological assays is common, thus neglecting the contribution of WP infections in those countries where TTI incidence is highest. Finally, posttransfusion surveillance is lacking, such that recipients who acquire TTIs are very unlikely to be recognized as such; rather, these infections will be attributed to acquisition by other modalities.

Enhanced methods to respond and reduce transmission of TTIs

Pathogen-reduced blood components

A mainstay of the safety profile of manufactured plasma derivatives since the 1980s has been the use of physical and chemical processes to inactivate pathogenic organisms in donated plasma. This proactive approach addresses EIDs even before they are known to be a TT risk.

Application of PRT to cellular blood components (eg, red blood cells [RBCs] and platelets) is more challenging given the need to kill pathogens selectively without affecting the therapeutic efficacy of the transfused cells.[14,15] Since 2005, pathogen-reduced (PR) platelets using 2 different PRTs have been in use in many European and international settings.[119] One of these technologies was licensed by FDA in late 2014 and is currently being used on part of the US apheresis platelet supply. A similar PRT for fresh-frozen plasma is also FDA licensed but has seen very limited introduction into the United States. PR processes have been developed for treating RBC components or whole blood; these technologies are undergoing clinical trials but are not yet commercially available. Assuming that therapeutic efficacy is maintained and cost

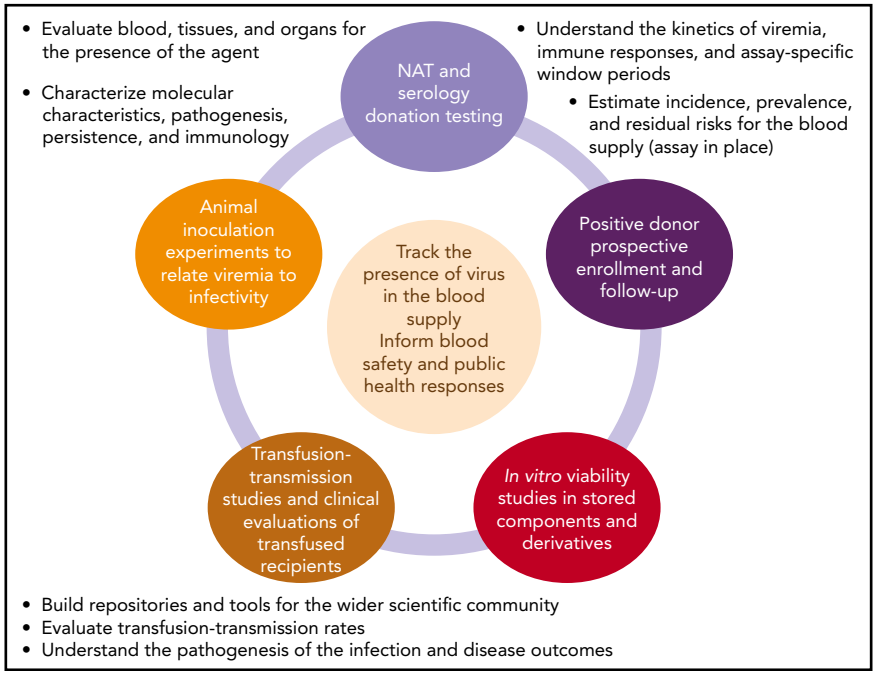

Figure 2. Methodologies to assess transfusion-transmission risk and, through follow-up studies of blood donors and recipients, to provide insights into epidemiology, natural history, and pathogenesis of emerging infectious diseases (eg, ZIKV). Reprinted from Lanteri et al with permission.[126]

issues can be addressed, wide adoption of universal PRT might allow for the relaxation of redundant donor laboratory screening and donor questioning/deferrals. A fully PRT blood supply could reshape the response to new EIDs given that there would be less pressure to develop screening assays. Caveats are that not all infectious agents are inactivated by PRT (non-enveloped viruses and prions show variable resistance) and each manufacturer's process must be independently evaluated.

Decision-making considerations including health economics

Consequent to the TT-HIV and HCV crises in the 1980s and 1990s, blood-safety policies in many countries have been based on a precautionary paradigm. More recently, consideration has been given to defining a risk level deemed to be tolerable, balancing recipient safety, blood availability, cost, logistics, and stakeholder concerns. This has been formalized into RBDM that has been used by several national blood-collection agencies, in partnership with national regulatory authorities and international transfusion medicine organizations.[120] In the United States, where the FDA approves/licenses new tests, technologies, and donor eligibility requirements, there is no organization that has the authority to apply the full spectrum of RBDM analyses in a manner that is binding on blood collection centers and hospitals.

CE of many TTI risk-mitigation interventions has been calculated. Initial adoption of serological testing for the classic TT viruses was cost-saving, whereas addition of newer and more expensive tests, such as NAT and tests for lower-risk agents, have much lower CE and add significantly to the cost of blood products (Figure 1). The determination of acceptable CE is based on societal willingness to pay, and factors that impact that decision are complex and culturally nuanced. Many blood-safety interventions routinely exceed the widely cited clinical medicine threshold of $50 000 to $100 000 per quality-adjusted life year (QALY)[121] by at least 10-fold (eg, the incremental CE of NAT for HIV/HCV/HBV and WNV NAT are ~$1.3 million per QALY), yet have been deemed acceptable to maintain public trust in blood safety.

The 2015 to 2017 ZIKV pandemic is illustrative of the challenge of balancing a timely and precautionary response to an emerging TTI threat with economic considerations. Test availability was dependent upon the need to enlist industry partners to develop and commercialize assays rapidly, despite uncertainty of actual or sustainable return on investment. FDA-mandated ID-NAT testing was implemented throughout the United States in 2016 (despite uncertain TT risk) at a projected annual cost of $137 million.[53] CE modeling subsequent to implementation of donor screening suggests that the cost utility is vanishingly low (~$300 million per QALY)[55] based on risk to transfusion recipients coupled with the lack of ZIKV$^+$ donations in 2017 and 2018 following dissipation of the epidemic. Hence ongoing ZIKV testing represents a theoretical benefit at extraordinary cost.[54]

US blood-collection centers are under severe economic pressure due to declining blood utilization and a reimbursement structure that is increasingly removed from the true costs of production.[122] Blood is most often transfused in the hospital inpatient setting in which its costs are embedded in a diagnostic related group and poorly reimbursed to the hospital. Thus, hospitals are resistant to price escalation, resulting in relatively static blood component pricing in the current highly competitive and commoditized US blood-provider environment, and a decade of "cost-containment" practices at hospitals. This has raised the question of the sustainability of the blood industry to innovate and contend with EIDs.[123]

Once implemented, donor screening tests are rarely abandoned. A new approach is needed whereby novel assays and technologies like PRT that improve on existing strategies, replace rather than add to existing safety measures. In this way, several tests could be discontinued without compromising

transfusion-recipient safety (such as happened with HIV-1 p24 antigen testing). Universal PRT could allow donor testing to be significantly revised (eg, by enhancing multiplexing while reducing sensitivity and costs). However, because many blood-safety interventions are executed under FDA mandates, this will require the FDA to reassess its requirements.

Conclusions

This review has highlighted responses to established TTIs and our evolving and increasingly systematic approach to addressing EID threats. In addition to enhancing recipient safety, operational data from blood-donor screening combined with multifaceted research efforts (Figure 2) are of broad public health and scientific value.[124-126] US government agency–funded (eg, National Institutes of Health [NIH], FDA, and Centers for Disease Control and Prevention [CDC]), TTI-focused research programs[127-130] have served to advance the understanding of etiology, diagnostics, natural history, and pathogenesis of infectious diseases.

Authorship

Contribution: M.P.B., E.M.B., and S.K. worked collaboratively to develop this review, including organizing content; reviewing the literature; drafting and revising the text, table, and figures; and reading and approving the final submission.

Conflict-of-interest disclosure: M.P.B. is an employee of Vitalant (previously Blood Systems), which co-owns Creative Testing Solutions (both not-for-profit corporations), which performs TTI testing on two-thirds of US blood collections; Vitalant Research Institute receives research funding and M.P.B. has received meeting speaker sponsorship and honoraria from Grifols, Roche, Ortho, and Hologic, and is on the scientific advisory board of Quotient Diagnostics. E.M.B. is a co-investigator on the Miplate trial to compare efficacy of Mirasol (pathogen-reduced) platelets with standard-issue platelets. S.K. provides paid consulting services to Cerus Corporation, which produces a technology to manufacture pathogen-reduced blood components.

ORCID profiles: M.P.B., 0000-0002-1446-125X; E.M.B., 0000-0001-8181-9517.

Correspondence: Michael P. Busch, Vitalant Research Institute, 270 Masonic Ave, San Francisco, CA 94118; e-mail: mbusch@vitalant.org.

Footnote

Submitted 20 November 2018; accepted 3 February 2019. Prepublished online as *Blood* First Edition paper, 26 February 2019; DOI 10.1182/blood-2018-11-833996.

REFERENCES

1. Stramer SL, Hollinger FB, Katz LM, et al. Emerging infectious disease agents and their potential threat to transfusion safety. *Transfusion*. 2009;49(suppl 2):1S-29S.
2. Glynn SA, Busch MP, Dodd RY, et al; NHLBI Emerging Infectious Disease Task Force convened November 7, 2011. Emerging infectious agents and the nation's blood supply: responding to potential threats in the 21st century. *Transfusion*. 2013;53(2):438-454.
3. Atreya C, Nakhasi H, Mied P, et al. FDA workshop on emerging infectious diseases: evaluating emerging infectious diseases (EIDs) for transfusion safety. *Transfusion*. 2011;51(8):1855-1871.
4. Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. *Transfusion*. 2010;50(10):2080-2099.
5. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. *Blood*. 2008;112(7):2617-2626.
6. Busch M. Infectious risks of blood transfusions: recent advances in testing technologies and new approaches to surveillance and decision-making. *ISBT Sci Ser*. 2014;9(1):276-280.
7. Stramer SL, Dodd RY; AABB Transfusion-Transmitted Diseases Emerging Infectious Diseases Subgroup. Transfusion-transmitted emerging infectious diseases: 30 years of challenges and progress. *Transfusion*. 2013;53(10 Pt 2):2375-2383.
8. Busch MP, Caglioti S, Robertson EF, et al. Screening the blood supply for West Nile virus RNA by nucleic acid amplification testing. *N Engl J Med*. 2005;353(5):460-467.
9. Stramer SL, Fang CT, Foster GA, Wagner AG, Brodsky JP, Dodd RY. West Nile virus among blood donors in the United States, 2003 and 2004. *N Engl J Med*. 2005;353(5):451-459.
10. Galel SA, Williamson PC, Busch MP, et al; cobas Zika IND Study Group. First Zika-positive donations in the continental United States. *Transfusion*. 2017;57(3 Pt 2):762-769.
11. Williamson PC, Linnen JM, Kessler DA, et al. First cases of Zika virus-infected US blood donors outside states with areas of active transmission. *Transfusion*. 2017;57(3 Pt 2):770-778.
12. Petrik J, Lozano M, Seed CR, et al. Hepatitis E. *Vox Sang*. 2016;110(1):93-130.
13. Hewitt PE, Ijaz S, Brailsford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. *Lancet*. 2014;384(9956):1766-1773.
14. Kleinman S, Stassinopoulos A. Risks associated with red blood cell transfusions: potential benefits from application of pathogen inactivation. *Transfusion*. 2015;55(12):2983-3000.
15. Kleinman S, Reed W, Stassinopoulos A. A patient-oriented risk-benefit analysis of pathogen-inactivated blood components: application to apheresis platelets in the United States. *Transfusion*. 2013;53(7):1603-1618.
16. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med*. 1996;334(26):1685-1690.
17. Glynn SA, Kleinman SH, Wright DJ, Busch MP; NHLBI Retrovirus Epidemiology Donor Study. International application of the incidence rate/window period model. *Transfusion*. 2002;42(8):966-972.
18. 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(11):2454-2489.
19. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003;17(13):1871-1879.
20. Biswas R, Tabor E, Hsia CC, et al. Comparative sensitivity of HBV NATs and HBsAg assays for detection of acute HBV infection. *Transfusion*. 2003;43(6):788-798.
21. Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. *Transfusion*. 2005;45(6):994-1002.
22. Busch MP, Murthy KK, Kleinman SH, et al. Infectivity in chimpanzees (Pan troglodytes) of plasma collected before HCV RNA detectability by FDA-licensed assays: implications for transfusion safety and HCV infection outcomes. *Blood*. 2012;119(26):6326-6334.
23. Stramer SL, Glynn SA, Kleinman SH, et al; National Heart, Lung, and Blood Institute Nucleic Acid Test Study Group. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. *N Engl J Med*. 2004;351(8):760-768.
24. Roth WK, Busch MP, Schuller A, et al. International survey on NAT testing of blood donations: expanding implementation and yield from 1999 to 2009. *Vox Sang*. 2012;102(1):82-90.
25. Bruhn R, Lelie N, Custer B, Busch M, Kleinman S; International NAT Study Group. Prevalence of human immunodeficiency virus RNA and antibody in first-time, lapsed, and repeat blood donations across five international regions and relative efficacy of alternative screening scenarios. *Transfusion*. 2013;53(10 Pt 2):2399-2412.

26. Bruhn R, Lelie N, Busch M, Kleinman S; International NAT Study Group. Relative efficacy of nucleic acid amplification testing and serologic screening in preventing hepatitis C virus transmission risk in seven international regions. *Transfusion*. 2015;55(6):1195-1205.

27. Custer B. Health economics in blood safety. In: Sha H, Dodd RY, eds. Blood Safety: A Guide to Monitoring and Responding to Potential New Threats. Cham, Switzerland: Springer International Publishing; 2019: 53-81.

28. Janssen MP, van Hulst M, Custer B, ABO RBDM Health Economics and Outcomes Working Group & Collaborators. An assessment of differences in costs and health benefits of serology and NAT screening of donations for blood transfusion in different western countries. [published correction appears in *Vox Sang*. 2018;113(1):88]. *Vox Sang*. 2017;112(6):518-525.

29. Sullivan MT, Williams AE, Fang CT, Grandinetti T, Poiesz BJ, Ehrlich GD; The American Red Cross HTLV-I/II Collaborative Study Group. Transmission of human T-lymphotropic virus types I and II by blood transfusion. A retrospective study of recipients of blood components (1983 through 1988). *Arch Intern Med*. 1991;151(10): 2043-2048.

30. Kleinman S, Swanson P, Allain JP, Lee H. Transfusion transmission of human T-lymphotropic virus types I and II: serologic and polymerase chain reaction results in recipients identified through look-back investigations. *Transfusion*. 1993;33(1): 14-18.

31. Fiebig E, Murphy EL, Busch MP. Human immunodeficiency virus, human T-cell lymphotropic viruses, and other retroviruses. In: Hillyer CD, Silberstein LE, Ness PM, Anderson KC, Roback JD, eds. Blood Banking and Transfusion Medicine: Basic Principles and Practice. Philadelphia, PA: Churchill Livingstone; 2009:447-464.

32. Drew WL, Tegtmeier G, Alter HJ, Laycock ME, Miner RC, Busch MP. Frequency and duration of plasma CMV viremia in seroconverting blood donors and recipients. *Transfusion*. 2003;43(3):309-313.

33. Ziemann M, Juhl D, Görg S, Hennig H. The impact of donor cytomegalovirus DNA on transfusion strategies for at-risk patients. *Transfusion*. 2013;53(10):2183-2189.

34. Hudnall SD, Chen T, Allison P, Tyring SK, Heath A. Herpesvirus prevalence and viral load in healthy blood donors by quantitative real-time polymerase chain reaction. *Transfusion*. 2008;48(6):1180-1187.

35. Compston LI, Sarkobie F, Li C, Candotti D, Opare-Sem O, Allain JP. Multiplex real-time PCR for the detection and quantification of latent and persistent viral genomes in cellular or plasma blood fractions. *J Virol Methods*. 2008;151(1):47-54.

36. Juhl D, Mosel C, Nawroth F, et al. Detection of herpes simplex virus DNA in plasma of patients with primary but not with recurrent infection: implications for transfusion medicine? *Transfus Med*. 2010;20(1):38-47.

37. Hudnall SD, Chen T, Rady P, Tyring S, Allison P. Human herpesvirus 8 seroprevalence and viral load in healthy adult blood donors. *Transfusion*. 2003;43(1):85-90.

38. Vamvakas EC. Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis. *Transfus Med Rev*. 2005;19(3): 181-199.

39. Smith D, Lu Q, Yuan S, Goldfinger D, Fernando LP, Ziman A. Survey of current practice for prevention of transfusion-transmitted cytomegalovirus in the United States: leucoreduction vs. cytomegalovirus-seronegative. *Vox Sang*. 2010;98(1):29-36.

40. Petersen LR, Busch MP. Transfusion-transmitted arboviruses. *Vox Sang*. 2010; 98(4):495-503.

41. Pealer LN, Marfin AA, Petersen LR, et al; West Nile Virus Transmission Investigation Team. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med*. 2003;349(13): 1236-1245.

42. 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(3): 153-161.

43. Betsem E, Kaidarova Z, Stramer SL, et al. Correlation of West Nile virus incidence in donated blood with West Nile neuroinvasive disease rates, United States, 2010-2012. *Emerg Infect Dis*. 2017;23(2):212-219.

44. Lanteri MC, Busch MP. Dengue in the context of "safe blood" and global epidemiology: to screen or not to screen? *Transfusion*. 2012;52(8):1634-1639.

45. Sabino EC, Loureiro P, Lopes ME, et al; International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III. Transfusion-transmitted dengue and associated clinical symptoms during the 2012 epidemic in Brazil. *J Infect Dis*. 2016; 213(5):694-702.

46. Busch MP, Sabino EC, Brambilla D, et al; International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Duration of dengue viremia in blood donors and relationships between donor viremia, infection incidence and clinical case reports during a large epidemic. *J Infect Dis*. 2016;214(1):49-54.

47. Simmons G, Brès V, Lu K, et al. High incidence of Chikungunya virus and frequency of viremic blood donations during epidemic, Puerto Rico, USA, 2014. *Emerg Infect Dis*. 2016;22(7):1221-1228.

48. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. *N Engl J Med*. 2016; 374(16):1552-1563.

49. Food and Drug Administration. Recommendations for Donor Screening. Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus. Silver Spring, MD: US Department of Health and Human Services; 2016.

50. Chevalier MS, Biggerstaff BJ, Basavaraju SV, et al. Use of blood donor screening data to estimate Zika virus incidence, Puerto Rico, April-August 2016. *Emerg Infect Dis*. 2017; 23(5):790-795.

51. Food and Drug Administration. Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components: Guidance for Industry. Silver Spring, MD: US Department of Health and Human Services; 2018.

52. Saá P, Proctor M, Foster G, et al. Investigational testing for Zika virus among U.S. blood donors. *N Engl J Med*. 2018; 378(19):1778-1788.

53. Ellingson KD, Sapiano MRP, Haass KA, et al. Cost projections for implementation of safety interventions to prevent transfusion-transmitted Zika virus infection in the United States. *Transfusion*. 2017;57(suppl 2): 1625-1633.

54. Bloch EM, Ness PM, Tobian AAR, Sugarman J. Revisiting blood safety practices given emerging data about zika Virus. *N Engl J Med*. 2018;378(19):1837-1841.

55. Russel WA, Stramer SL, Busch MP, Custer B. Screening the blood supply for Zika virus in the 50 U.S. states and Puerto Rico: a cost-effectiveness analysis. *Ann Intern Med*. 2019; 170(3):164-174.

56. Jimenez A, Shaz BH, Bloch EM. Zika virus and the blood supply: what do we know? *Transfus Med Rev*. 2017;31(1):1-10.

57. Leiby D, O'Brien SF, Wendel S, et al; WPTTID Subgroup on Parasites. International survey on the impact of parasitic infections: frequency of transmission and current mitigation strategies. *Vox Sang*. 2019;114(1):17-27.

58. Siegel SE, Lunde MN, Gelderman AH, et al. Transmission of toxoplasmosis by leukocyte transfusion. *Blood*. 1971;37(4):388-394.

59. Jimenez-Marco T, Fisa R, Girona-Llobera E, et al. Transfusion-transmitted leishmaniasis: a practical review. *Transfusion*. 2016; 56(suppl 1):S45-S51.

60. Food and Drug Administration. Topic I: Issue Summary: Strategies for Implementation of Antibody and Nucleic Acid-based Testing for Babesia microti in Blood Donors. Silver Spring, MD: US Department of Health and Human Services; 2015.

61. Krause PJ, Spielman A, Telford SR III, et al. Persistent parasitemia after acute babesiosis. *N Engl J Med*. 1998;339(3):160-165.

62. Herwaldt BL, Linden JV, Bosserman E, Young C, Olkowska D, Wilson M. Transfusion-associated babesiosis in the United States: a description of cases. *Ann Intern Med*. 2011; 155(8):509-519.

63. Vannier E, Krause PJ. Human babesiosis. *N Engl J Med*. 2012;366(25):2397-2407.

64. Bloch EM, Herwaldt BL, Leiby DA, et al. The third described case of transfusion-transmitted Babesia duncani. *Transfusion*. 2012;52(7):1517-1522.

65. Levin AE, Williamson PC, Bloch EM, et al. Serologic screening of United States blood donors for Babesia microti using an investigational enzyme immunoassay. *Transfusion*. 2016;56(7):1866-1874.

66. Moritz ED, Winton CS, Johnson ST, et al. Investigational screening for Babesia microti in a large repository of blood donor samples from nonendemic and endemic areas of the United States. *Transfusion*. 2014;54(9): 2226-2236.

67. Brès V, Self D, Ocampo D, et al. Performance characteristics of a transcription-mediated amplification assay on a fully automated system to detect Babesia in blood donations. In: Proceedings of the AABB Annual Meeting; 22-25 October 2016; Orlando, FL.

68. Moritz ED, Winton CS, Tonnetti L, et al. Screening for Babesia microti in the U.S. blood supply. *N Engl J Med*. 2016;375(23): 2236-2245.

69. Bakkour S, Chafets DM, Wen L, et al. Minimal infectious dose and dynamics of Babesia microti parasitemia in a murine model. *Transfusion*. 2018;58(12):2903-2910.

70. Ward SJ, Stramer SL, Szczepiorkowski ZM. Assessing the risk of Babesia to the United States blood supply using a risk-based decision-making approach: Report of AABB's Ad Hoc Babesia Policy Working Group (original report). *Transfusion*. 2018; 58(8):1916-1923.

71. Custer B, Agapova M, Bruhn R, et al. Epidemiologic and laboratory findings from 3 years of testing United States blood donors for Trypanosoma cruzi. *Transfusion*. 2012; 52(9):1901-1911.

72. Centers for Disease Control and Prevention (CDC). Blood donor screening for chagas disease--United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. 2007;56(7):141-143.

73. Dodd R, Groves JA, Townsend RL, et al. Impact of one-time testing for Trypanosoma cruzi antibodies among blood donors in the United States. *Transfusion*. 2019;59(3): 1016-1023.

74. Food and Drug Administration. Use of Serological Tests to Reduce the Risk of Transmission of Trypanosoma cruzi Infection in Blood and Blood Components: Guidance for Industry. Silver Spring, MD: US Department of Health and Human Services; 2017.

75. Food and Drug Administration. *Recommendations for Donor Questioning, Deferral, Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Malaria*. Silver Spring, MD: US Department of Health and Human Services; 2013.

76. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*. 2001;344(26):1973-1978.

77. Bloch EM. Residual risk of bacterial contamination: what are the options? *Transfusion*. 2017;57(10):2289-2292.

78. Erony SM, Marshall CE, Gehrie EA, et al. The epidemiology of bacterial culture-positive and septic transfusion reactions at a large tertiary academic center: 2009 to 2016. *Transfusion*. 2018;58(8):1933-1939.

79. Hong H, Xiao W, Lazarus HM, Good CE, Maitta RW, Jacobs MR. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. *Blood*. 2016;127(4):496-502.

80. Brecher ME, Hay SN. Bacterial contamination of blood components. *Clin Microbiol Rev*. 2005;18(1):195-204.

81. Fuller AK, Uglik KM, Savage WJ, Ness PM, King KE. Bacterial culture reduces but does not eliminate the risk of septic transfusion reactions to single-donor platelets. *Transfusion*. 2009;49(12):2588-2593.

82. Hong H, Xiao W, Lazarus HM, Good CE, Maitta RW, Jacobs MR. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. *Blood*. 2016;127(4):496-502.

83. Bloch EM, Marshall CE, Boyd JS, et al. Implementation of secondary bacterial culture testing of platelets to mitigate residual risk of septic transfusion reactions. *Transfusion*. 2018;58(7):1647-1653.

84. Li JW, Brecher ME, Jacobson JL, et al. Addressing the risk of bacterial contamination in platelets: a hospital economic perspective. *Transfusion*. 2017;57(10): 2321-2328.

85. Food and Drug Administration. Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion: Draft Guidance for Industry. Silver Spring, MD: US Department of Health and Human Services; 2018.

86. Urwin PJ, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review study. *Vox Sang*. 2016;110(4):310-316.

87. Crowder LA, Schonberger LB, Dodd RY, Steele WR. Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk. *Transfusion*. 2017;57(8):1875-1878.

88. Turner ML, Ludlam CA. An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products. *Br J Haematol*. 2009;144(1):14-23.

89. Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. *Transfus Med Rev*. 2008;22(1):58-69.

90. Ponte ML. Insights into the management of emerging infections: regulating variant Creutzfeldt-Jakob disease transfusion risk in the UK and the US. *PLoS Med*. 2006;3(10): e342.

91. Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Three reported cases of variant Creutzfeldt-Jakob disease transmission following transfusion of labile blood components. *Vox Sang*. 2006;91(4):348.

92. Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet*. 2004;364(9433): 527-529.

93. Coste J, Prowse C, Grabmer C, et al. Prion reduction of red-blood-cells. *Vox Sang*. 2012;103(3):260-272.

94. Concha-Marambio L, Pritzkow S, Moda F, et al. Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease. *Sci Transl Med*. 2016;8(370):370ra183.

95. Bougard D, Brandel JP, Bélondrade M, et al. Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. *Sci Transl Med*. 2016;8(370):370ra182.

96. Diack AB, Will RG, Manson JC. Public health risks from subclinical variant CJD. *PLoS Pathog*. 2017;13(11):e1006642.

97. Morales R, Duran-Aniotz C, Castilla J, Estrada LD, Soto C. De novo induction of amyloid-β deposition in vivo. *Mol Psychiatry*. 2012; 17(12):1347-1353.

98. Prusiner SB. Cell biology. A unifying role for prions in neurodegenerative diseases. *Science*. 2012;336(6088):1511-1513.

99. Edgren G, Hjalgrim H, Rostgaard K, et al. Transmission of neurodegenerative disorders through blood transfusion: a cohort study. *Ann Intern Med*. 2016;165(5):316-324.

100. Dodd RY. Emerging infections and transfusion safety. In: Murphy MF, Pamphilon DH, Heddle NM, eds. Practical Transfusion Medicine. 4th ed. West Sussex, United Kingdom: Wiley-Blackwell; 2013:161-167.

101. AABB. Emerging infectious disease agents and their potential threat to transfusion safety. http://www.aabb.org/tm/eid/pages/default.aspx. Accessed 7 January 2019.

102. EUFRAT user manual. Solna, Sweden: European Centre for Disease Prevention and Control; 2018.

103. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012; 367(19):1814-1820.

104. Stramer S, Dodd RY, Chiu CY. Advances in testing technology to ensure transfusion safety: NAT and beyond. *ISBT Sci Ser*. 2015; 10(suppl 1):55-64.

105. Lombardi VC, Ruscetti FW, Das Gupta J, et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome [published correction appears in *Science*. 2011;334(6053):176] [retracted in *Science*. 2011;334(6063):1636]. *Science*. 2009;326(5952):585-589.

106. Lo SC, Pripuzova N, Li B, et al. Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors [published correction appears in *Proc Natl Acad Sci USA*. 2010;107(44):19132] [retracted in *Proc Natl Acad Sci USA*. 2012;109(1):346]. *Proc Natl Acad Sci USA*. 2010;107(36):15874-15879.

107. Simmons G, Glynn SA, Holmberg JA, et al. The Blood Xenotropic Murine Leukemia Virus-Related Virus Scientific Research Working Group: mission, progress, and plans. *Transfusion*. 2011;51(3):643-653.

108. Lee D, Das Gupta J, Gaughan C, et al. In-depth investigation of archival and prospectively collected samples reveals no evidence for XMRV infection in prostate cancer. *PLoS One*. 2012;7(9):e44954.

109. Lo SC, Pripuzova N, Li B, et al. [Retracted] Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors [retraction of *Proc Natl Acad Sci USA*. 2010;

107(36):15874-15879]. *Proc Natl Acad Sci USA*. 2012;109(1):346.

110. Paprotka T, Delviks-Frankenberry KA, Cingöz O, et al. Recombinant origin of the retrovirus XMRV. *Science*. 2011;333(6038):97-101.

111. Simmons G, Glynn SA, Komaroff AL, et al; Blood XMRV Scientific Research Working Group (SRWG). Failure to confirm XMRV/MLVs in the blood of patients with chronic fatigue syndrome: a multi-laboratory study. *Science*. 2011;334(6057):814-817.

112. Custer B, Janssen MP; Alliance of Blood Operators Risk-Based Decision-Making (RBDM) Initiative. Health economics and outcomes methods in risk-based decision-making for blood safety. *Transfusion*. 2015;55(8):2039-2047.

113. Weimer A, Tagny CT, Tapko JB, et al. Blood transfusion safety in sub-Saharan Africa: a literature review of changes and challenges in the 21st century. *Transfusion*. 2019;59(1):412-427.

114. 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(2):164-180.

115. Opoku-Okrah C, Feglo P, Amidu N, Dakorah MP. Bacterial contamination of donor blood at the Tamale Teaching Hospital, Ghana. *Afr Health Sci*. 2009;9(1):13-18.

116. Bloch EM, Shah A, Kaidarova Z, et al; Anglophone Africa Transfusion Research Group. A pilot external quality assurance study of transfusion screening for HIV, HCV and HBsAG in 12 African countries. *Vox Sang*. 2014;107(4):333-342.

117. Laperche S; Francophone African Group for Research in Blood Transfusion. Multinational assessment of blood-borne virus testing and transfusion safety on the African continent. *Transfusion*. 2013;53(4):816-826.

118. Prugger C, Laperche S, Murphy EL, et al. Screening for transfusion transmissible infections using rapid diagnostic tests in Africa: a potential hazard to blood safety? *Vox Sang*. 2016;110(2):196-198.

119. Devine DV, Schubert P. Pathogen inactivation technologies: the advent of pathogen-reduced blood components to reduce blood safety risk. *Hematol Oncol Clin North Am*. 2016;30(3):609-617.

120. Leach Bennett J, Devine DV. Risk-based decision making in transfusion medicine. *Vox Sang*. 2018;113(8):737-749.

121. Custer B, Hoch JS. Cost-effectiveness analysis: what it really means for transfusion medicine decision making. *Transfus Med Rev*. 2009;23(1):1-12.

122. Wald M. Blood industry shrinks as transfusions decline. New York, NY: The New York Times; 22 August 2014.

123. Klein HG, Hrouda JC, Epstein JS. Crisis in the sustainability of the U.S. blood system. *N Engl J Med*. 2017;377(15):1485-1488.

124. Busch MP. Transfusion-transmitted viral infections: building bridges to transfusion medicine to reduce risks and understand epidemiology and pathogenesis. *Transfusion*. 2006;46(9):1624-1640.

125. Busch MP. Lessons and opportunities from epidemiologic and molecular investigations of infected blood donors. *Transfusion*. 2006;46(10):1663-1666.

126. Lanteri MC, Kleinman SH, Glynn SA, et al. Zika virus: a new threat to the safety of the blood supply with worldwide impact and implications. *Transfusion*. 2016;56(7):1907-1914.

127. Custer B, Stramer SL, Glynn S, Williams AE, Anderson SA. Transfusion-transmissible infection monitoring system: a tool to monitor changes in blood safety. *Transfusion*. 2016;56(6 Pt 2):1499-1502.

128. Dodd RY, Notari EP, Nelson D, et al; NHLBI Retrovirus Epidemiology Donor Study (REDS)-II. Development of a multisystem surveillance database for transfusion-transmitted infections among blood donors in the United States. *Transfusion*. 2016;56(11):2781-2789.

129. Kleinman S, King MR, Busch MP, et al. The National Heart, Lung, and Blood Institute retrovirus epidemiology donor studies (Retrovirus Epidemiology Donor Study and Retrovirus Epidemiology Donor Study-II): twenty years of research to advance blood product safety and availability. *Transfus Med Rev*. 2012;26(4):281-304.

130. Kleinman S, Busch MP, Murphy EL, Shan H, Ness P, Glynn SA; National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III). The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III): a research program striving to improve blood donor and transfusion recipient outcomes. *Transfusion*. 2014;54(3 Pt 2):942-955.

2019 133: 1854-1864
doi:10.1182/blood-2018-11-833996 originally published online February 26, 2019

Prevention of transfusion-transmitted infections

Michael P. Busch, Evan M. Bloch and Steven Kleinman

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.