Blood system changes since recognition of transfusion-associated AIDS

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The year 2013 brought us to the close of the third decade since the discovery of human immunodeficiency virus (HIV), originally called lymphadenopathy-associated virus or human T-lymphotropic virus Type 3 (HTLV-III), as the cause of AIDS.[1-6] This landmark occasions a time for reflection on the transformations of the blood system that were set in motion by recognition of transfusion-associated AIDS (TAA). While the decade of the 1980s was characterized by rapid introduction of novel strategies to address an unprecedented challenge, changes made in the 1990s, though independently significant, were also reactive, as the system tried to define and incorporate the lessons of TAA. In the latter decade, criticisms of prior decision making, coupled with new technology options, led to a broad-based initiative to enhance blood safety. In the new millennium, ongoing efforts to address blood safety have focused repeatedly on threats from known and emerging infectious diseases. However, concerns have arisen about a trend of increasing safety costs with progressively decreasing added benefits. This commentary summarizes key changes to the blood system during this 30-year period and discusses the evolving framework for blood safety decision making that is taking form.

ABBREVIATIONS: ASH = Assistant Secretary for Health; BOTSEC = Blood, Organ and Tissue Safety Executive Council; CFS = chronic fatigue syndrome; HHS = Department of Health and Human Services; IOM = Institute of Medicine; NANBH = non-A, non-B hepatitis; TAA = transfusion-associated AIDS; TAH = transfusion-associated hepatitis; vCJD = variant Creutzfeldt-Jakob disease; WNV = West Nile virus; XMRV = xenotropic murine leukemia virus–related virus.

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INFECTIOUS CONCERNS BEFORE RECOGNITION OF TAA

The fact that transfusions could transmit infectious diseases, namely, bacterial infections, syphilis, and hepatitis, was recognized before TAA with progressive interventions dating back to the dawn of blood banking. Donor testing for antibodies to syphilis began in 1938.[7] Bacterial infections, a major threat at the time of World War II, were later decreased by cold storage of whole blood and red blood cells (RBCs) in plastic containers.[5,7] In the 1970s, transfusion-associated hepatitis (TAH) was largely prevented by near elimination of paid donation through product labeling to identify paid collections, concurrent with testing for hepatitis B virus (HBV) infections.[5] However, the medical importance of the residual hepatitis risk, mostly attributed to non-A, non-B hepatitis (NANBH), was recognized slowly.[5] With the acute threat of bacterial infections largely controlled, syphilis effectively prevented, and the full consequences of NANBH transmission unappreciated, the blood community in the late 1970s was more focused on systemic issues of economic competition and supply instabilities than on transmissible disease. Then came AIDS!

DELAYED GOVERNMENTAL RESPONSE TO TAA

AIDS was first reported as a "gay-related immune deficiency" in 1981, but soon was identified in other risk groups including sex workers, Haitian entrants to the United States, and injection drug users.[3,4] Evidence for transfusion transmission emerged in 1982 when a few cases of AIDS were reported in hemophilia patients and later in transfusion recipients. However, despite a number of high-level federal meetings, actions by the national government to contain the AIDS risk from transfusion were not undertaken until 1983.[8] Although transfusion transmission of HIV undoubtedly took place at least 5 years

before the recognition of TAA due to the very long asymptomatic period of the disease, the delay in a response to TAA subsequent to these initial reports of disease in persons with hemophilia and transfusion recipients also contributed to the AIDS tragedy. Rage within the hemophilia community, due both to the fact of transmission of a fatal infection and to the failure of authorities to provide adequate warnings and preventions, was expressed in a demand for a congressional investigation. Members of Congress instead directed the Department of Health and Human Services (HHS) to look into the matter. This was accomplished through a contract with the Institute of Medicine (IOM) to study the evolving HIV-related events impacting blood safety and the decision-making process in this crisis period.

In its report, entitled "HIV and the Blood Supply: An Analysis of Crisis Decision Making (1995),"[9] the IOM found no wrongdoing by organizations or officials, but identified failed opportunities to better protect public health. These failures to act more rapidly and aggressively in the face of TAA were seen to unmask an underlying weakness in the ability of federal agencies to address a new threat in the face of substantial scientific uncertainty. This weakness was attributed to systemic deficiencies, primarily of leadership and coordination. In particular, the IOM criticized the federal agencies for lack of top-level leadership needed to overcome inherent bureaucratic inertia; absence of a systematic approach within advisory committees sufficient to maintain their focus; over dependency on the regulated industry as a source of data given the inherent conflict of interest; and failure to engage in forward thinking both with respect to new technologies and emerging safety threats. As a consequence, the risk of TAA was severely underestimated; patients and care providers were not suitably warned of the risk; and resistance to a change in the status quo caused delayed intervention. In a set of 14 recommendations directed primarily at federal agencies, the IOM called for a more responsive and integrated decision-making process including establishment of a Blood Safety Council reporting to a designated Blood Safety Director within HHS and a standing "expert panel" to assure communication of blood product risks and alternatives to their use both to care providers and to the public. Specifically to the Food and Drug Administration (FDA), the IOM recommended that, "Where uncertainties or countervailing public health concerns preclude eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm." While not itself a mandate, the IOM's admonition that the FDA should institute measured precautions in the face of uncertainty has become a dominant factor in blood safety decision making. A more vigilant and proactive FDA approach to blood safety unfortunately has had the unintended consequence of dramatically increasing the manufacturing costs and therefore the price of blood.[10]

BLOOD SAFETY IN THE POST-TAA ERA

The HHS response to the IOM report established a new landscape for federal oversight of the blood system, which continues to the present day. The present structure includes the Assistant Secretary for Health (ASH) as the blood safety director; heads of Public Health Service and related agencies as members of a Blood, Organ and Tissue Safety Executive Council (BOTSEC); and an HHS Secretary's Advisory Committee for Blood and Tissue Safety and Availability (formerly the Advisory Committee for Blood Safety and Availability). The ASH is the acknowledged national blood safety director with final responsibility and authority for decisions regarding blood safety and availability. An interagency Blood, Organ and Tissue Safety Working Group meets monthly by teleconference, more often when necessary, and the BOTSEC meets approximately quarterly face to face with the ASH to provide information and guidance regarding current and emerging issues involving the nation's blood supply.[11] Unlike FDA's Blood Products Advisory Committee, whose function is to provide external scientific advice relevant to regulation, the Secretary's advisory committee is empowered to discuss broad legal, ethical, social, and economic issues affecting the blood system. To give voice to patient concerns, both advisory committees seat voting representatives of communities that have been particularly affected by TAA. Additionally, in response to a series of congressional hearings, reports from the Government Accountability Office, and the IOM study, the FDA developed and HHS subsequently adopted a comprehensive "blood action plan"[12] designed to address the identified shortcomings, to ensure greater coordination among the department's public health agencies, and to increase the effectiveness of the FDA's scientific and regulatory activities. Notably, the post-TAA era has witnessed an aggressive effort by the FDA to improve blood safety through enforcement of cGMP in blood product collection and processing aligned with the model of pharmaceutical manufacturing and a more formal relationship than blood establishments experienced in the past. The FDA initiative also involved promotion of automation to reduce human errors, including use of validated blood bank software. An intensive program of field inspections designed to assure universal regulatory compliance of blood collection establishments resulted in a number of court-enforced voluntary injunctions (consent decrees).

Known and emerging infectious threats to blood safety have continued to demand attention in the post-TAA era, repeatedly testing whether the lessons of TAA were learned. Are we prepared to deal with potential threats from bioterrorism agents? How much effort should

be expended to prepare for an outbreak of chikungunya virus that might never happen? What should we do about pandemic influenza and Middle East respiratory syndrome coronavirus in the absence of studies to establish the presence or absence of viremia in the course of the infections? Does it make sense to screen all blood donations when risks of babesiosis and dengue are seasonal and geographical? What changes to the current paradigm of donor screening and testing can be considered when pathogen reduction becomes available for all blood components? More generally, as we become increasingly proactive in addressing infectious risks, are we misdirecting resources that could be better spent to improve blood safety in other ways? Readers of this commentary are encouraged to ask themselves whether the lessons of TAA have been optimally incorporated during the decades of challenge and response that followed.

LOOKING BACK: THE EARLY RESPONSE TO TAA AND OTHER RETROVIRUSES

A sentinel event in the history of blood safety was the recognition and response to TAA. Although the etiology remained unknown, the report of AIDS in three persons with hemophilia A in July 1982 suggested a blood-borne pathogen as the causative agent.[3] These three individuals were reported to be heterosexual, had no other known AIDS risk factors, and had all received frequent administration of Factor VIII concentrate. The evidence for transmission of the "AIDS agent" through blood was further strengthened in December 1982 by the report of a 20-month-old infant in San Francisco who had developed unexplained immunodeficiency after transfusion of multiple blood products to treat erythroblastosis fetalis.[4] One of the blood donors was a man who was healthy at the time of donation, but subsequently died of AIDS.

To address the possibility that AIDS was associated with the receipt of blood and blood products, the Centers for Disease Control and Prevention (CDC) convened a meeting on January 4, 1983, with participation by the FDA, the National Hemophilia Foundation, blood banking officials, and patient advocacy groups. From the CDC perspective, the purpose of the meeting was to discuss how to reduce the risk of AIDS in transfusion recipients and persons with hemophilia in the absence of a test for the etiologic agent. Several possible strategies were presented, including deferral of blood donations by persons known to be at increased risk for AIDS and the use of surrogate tests to identify persons at increased risk of transmission, such as those with detectable antibody to hepatitis B core antigen (anti-HBc) or low CD4/CD8 T-cell ratios. However, the meeting turned into a contentious debate about the existence of AIDS in transfusion recipients and persons with hemophilia, and no agreement was reached on a risk reduction strategy.

On March 4, 1983, the US Public Health Service published the first recommendations for prevention of AIDS.[8] Among the recommendations was a statement that, "As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood." In addition to persons with clinical evidence of AIDS and their sexual partners, those considered to be at increased risk included "sexually active homosexual or bisexual men with multiple partners; Haitian entrants to the United States; present or past abusers of IV drugs; patients with hemophilia; and sexual partners of individuals at increased risk for AIDS." At the time, these recommendations were controversial. In particular, restricting blood donation by homosexual men was seen as a civil rights issue, and deferring donations by Haitian entrants undoubtedly led to discrimination against Haitian Americans. From a public health perspective, however, these measures were needed to increase blood safety.

With the identification of HIV, screening of donated blood and plasma became possible. Bulk preparations of the virus, known at the time as HTLV-III, were provided by the National Cancer Institute to diagnostics companies for the development of antibody detection tests. The first such screening test, developed by Abbott Laboratories, was approved by the FDA in March 1985. Because of concerns that persons would donate blood for the purpose of learning their HIV infection status, the CDC funded the first alternative HIV test sites, where individuals could obtain free and confidential testing. Blood banks also established the option of confidential unit exclusion to allow persons who had donated blood to confidentially indicate that the blood should not be used for transfusion. A watershed event in blood safety was the statement by the FDA commissioner at a September 1994 workshop that nucleic acid technology should be implemented to close the window period for HIV detection by serology. This technology had been considered too costly and cumbersome for practical application in blood banking. The introduction of direct testing for HIV in donor blood, first by p24 antigen assays, which proved largely unproductive,[13] and then by nucleic acid tests (NATs) for viral RNA, which proved beneficial, put to rest a decade of concern about residual HIV risk from donations in the 3- to 6-week infectious "window period" before seroconversion dependent on the sensitivity of different screening tests. The successful adaptation of NAT to donor screening, including testing of specimens in small pools of 16 to 24, established a new era in risk reduction from transfusion-transmitted viral diseases. In addition to increasing the safety of transfused blood, HIV antibody screening of donors led to "lookback" programs in which recipients of previous unscreened donations from infected donors were identified. These recipients were found to be at substantial risk for infection.[14,15] Although no effective

treatment was available at the time, infected recipients could be counseled to reduce the risk of HIV transmission to others.

Another retrovirus, HTLV-I, was also found to cause disease, including adult T-cell leukemia or lymphoma and HTLV-1 associated myelopathy or tropical spastic paraparesis. The virus can be transmitted by transfusion of cellular blood products, but not plasma fraction or plasma derivatives.[16] In November 1988, the FDA issued guidance recommending antibody testing of donated whole blood and cellular components for HTLV-I. Because of a high degree of sequence homology, the currently approved HTLV-I screening assay also detects antibodies to HTLV-II, a virus with transmission routes similar to HTLV-I but with less clear disease associations. Although not FDA approved, Western blot and PCR tests can be used to distinguish between the two viruses.

GOVERNMENT'S ROLE IN THE IDENTIFICATION AND PREVENTION OF TAH

World War II led to recognition of the frequent occurrence of hepatitis among military personnel through the confluence of contaminated water, massive immunizations, and for the first time, blood transfusion. It was during this time that food- and water-borne "infectious hepatitis" was distinguished from parenterally transmitted "serum hepatitis" and these entities were later termed hepatitis A and B, respectively. In 1943, Beeson[17] reported seven cases of jaundice occurring 1 to 4 months after transfusion of blood or plasma. A dramatic outbreak of hepatitis involving 50,000 US soldiers was traced to serum-contaminated preparations of yellow fever vaccine, which conclusively documented parenteral transmission. Decades later, this outbreak was shown by Seeff and colleagues[18] to be due to the hepatitis B virus.

The US Army extensively studied serum hepatitis during and after the war and characterized both the epidemiology and the resultant disease, but could not identify the causative agent. The etiologic breakthrough began in the early 1960s with the discovery of the Australia antigen by Blumberg and coworkers at the National Institutes of Health (NIH).[19] This single finding changed the course of hepatitis history when in 1968, the Australia antigen was shown by the Blumberg group to be associated with viral hepatitis[20] and then by Prince and colleagues[21] to be specifically associated with hepatitis B. In England, Dane and coworkers[22] showed by immune electron microscopy that the Australia antigen represented the envelope protein of HBV and it was renamed the hepatitis B surface antigen (HBsAg). The serologic distinctions between hepatitis A and B were further solidified by the controversial, but definitive prospective studies by Krugman and colleagues[23] at the Willowbrook State School. The US government played a pivotal role in these momentous events, first through the initial discovery of the Australia antigen in the intramural program at NIH and then through extensive grant support of the Blumberg laboratory at the Institute for Cancer Research in Philadelphia.

In the late 1960s and early 1970s, prospective studies at the NIH Clinical Center revealed several critical elements of TAH, including:

1. That the primary risk factor for TAH was the use of paid donor blood[24] confirming earlier studies;[25] in 1972, this led to an FDA mandate requiring the labeling of paid donor blood, which effectively resulted in the near-universal adoption of blood collection only from unpaid volunteers, one of the most important transfusion-transmitted infectious disease interventions ever implemented.
2. That HBsAg testing of blood donors was effective even when using insensitive techniques such as agar gel diffusion and counterelectropherseis;[26] nationwide testing for HBsAg was delayed until more practical and confirmable assays were introduced in 1972.
3. That the simultaneous implementation of 100% volunteerism and first-generation HBsAg screening reduced the incidence of TAH from 30% to approximately 10%[26] and that this massive reduction was more dependent on the donor source than on blood screening because HBV was shown to account for less than 30% of total TAH.
4. That after discovery of the hepatitis A virus (HAV) by Feinstone and coworkers at NIH,[27] it became evident that HAV was not responsible for the residual cases of TAH, giving rise to the cumbersome, but nonpresumptive designation NANBH.[28]

While intensive efforts to isolate the NANBH agent in the decade from 1975 to 1985 were unsuccessful, studies at the NIH and CDC revealed that the agent was small, lipid-enveloped and most similar to the small RNA alpha and flaviviruses.[29-31] Despite the absence of a specific test for detecting the NANBH agent, TAH incidence declined because of the more judicious use of blood fostered by the recognition that NANBH could result in cirrhosis and death[32] and by the devastating consequences of transfusion-transmitted HIV.[5] Further, in the absence of specific NANBH assays, surrogate assays were advocated. The Transfusion Transmitted Virus Study, supported by the National Heart, Lung and Blood Institute, published a retrospective analysis of a prospective study that showed that alanine aminotransferase (ALT) testing of donors might effect a 30% reduction in TAH incidence.[33] This was confirmed by a similar analysis of the NIH prospective TAH study,[34] but implementation of ALT donor screening at the NIH failed to demonstrate the predicted benefit.[35] Similar retrospective testing of the Transfusion Transmitted Virus Study[36] and the NIH[37] prospective studies

suggested that anti-HBc testing might result in a 30% to 40% reduction in TAH, and this fostered the voluntary introduction of ALT and anti-HBc donor testing in 1986 to 1987; the FDA recommended routine donor testing for anti-HBc in 1992. Although anti-HBc screening was introduced specifically to detect HBV carriers who were HBsAg negative (now termed occult hepatitis B), it also served as a surrogate for NANB carriers and for seronegative HIV carriers because of overlapping transmission routes. Had anti-HBc surrogate testing been introduced in the early 1980s it presumably would have prevented some cases of transfusion-transmitted AIDS and NANBH. This delayed implementation was the basis for extensive litigation, but also served as the driver for the IOM recommendation of invoking the "precautionary principle" when weighing new donor screening interventions and this precautionary approach has significantly improved transfusion safety.

Industry has played a major role in hepatitis prevention, first by developing increasingly sensitive assays for HBsAg, by developing nucleic acid detection assays for all the major viruses, and particularly by cloning the NANB agent.[38] The latter was a monumental achievement by Chiron Corporation in collaboration with Dan Bradley at the CDC. Using the then-novel technique of expression cloning, these investigators identified a single clone among millions tested that reacted with serum from patients with NANBH. Houghton and associates at Chiron then "walked" the genome, characterized an antigen derived from the nonstructural region of the viral genome, and developed an antibody assay to detect this viral protein.[39] Studies at the NIH[40] confirmed that the cloned agent, designated hepatitis C virus (HCV), was detected in virtually all NANBH cases and identified an implicated donor in near 90% of these cases. First-generation anti-HCV testing was introduced in 1990 and second-generation assays in 1992. Prospective studies at the NIH Clinical Center documented the virtual eradication of TAH by 1997;[35] mathematical modeling after the introduction of NAT screening in 1999 predicts that the current risk of transfusion-related hepatitis C is approximately one case in every 2 million transfusions, approximately the same risk as being hit by lightning.

OTHER AGENTS OF CONCERN

West Nile virus: accelerated development of screening assays and a new testing paradigm

West Nile virus (WNV) was first identified in the United States in 1999 after an outbreak of encephalitis in New York. Four cases of unexplained fever and encephalitis in recipients of organ transplants from a common donor proved to be caused by WNV and raised the possibility of transmission through blood transfusion. Initial efforts to screen blood donors using signs and symptoms of WNV infection proved ineffective.[41] In 2002, a total of 4156 cases of human illness were reported, and at least 21 people contracted WNV through transfusion, six of whom died.[42] The rapid expansion of WNV across the United States and reported to BOTSEC by the CDC lent urgency to developing a screening test before the next epidemic season.[43] The FDA requested that industry develop such a test; the National Heart, Lung and Blood Institute provided $3.47 million in research support; the American Red Cross provided 35,000 archived specimens; and the FDA facilitated rapid national test implementation and ultimate approval. Although development of blood screening tests usually takes years, the NAT assay for WNV was available for the 2003 epidemic season, building on technology platforms already developed for HIV and HCV. West Nile virus was the first acute infection with a short asymptomatic viremia and an epidemic spread to warrant routine donor testing and demonstrated a successful collaboration of government, blood collectors, and the diagnostics industry.[44,45]

A footnote to the WNV screening success was the recognition that testing of pooled samples was insufficiently sensitive to detect low-titer viremia in blood donations, including in the infectious preseroconversion donations commonly encountered during epidemic spread. However, universal testing of individual units in nonepidemic areas nationwide was inefficient and costly. This problem was solved through a novel strategy of triggering individual testing based on the yield of pool testing. This approach effectively detected and interdicted approximately 1400 potentially infectious blood donations during 2003 to 2005.[46]

Variant Creutzfeldt-Jakob disease: decision making in the face of scientific uncertainty

The emergence of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom and France first reported in 1996 posed what has been arguably the most challenging blood safety problem for decision makers since the beginning of the AIDS epidemic. Like AIDS, vCJD presented a new disease with unknown transmission dynamics, the potential for transmission through blood transfusion, the recognition of a novel infectious agent (prions), and near invariable fatality.[47] vCJD was linked to bovine spongiform encephalopathy, a disease recognized in the United Kingdom since 1986, so the incubation period of the disease was assumed to be lengthy. The scope of the epidemic was and remains unknown.[48,49] For prions, unlike for bacteria and viruses, no technology for developing diagnostic or screening assays was available.

The FDA established a Transmissible Spongiform Encephalopathies Advisory Committee to assure focused, objective, and transparent input to its decision making. Based on the available epidemiologic data in 1999, the FDA recommended that blood components collected from donors diagnosed with vCJD be withdrawn and developed

a mathematical model for indefinite donor deferral based on geographic exposure (donors who resided in the United Kingdom for a total of 6 months or more, between 1980 and 1996) that eliminated an estimated 87% of donor exposure-days to bovine spongiform encephalopathy in the United Kingdom with a projected loss of approximately 2% of donors, which was considered a difficult balance of safety and supply, necessitating close monitoring of the blood supply.[50] Based on continuing surveillance of vCJD, the geographic exclusion was expanded in 2002, providing approximately a 90% reduction in total risk-weighted person-days of donor exposure to bovine spongiform encephalopathy in western Europe including the United Kingdom with an estimated total donor loss of approximately 7%. The question of blood transmission was answered when the United Kingdom reported four cases of vCJD infections associated with blood transfusion that occurred between 2003 and 2007.[51] All four recipients had received transfusions of nonleukoreduced RBCs between 1996 and 1999, which confirmed the long incubation. Only time will tell whether the steps taken in the United States will prove both warranted and sufficient, but the policy reflects adoption of a "partial solution" when it appears to reduce risk and an attempt to act expeditiously and responsibly with a benefit-to-risk model to address risk in the face of scientific uncertainty.

Chagas disease: lessons learned

Chagas disease, caused by the protozoa *Trypanosoma cruzi*, affects an estimated 8 million people globally; an estimated 300,000 people in the United States and Canada are infected. Most infections are found in immigrants from Latin America. Whereas most new infections are vector borne, transmission by blood transfusion is well recognized. Six transmissions had been reported in the United States before the ability to screen blood donors.[52] As early as 1989, the FDA Blood Products Advisory Committee recognized that while only 20% to 30% of those infected with *T. cruzi* develop symptomatic disease, the infection is lifelong in the absence of early treatment and can be fatal.[53] In view of increasing immigration to the United States from endemic regions, the Blood Products Advisory Committee recommended testing donors when a suitable test became available. Donor history screening proved insufficiently sensitive and specific. Not until 2006 was a test found suitable for licensure. Shortly thereafter, the major blood collectors undertook universal donor screening for antibodies to *T. cruzi*.

In retrospect, an earlier study in Los Angeles and Miami suggested that seropositivity did not equate with infectivity; none of 18 recipients of blood from a subsequently identified seropositive donor had evidence of infection.[54] Two years of screening in the United States established that whereas the seroprevalence may be as high as 1 in 13,292 donors in some regions, infections confirmed by lookback studies are rare.[55,56] Reexamination by the FDA of its decision to recommend universal donor screening led to a novel policy of once-in-a-lifetime donor testing based on the demonstrated rarity of acute or incident *T. cruzi* infections in US donors.

Anthrax: bioterrorism, public concern, and the blood supply

Anthrax is caused by infection with a spore-forming Gram-positive bacterium *Bacillus anthracis* found globally in temperate zones, but uncommon in the United States.[57] Only seven cases of cutaneous anthrax had been reported to the CDC between 1980 and 2000 when in 2001 an outbreak of bioterrorism-related anthrax resulted in 22 confirmed or suspected cases including five fatalities.[58] This episode raised public concern about the blood supply during a period of high anxiety regarding threats of bioterrorism.

Bacteremia is present during fulminant cutaneous and respiratory anthrax; however, bacteremia in asymptomatic individuals has not been described. The period between exposure to *B. anthracis* and development of clinical anthrax is reported as 1 to 7 days but may be as long as 60 days. Little information exists regarding transmission via blood transfusion from an asymptomatic individual who has been exposed to *B. anthracis*. No such cases have been reported and no licensed diagnostic or blood donor screening test exists.

The FDA received several inquiries regarding the risk to the blood supply from donors in direct contact with material contaminated with *B. anthracis*. After consulting with experts at the CDC, the NIH, and the US Army Medical Research Institute for Infectious Diseases, the FDA issued guidance regarding measures to reduce possible risk for transmission of anthrax from blood.[59] The guidance did not recommend any changes to standard donor screening and blood collection procedures, but emphasized that standard blood collection procedures already in place include deferral of any donor who is not in good health at the time of donation. Nevertheless, to address public concerns as well as the dearth of scientific information regarding blood transmission, the FDA provided prudent but specific recommendations concerning donors with a confirmed medical diagnosis of anthrax or proven colonization with *B. anthracis* and provided criteria for product quarantine and retrieval related to reports of postdonation illness.[59]

Xenotropic murine leukemia virus–related virus: blood safety and validation of the scientific method

In 2009, the journal *Science* reported that a gamma retrovirus, xenotropic murine leukemia virus–related

virus (XMRV) was isolated from blood in two-thirds of patients diagnosed with chronic fatigue syndrome (CFS) and, most alarmingly, in 3.7% of healthy subjects.[60] A second article reported a related retrovirus (pMLV) with an even higher prevalence of 6.8% among blood donors.[61] These reports generated enormous public interest and concern. Given the possibility that XMRV could be transmitted by transfusion, immediate calls arose to screen blood donors for signs and symptoms of CFS and to test donations for XMRV. At the same time, intensive efforts were being undertaken worldwide to resolve this potential safety concern.

A federal interagency working group met repeatedly by teleconference and electronic communication, and laboratories within the CDC, NIH, and FDA invested resources into investigating discrepant laboratory results.[62] Additionally, representatives of the CDC, the FDA, and the intra- and extramural programs at the NIH participated in a public–private interorganizational task force assembled within 60 days by the AABB (formerly American Association of Blood Banks).[63] The result was voluntary implementation of an interim AABB recommendation that blood collectors should "actively discourage potential donors who have been diagnosed by a physician with CFS, chronic fatigue and immune dysfunction syndrome, or myalgic encephalomyelitis from donating blood" and ultimately definitive laboratory evidence that XMRV or pMLV bore no association with CFS and posed no threat to the blood supply.[64,65]

Ongoing threats and challenges

Several infectious threats are currently challenging federal decision makers. Bacterial contamination of platelets is a clearly identified risk that is being addressed with "partial solutions," culture, and point-of-issue serologic testing.[66] Hepatitis E virus is known to be transfusion transmitted, but potential disease burden has not been defined.[67] The geographic and travel exclusions to limit the risk of malaria transmission continue to be refined pending development of screening assays or pathogen reduction technology. Surveillance for the coronaviruses responsible for severe acute respiratory syndrome and Middle East respiratory syndrome is active and the possibility that these agents as well as pandemic influenza and monkey pox might be transfusion transmitted or disrupt blood donation is unresolved. The possibility of seasonal and geographic-based donor screening with validated tests for dengue and babesiosis has been modeled even as pilot studies of screening assays are ongoing.[68,69] Pathogen reduction technology offers an alternative approach to risk mitigation. Such technology would change the risk–benefit paradigm both for the known infectious agents and for those likely to threaten the blood supply in the future.[70] Federal decision makers are involved in determining when and how this technology should be applied to the nation's blood and blood components.

CONCLUSION

The federal response to transfusion-transmitted infections has evolved dramatically since the emergence of HIV as a transfusion-transmitted infection. The philosophy of risk management has become more precautionary and patient focused, yet still data driven. Regulation of not-for-profit blood collectors has become more formal and stringent. Manufacturers of blood components are now held accountable for meeting cGMP standards similar to those that apply to the manufacture of medical devices and pharmaceutical-type drugs. A new and arguably more responsive federal structure for addressing issues of blood safety and availability has been adopted. The decision-making structure places a premium on clear lines of authority, internal and public communication, flexibility, and coordination among the federal agencies with major roles in blood safety. Federal agencies have encouraged public discourse through workshops, joint initiatives with industry, and participation in public–private partnerships with professional societies and blood collectors. These adjustments have allowed federal agencies to respond with appropriate urgency to the differing situations posed by emerging infectious agents in the era since recognition of TAA 30 years ago.[71]

CONFLICT OF INTEREST

None.

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