Emerging infectious agents and the nation's blood supply: responding to potential threats in the 21st century

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In the early 1990s, the Department of Health and Human Services (DHHS) asked the Institute of Medicine (IOM) to assess how the government, the private sector, and other stakeholders had responded to the human immunodeficiency virus (HIV) epidemic and its impact on blood safety. In its executive summary published in **TRANSFUSION**,[1] the IOM Committee to Study HIV Transmission Through Blood and Blood Products noted that although stakes were high, decisions had to be made under a cloud of uncertainty and that responses were slowed by imprecise and incomplete knowledge, personal and institutional biases, and ultimately by failures in leadership. Emphasizing that blood safety is a shared responsibility, the IOM Committee issued 14 recommendations related to structure and policy including the designation of a Blood Secretary Director by DHHS, the establishment of a Blood Safety Council by the US Public Health Service (PHS), and several recommendations to the Federal agencies involved in the evaluation of an infectious threat, in particular, the Food and Drug Administration (FDA).

Since then, these recommendations have been implemented and the blood safety community (blood collectors, blood safety experts, and relevant Federal agencies) has responded to other emerging infectious disease (EID) threats, such as West Nile virus (WNV) and most recently the xenotropic murine leukemia virus–related virus (XMRV). Responding to any new threat entails assessing the risk to the blood supply and recipients' health; evaluating how best to manage and/or control each potential risk; and communicating this information to blood donors, recipients, physicians, and the general public. Although the FDA has the regulatory authority to develop guidance documents and new regulations in response to EID threats based on available data, the challenge of generating that data and responding to potential risks requires concerted and coordinated actions by the multiple PHS agencies (Centers for Disease Control and Prevention [CDC], FDA, National Institutes of Health [NIH]) and by the broader transfusion medicine community (AABB and blood providers). It is therefore incumbent upon the transfusion medicine professionals to collect and provide robust data in a timely manner to policymakers to inform their decision process, as well as take an active role in risk communication. All stakeholders must recognize what they can do and provide leadership and timely research and risk assessments. In so doing, they must take a hard look at their responses and learn lessons from history. Such a process does not involve a confirmation or criticism of what has been done in previous responses to potential threats to the blood supply, but an assessment of how responses can be improved for future threats.

ABBREVIATIONS: CFS = chronic fatigue syndrome; DHHS = Department of Health and Human Services; EID(s) = emerging infectious disease(s); ID = individual donation; IOM = Institute of Medicine; ME = myalgic encephalomyelitis; MLV = murine leukemia virus; NA(s) = nucleic acid(s); NANBH = non-A, non-B hepatitis; NHLBI = National Heart, Lung, and Blood Institute; PHS = Public Health Service; PTH = posttransfusion hepatitis; SARS = severe acute respiratory syndrome; SRWG = Scientific Research Working Group; vCJD = variant Creutzfeldt-Jakob disease; WB = whole blood; XMRV = xenotropic murine leukemia virus–related virus.

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In the aftermath of the recent XMRV investigation and the inevitable occurrence of future infectious threats, the National Heart, Lung, and Blood Institute (NHLBI) convened an expert task force charged with evaluating how lessons from previous EID blood safety threat assessments could be used to optimize future response strategies. The task force was asked to review and discuss responses to past epidemics and recent EIDs and to consider: What worked? What could have worked better? What data are necessary to assess blood safety risk? Who needs to be engaged in the evaluation of risk; that is, who are the stakeholders? What methods and/or processes need to be in place and when? What resources, infrastructure, and capacity are needed? How best to train future experts? And how can a scientific culture be encouraged that encourages cooperation?

In a first session, responses to earlier epidemics were examined, followed by a discussion on responses to recent agents of concern, including an in-depth look at the latest potential threat, XMRV. A general overview of other agents of potential concerns (the horizon) ensued followed by a general discussion on lessons learned and consideration of future strategies. This report summarizes the results of these discussions.

SESSION 1: RESPONSE TO EARLIER EPIDEMICS (20TH CENTURY)

Transfusion AIDS (HIV)

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The possibility that AIDS could be transmitted through blood and blood products was first formally discussed in December 1982 in *Morbidity and Mortality Weekly Report* (*MMWR*),[2] almost 6 months after the first reports of *Pneumocystis carinii* pneumonia in patients with hemophilia[3] and almost 18 months after the first reports of *P. carinii* pneumonia in homosexual men.[4] In January 1983 the CDC convened a workgroup to review existing information on transfusion- and factor concentrate–associated AIDS cases and to identify opportunities to prevent AIDS in blood recipients and persons with hemophilia. At that time persons with hemophilia accounted for only six of more than 800 reported AIDS cases, with five additional cases established as possibly transfusion related. A large lookback program had found that only 10 of 140 AIDS patients interviewed in San Francisco reported donating blood during previous years. In a statement issued later in January 1983, the CDC workgroup simply noted that "the possibility of blood borne transmission, still unproven, has been raised." Furthermore, the cause of AIDS was still unknown in January 1983, but because existing data showed that the vast majority of homosexual men and intravenous (IV) drug users tested positive for surrogate markers such as antibodies against the hepatitis B virus (HBV; anti-HBc), the workgroup remarked that use of "non-specific markers" was under evaluation. No agency took responsibility for prevention of transfusion-transmitted AIDS.

Although the workgroup considered several interventions to exclude risk groups from donating blood, there were concerns about adopting a confrontational approach toward potential higher-risk donors. Thus the 1983 statement noted that direct or indirect questions regarding donors' sexual preferences were inappropriate. Nonetheless, the blood bank in San Francisco developed a process whereby donors could discreetly exclude themselves by answering "yes" or "no" to a block of questions about known AIDS risk factors. By mid-1983 many blood collection organizations, particularly those in cities at high risk, had adopted a donor qualification process known as self-deferral by which presenting donors were provided with information about AIDS risk factors and where those with such risk factors were asked not to donate. There was also outreach to homosexual community organizations to discourage donation from at-risk men. In New York City, and later elsewhere, the "confidential unit exclusion" procedures were introduced that allowed individuals to give blood but then inform the blood bank of their nondisclosed risk behaviors so the blood units would be discarded or used for research.

Blood banks in the San Francisco bay area also began to implement "surrogate" tests such as T-cell helper/suppressor ratios (Stanford University Blood Bank) or anti-HBc testing of blood donors (Irwin Memorial Blood Bank). Of note, flow cytometry equipment for performing T-cell ratios was not available outside of limited research labs and anti-HBc testing yielded many false positives, and no confirmatory tests were available. Moreover, there were concerns that positive surrogate tests would be concerning to donors, that homosexual men would donate blood simply to get the test, and that elimination of homosexual donors would negatively affect the blood supply. Once the homosexual community learned of the potential risks, many in the community stopped donating blood. By 1984, great concerns had arisen in the patient community, and there was a general fear of blood originating from San Francisco. Additionally, the performance characteristics of the anti-HBc test remained of concern. A larger study[5] of transfusion-transmitted AIDS was published in January 1984, and by December 1984 the number of transfusion-related AIDS cases had risen to more than 100.

HIV was discovered in the spring of 1984, with high rates of virus isolation and antibody detection in homosexual men, and several studies pointed to this virus as the causative agent of AIDS. Questioning of potential donors was not further optimized because blood banks expected that HIV tests would soon be available. Yet HIV antibody tests were not available until 1985. Lookback studies found that more than 30% of donors testing positive for

HIV were also reactive for anti-HBc and that approximately 90% of recipients transfused with blood from HIV-infected or suspected cases acquired infection. An analysis of donation histories of HIV-infected donors in San Francisco, HIV infection prevalence among homosexual men in San Francisco, and HIV donation rates by subsequently identified infected donors estimated that the incidence of transfusion-transmitted HIV infection rose rapidly, from the first occurrence in 1978 to a peak in 1982 of approximately 1% per unit transfused and that more than 2000 recipients in San Francisco alone had been infected with HIV through transfusions.[6] The analysis also showed that donor selection and education efforts had been effective in curbing the number of donations by infected individuals. Donations by individuals who later tested positive for HIV or developed clinical AIDS had declined by 75% by the time anti-HBc testing was implemented and by 90% by the time HIV-specific testing was available.

It was hoped that the implementation of HIV antibody testing would eliminate transfusion-transmitted AIDS, but breakthrough cases were detected shortly after introduction of HIV testing, indicating that antibody screening had not eliminated the risk.[7] These cases were related primarily to homosexual men who had initially tested negative for anti-HIV but later seroconverted after donating blood, which led to improvements in donor eligibility criteria including the exclusion of all males who had had sex with another male since 1977. A further study found an infectious window period of 56 days from infection to detectable antibody conversion by the first-generation screening assays.[8] Later improvements in the sensitivity of antibody assays reduced this preseroconversion infectious window period to approximately 3 weeks, and the subsequent additions of p24 antigen and its replacement with nucleic acid testing (NAT) virtually eliminated this window, resulting in current risk estimates of approximately 1 infectious unit per 1.5 million transfused units. In fact, six transmissions have been reported in the United States since 1999, when NAT was implemented, during which time from 13 to 17 million whole blood (WB) donations per year were processed and distributed. Even more impressive, the implementation of viral inactivation steps, in addition to donor selection and HIV testing has eliminated transmission of HIV by plasma derivatives, with no cases reported in more than 20 years.

The experience with transfusion-transmitted AIDS showed that infection with an agent having a long asymptomatic incubation period can spread in the blood supply for years before recognition, resulting in fatal infection of transfusion recipients. Blood bankers had been slow to recognize the magnitude of the problem and to implement additional safety procedures such as enhanced donor selection, surrogate testing, and plasma treatment measures that might have reduced HIV transmission. Even after HIV screening was implemented, it took several years to address the persistent risk of window-phase HIV infection. Yet these failures led to the transformation of the blood safety field into a highly regulated, science-based field that proactively addresses potential transfusion-related EIDs.

Discussion points

1. Responses to HIV/AIDS were slowed because this virus was different from any that had been seen previously. Until the etiologic agent was identified and serology deployed, the epidemiology of HIV infection was unclear. The long latency from infection to symptoms and high disease risk in infected persons only became clear once serology was possible. Responding to the initial uncertainty surrounding HIV required a new paradigm of precaution that was foreign to the blood community who preferred to wait for more certain information before intervening aggressively and uniformly.
2. Starting in March 1985, three HIV tests were (quickly) licensed. The ability to respond to future threats and move tests through the approval process may also take a long time, emphasizing the importance of having all stakeholders including manufacturers, the blood community, and the FDA involved as soon as possible.

Non-A, non-B hepatitis C virus

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Viral hepatitis has long been recognized as a major adverse outcome of transfusion and, indeed, in the 1960s and early 1970s, prospective studies suggested that 10% or more of blood recipients were affected. Hepatitis A and B had been differentiated on epidemiologic and clinical grounds before the discovery of hepatitis B surface antigen (HBsAg) in 1968. At that time, posttransfusion hepatitis (PTH) was thought to be entirely due to HBV. Insensitive tests for HBsAg were implemented as a blood safety measure, starting in 1970 to 1971 and had some very limited impact on PTH, although a much greater impact was attributed to careful donor selection methods and the avoidance of paid donations. Even the introduction of highly sensitive radioimmunoassays in 1973 further reduced the incidence of PTH only by 20%. The recognition of hepatitis A virus (HAV) and the development of diagnostic tests revealed that the vast majority of residual PTH was not due to HAV or HBV, and the term non-A, non B hepatitis (NANBH) was coined. Efforts to identify the causative agent started, but did not succeed until 1989. In the meantime, large, multicenter prospective studies of PTH were executed.[9] These studies revealed epidemiologic relationships between surrogate markers (elevated

alanine aminotransferase [ALT] levels and the presence of anti-HBc) in donors and PTH in recipients.[10,11] In 1982, the introduction of donor testing for surrogate markers was predicted to reduce NANBH transmission by 30% to 60%; such testing was not widely implemented until 1986. This delay was attributable to a number of factors including concern about loss of donors, uncertainty about the true severity of NANBH, and the need to manage the HIV/AIDS epidemic.

The recognition and characterization of NANBH involved studies in several disciplines including epidemiology, pathology, and prospective clinical posttransfusion studies. New solutions were needed to overcome the unique challenges presented by NANBH. Because hepatitis viruses could not be grown in tissue culture, investigations relied on inoculation of nonhuman primates. In addition, unlike HBV, it had not proven possible to detect antibodies to any putative causative agent. Further, today's more rapid pathogen discovery techniques were not available and hepatitis C virus (HCV) was cloned through an incredibly painstaking manual process.

As a result of arduous cloning experiments using plasma blindly passaged in chimpanzees infected with NANBH, with the belief that the agent was an enveloped togavirus, HCV was eventually identified in 1989 and specific tests for antibodies to HCV were developed.[12,13] It became clear that essentially all NANBH was due to transmission of HCV and routine testing for this antibody by first-generation assays was implemented in 1990, followed by implementation of antibody tests with increased sensitivity starting in 1992. NAT for HCV was additionally implemented in 1999 and, currently, it is estimated that the residual risk of transfusion-transmitted HCV in the United States is 1 per 1.5 million blood components.[14]

The experience with NANBH illustrates the power of persistence and teaches us some lessons about the benefits and risks of surrogate testing. Although these tests were useful in eliminating potentially infected donors, many donors were excluded even though they were not carriers of HCV. In addition, lessons from the NANBH and/or HCV story might not apply to the 21st century. For example, the virus associated with severe acute respiratory syndrome (SARS) was identified within 24 hours after samples were received. On the other hand, we should recognize that it is likely that the increased use of molecular genetics and genomic methods to identify viruses will lead to the discovery of many viruses without associated diseases.

Discussion points

1. Examining emerging threats does not mean ignoring existing threats. The response to NANBH was prolonged, in part, because the scientific community was focused on HIV.
2. The majority of discussions regarding NANBH and surrogate testing focused not on the need to protect patients but on the potential impact of donor deferral on blood availability. The AIDS epidemic caused a massive shift in focus to blood safety.
3. In the current era of molecular virology, many viruses will be identified without associated diseases. A baseline estimate of viral sequences in humans has not yet been established, but the human microbiome is under active investigation. Two NIH grants are specifically addressing plasma viral discovery programs.
4. Viruses such as HCV and HIV remain significant public health problems in the developing world, in the face of the constraints against implementation of the resource-intensive solutions used in the developed world.
5. At the NIH blood bank, evaluation of ALT testing after it was implemented indicated that it did not appear to be effective in reducing NANBH cases, and a cost–benefit analysis was unable to define a precise financial estimate for the benefits of ALT testing. Surrogate testing for other agents remains controversial although strict interpretations of the precautionary principle would encourage use of such a testing approach.

SESSION 2: RESPONSE TO RECENT AGENTS OF CONCERN

WNV

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WNV, a mosquito-borne flavivirus, was first recognized in the United States in New York City in 1999 and spread across North America by 2002.[15,16] Absent documented transfusion transmission, the transfusion medicine community took a wait-and-see approach during the first four transmission seasons. Familiarity with models developed at CDC to estimate the risk associated with WNV-viremic donors (and the lessons from recent experiences with HIV and NANBH and/or HCV) facilitated a rapid response by the blood community, public health, regulators, and the medical device industry after transmission by transfusion (and organ transplantation) was documented during the 2002 summer epidemic.[16,17] A series of interventions were implemented to mitigate the WNV risk starting in the fall of 2002,[18] including a nonspecific deferral for symptoms consistent with WNV fever, quarantine of plasma for transfusion collected during periods of high WNV activity, and critically, the development and nationwide implementation of WNV NAT in minipools in June of 2003, less than 1 year after documentation of the first transfusion-transmitted infection.

This collaboration had a highly significant impact and the number of recognized transfusion-transmitted

WNV cases shrank from 23 to 6 from 2002 to 2003, compared with 4156 and 9862 vector-borne infections reported to CDC, respectively.[19,20] More than 700 viremic donations were interdicted during the first year of testing, and approximately 60,000 frozen blood products from high-incidence areas were withdrawn.[21,22] Since then, a large number of WNV-positive blood donations have been identified, primarily through minipool NAT.

The six transmissions recognized from the 2003 transmission season, and retrospective individual WNV NAT on stored donor samples, demonstrated that low-level viremia in asymptomatic donors was being missed with minipool testing. This resulted in development and implementation of algorithms to convert blood regions from pooled to more sensitive individual-donation (ID) testing during intervals with WNV activity in donors.[23] These triggers have evolved while recognizing the operational burden inherent in testing ID aliquots. A 2008 AABB Association Bulletin recommended that ID-NAT be triggered when two presumptively viremic donors are seen within a rolling 7 days. It made recommendations for establishing at-risk donor populations within a collection area, that WNV activity and donor testing be monitored in real time and converted to ID-NAT within 48 hours of reaching a trigger, and that ID aliquot testing continue for a minimum of 7 days with no viremic donors.[24]

Six additional cases of transfusion-transmitted WNV have been recognized from 2004 through 2011.[25] For perspective, these occurred against a background of more than 20,000,000 blood components transfused annually. These cases were attributed primarily to insensitive triggers and inefficient communication between neighboring centers. Accordingly, triggers have been continuously reassessed, and in some systems a single viremic donor in the presence of other WNV activity in a community may be used to implement ID screening. In addition, again based on models from CDC, some systems extend ID screening for 2 weeks or more beyond the last viremic donation.[26] Communication in the blood safety community has been reinforced, for example, using processes that include e-mail notification trees, daily examination of the AABB WNV Biovigilance Network website and other public health WNV surveillance sources. These are designed to ensure that overlapping collection regions are aware when there has been donor activity in their areas that should trigger ID screening for multiple organizations, even in the absence of viremic donors at one or more of those collection facilities.

The experience with WNV has also fostered collaborations and scientific publications with impact beyond the blood community. They have increased our understanding of the clinical expression, biology, and epidemiology of WNV in the United States, for example, allowing estimation of population incidence rates in areas of high donor incidence.[27]

The use of seasonal WNV testing has been discussed as a measure to enhance further the sensitivity of WNV detection in blood donors. This program involves the potential suspension of testing in the winter when human activity is minimal, combined with planned conversion to ID testing during historically high incidence weeks and months, anticipating the detection of donor infections. These steps might enhance the capacity to convert to ID testing during the transmission season by conserving resources in testing facilities during low-incidence periods. These proposals are based on the observation that 100% of viremic donors reported to the AABB Biovigilance website have been identified between mid-April and mid-December from 2006 to 2011.[25]

Discussion points

1. The response to WNV was rapid and appropriate (successful) and a model for responding to an emerging infectious agent. Success was possible in part because there was rapid consensus about the need to intervene and little controversy about the appropriate technology (NAT) required for doing so. In contrast, the response to NANBH was delayed in part because of concerns that nonspecific interventions might do more harm than good.
2. Public–private partnerships were critical to the successful responses to WNV emergence.
3. The most appropriate deployment of WNV NAT to prevent the maximum number of cases has not yet been determined, but the paucity of transfusion transmissions in recent years validates the iterative approach to triggering ID testing that evolved over several transmission seasons.
4. Expanding ID testing during the peak transmission interval in the summer has been discussed. The tiny number of transfusion-transmitted infections during recent seasons (one in 3 years through 2011) suggests that the value may be minimal. Barriers include a large increase in reagent and consumables consumption and staffing in high-throughput NAT laboratories.

Trypanosoma cruzi, Babesia, dengue viruses, and the variant Creutzfeldt-Jakob disease prion

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Trypanosoma cruzi, the parasite responsible for Chagas disease, results in chronic infection and can be silent for decades. Although infection is less prevalent in North America than in the endemic areas of South and Central America, a report of two transplant-associated cases in Los Angeles, California, in 2006 stated that the prevalence of Chagas disease in North America might be higher than previously thought, particularly in regions where a large

proportion of donors have emigrated from Chagas-endemic countries.[28] A recent study of risk factors in *T. cruzi* antibody–positive blood donors has identified that autochthonous transmission within the United States may also be more common than previously thought;[29] the vast majority of antibody confirmed-positive donors identified by the American Red Cross were at risk by virtue of being born or having resided in an endemic area. Studies attempting to identify at-risk donors through direct questioning have proven ineffective in that this strategy lacks sensitivity and specificity.[30] The first antibody screening test was licensed in the United States in December 2006 after clinical trials demonstrated efficacy.[31] Universal blood donation screening was implemented by most US blood centers early in 2007 with confirmed seropositive rates of 1 per 25,000 to 1 per 30,000 donations.[32] FDA guidance released in December 2010 allowed for a change to a selective testing strategy where a donor would be tested only once for *T. cruzi* antibody and, if negative, all future donations made by that donor would also be assumed to be negative. The safety of such a strategy is based on the absence of documented incident cases in the United States and low rates of transfusion transmission (<2%) from seropositive components, with documented transmissions confined to platelets (PLTs).[33]

A supplement published by **TRANSFUSION** in August 2009[34] identified three EID agents (among more than 68 such agents) as the highest-priority agents for which a blood safety intervention should be considered: the parasite *Babesia*, dengue viruses, and the prion responsible for causing variant Creutzfeldt-Jakob disease (vCJD). All are transmitted by transfusion, are associated with a clinically apparent or fatal disease, and lack an effective intervention. *Babesia* and dengue are also increasing in frequency and/or recognition. These and other emerging pathogens, including *T. cruzi*, share few common characteristics. Thus, generalization regarding these diverse agents is dangerous, and each may require a different approach relative to transfusion safety. Because the emergence of these pathogens is unpredictable, vigilance remains critical.

Babesia is an intraerythrocytic parasite that is geographically clustered in the northeastern and upper Midwestern regions of the United States; seven states are considered endemic.[34,35] Infection is generally mild and transient; intermittent parasitemia may occur for months to up to several years. The parasite is transmitted primarily by *Ixodes* ticks; this tick is also responsible for transmission of the bacterium that causes Lyme disease and other agents. Transfusion is increasingly recognized as a significant transmission route due to the lack of an effective intervention and the growing number of infected individuals reported. Since January 2011, cases of babesiosis are nationally notifiable. Transfusion-associated babesiosis has been documented in 162 cases from 1979 to 2009 (159 of *B. microti* and three of *B. duncani*).[36,37] Those at greatest risk from transfusion-transmitted infection include infants; the elderly; and individuals who are immunocompromised and asplenic and have red blood cell (RBC) disorders. Of the cases of transfusion-associated babesiosis reported, 77% occurred between 2000 and 2009, and all but four were associated with RBC components. The remainder was due to random-donor PLTs likely contaminated with residual RBCs. The parasite has been shown, via transfusion-transmitted cases, to survive for up to 42 days in RBCs and indefinitely, if cryopreserved.[34,36] RBC pathogen reduction is not available. Donors are asked a health history question during their predonation interview regarding a history of babesiosis, but this approach is insensitive. Questions regarding tick bites are also insensitive since the nymphal stage of the tick, which requires a blood meal for growth, is very small and those who recognize attached ticks remove them promptly; a 48-hour attachment period is required for babesia transmission. No FDA-licensed test is available for donor screening, although investigational new drug applications are in place using both antibody and NAT to ensure that both early, antibody-negative infections and later infections with lower levels of parasites may be detected.

Dengue is the most important arthropod (vector)-borne disease in the world caused by one of four types of dengue viruses.[34] More than 40% of the world's population, or approximately 2.5 billion people, are considered at risk with millions of cases occurring annually, most of which occur during explosive outbreaks in the tropics or subtropics. Approximately 75% of cases of dengue virus infection are unapparent, but can also range in severity from mild, nonspecific, acute febrile disease referred to as dengue fever to severe dengue, previously referred to as dengue hemorrhagic fever and dengue shock syndrome. Before 1970, only nine countries experienced severe dengue epidemics but now the disease has emerged or reemerged in more than 100 countries,[38] and in many Latin American and Asian countries, dengue is a leading cause of hospitalization and death among children. It is the leading cause of febrile illness among travelers returning to the United States from the Caribbean, Latin America, and South Central and Southeast Asia. Three clusters of transfusion transmission have been documented, the first in Hong Kong (one symptomatic recipient) followed by a report in Singapore (two recipients with dengue symptoms; one asymptomatic but seroconverted) and finally the most recently reported in Puerto Rico where the recipient developed dengue hemorrhagic fever (all reviewed by Stramer et al.[39]). No licensed RNA test is available for screening blood donations; antigen tests have limited sensitivity and antibody tests do not detect infectious units. Donors are not asked questions to define their risk of infection since no question at present would

be effective. Similarly, most infected individuals exhibit no symptoms and thus questions regarding symptom history would also be ineffective. Deferring donors who have traveled to endemic countries is complex and hampered by poor specificity and limited sensitivity.

vCJD, the human form of bovine spongiform encephalopathy, is a prion-associated, degenerative, and always fatal disease with a lengthy incubation period of 5 to 15 years.[34] The majority of the 225 vCJD cases reported worldwide through October 2011 have been observed in the United Kingdom (n = 176) after vCJD was first recognized as a distinct agent in 1996. Only three of the known cases remain alive. Although similar to sporadic, iatrogenic, and familial CJD, vCJD occurs primarily among younger individuals, presents with psychiatric symptoms, and generally has a longer course from diagnosis to death. Four cases of transfusion-transmitted vCJD have been recognized from 2003 to 2007, three of which resulted in the development of vCJD in the recipients with the fourth occurring in an individual who died of underlying disease but was found to harbor the agent in the spleen and at least one lymph node.[40] Of note, all transmissions were from nonleukoreduced blood components. There was a fifth possible transmission from Factor VIII concentrates.[41] Only three vCJD cases have been reported in the United States; two of those arose from exposure in the United Kingdom, and the other arose from exposure in Saudi Arabia. Data from a recent study suggest that all blood components can transmit the vCJD prion whether leukoreduced or not; leukoreduction, in the case of PLTs, extended the incubation period by 700 days in the sheep experimental model.[42] The experimental transmissions and human cases in recipients with known exposure to blood from donors who later developed vCJD highlight the high rate of infection among individuals exposed through transfusion. Although the risk for vCJD appears to be declining, the number of exposed individuals is unknown, and a second wave of infections is possible. Interventions that consist primarily of donor deferral based on a history of travel to the United Kingdom and other affected countries were implemented before evidence of transfusion-associated transmission was reported. The efficacy of this strategy is unknown and was implemented as a balance between theoretical risk reduction and manageable donor loss expected not to exceed 2% of presenting donors. No licensed test is available as a donor screen, and the development, licensure, and implementation of a screening test are unlikely in the United States.

Discussion points

1. Vigilance is critical since the variety of agents that may emerge may share no common characteristics with each other and none in common with prior agents for which blood safety interventions have been introduced.
2. Interventions may be required even before the documentation of transfusion transmission (e.g., vCJD).

RESPONSE TO XMRV

Infection with gamma retroviruses, simple viruses with no accessory genes, leads to sustained viremia and can induce solid tumors, immune dysfunction, and neurologic disorders. In October 2009, *Science* published a report that the gamma retrovirus XMRV, which had been detected previously in prostate cancer tissue, had been detected in the blood cells of patients with chronic fatigue syndrome (CFS).[43] This observation was consistent with previous studies showing apparent "clusters" of CFS, a temporal association between CFS and acute XMRV infection, and immune deficiencies similar to those seen in prostate cancer.[44] The *Science* article reported that investigators detected XMRV not only in 67% of patients with CFS, but also in almost 4% of healthy controls. XMRV infection could be seen in peripheral blood mononuclear cells (PBMNCs) and plasma. The authors thus raised the possibility that XMRV infection contributed to the pathogenesis of CFS, and an accompanying commentary further noted that in light of the presence of infectious virus in plasma and blood cells, blood-borne transmission was possible.[45]

In response to this potential EID threat, DHHS immediately facilitated the establishment and coordination of collaborative groups, both internal and external to DHHS: the AABB Interorganizational Task Force and the DHHS/NHLBI Blood XMRV Scientific Research Working Group (SRWG). The former took the lead on risk management and risk communication aspects of the response, whereas the latter was charged with the design and coordination of research studies to evaluate whether XMRV poses a threat to blood safety (risk assessment).

AABB Interorganizational Task Force

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Within 60 days of the *Science* publication, AABB convened an interorganizational task force and charged it with reviewing available data; recommending actions to be considered to mitigate a potential risk for blood-borne transmission; and advising AABB about ways to inform donors, recipients, physicians, and the general public about the risk of transfusion-related transmission of XMRV.[46] Among the evidence reviewed by the Task Force were the *Science* article, a *Proceedings of the National Academies of Science* report showing the presence of murine leukemia virus (MLV) nucleic acid (NA), distinct at the sequence level from XMRV, in 86% of CFS patients and 6.8% of controls,[47] and primate studies suggesting that IV

injections of XMRV led to viremia and seroconversion and describing tissue tropism.[48] There were also negative data from the United States and several other countries.[49-58] Although the Task Force never met face to face, monthly teleconferences kept participants current on published and unpublished information; electronic communication circulated prepublications to all members. The Task Force postulated several reasons for the discordant results, including geographic differences in populations, nonvalidated assays, differing definitions of CFS, and laboratory contamination. On the basis of the inconsistent available data and Task Force consensus, the AABB adopted a precautionary policy of donor education and self-deferral for persons with a history of CFS. The policy was instituted widely in the United States and in Canada. A summary of the data and the Task Force policy was published in **TRANSFUSION**. As more data became available, including the recombinant origin of XMRV in laboratory mice, evidence pointed to contamination of reagents from this recombinant agent.[59,60] On the basis of these data, the Task Force concluded that the few observed positive results represented false positives and that there was no evidence that XMRV poses a transfusion risk. This experience showed that an interorganizational task force can be formed rapidly and that the inclusion of representation from major stakeholders can provide that task force with credibility. In addition, the public–private partnership in the task force could share unpublished information and form consensus positions effectively, while allowing member organizations autonomy in deciding whether to act on a position or perform alternative actions. Moreover, the Task Force presented a single voice and focused on a rapidly evolving issue, which was helpful in addressing inquiries from the press.

Discussion points

1. The reaction and pressure by the patient population was an important dynamic in generating a call for action in terms of blood safety.
2. There were several polytropic viruses that were not XMRV, and one group also reported that they had found several NA sequences from variant viruses. Thus there were additional uncertainties about which viruses might have been associated with CFS.
3. Because of the possible negative effects of promulgating requirements too early, the FDA is willing to work cooperatively with the private sector on alternative actions until there is more certainty. For example, if the FDA feels industry is responding appropriately to a potential threat to the blood supply, it can withhold its own action.
4. A robust process is needed to decide which stakeholders should participate in decision making and to verify who has implemented recommendations.
5. There is a risk that information can be interpreted differently by different members of the task force. In addition, in cases of uncertainty, responses to potential threats can differ by group or jurisdiction. Although the AABB Task Force promoted agreement among members on decisions and statements, such agreement might not be necessary. A uniform process for the evaluation of evolving information should be in place, with standard criteria and values to be addressed by all groups as they make their decisions. Having such a process can allow groups to better explain the differences in their responses.

Blood XMRV SRWG

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The HHS/NHLBI Blood XMRV SRWG was charged with designing and coordinating studies to evaluate whether XMRV posed a threat to blood safety.[61] Several questions needed to be addressed before the SRWG could first be convened and appropriately function: Who should be engaged and participate in the SRWG? What resources and/or infrastructure were needed? How was the research going to be funded if the SRWG itself conducted studies?

In response to the first question, it was clear that a multidisciplinary approach was essential. Thus, the SRWG brought together retrovirologists with XMRV experience, experts in the field of CFS or myalgic encephalomyelitis (ME), blood banking and transfusion-transmitted infectious disease experts, statistical and epidemiology experts, and blood product regulatory experts. A liaison between the SRWG and the AABB Interorganizational Task Force was also appointed, and the NHLBI Chair was charged with reporting to the PHS Blood Organ and Tissue Senior Executive Committee (which reports to the Blood Secretary Director, Assistant Secretary for Health). The Working Group also engaged relevant advocacy groups, developers and manufacturers of high-throughput XMRV-NAT and -antibody assays and, from time to time, worked with ad hoc experts. Each SRWG participant's organization provided support in terms of effort and scientific expertise while NHLBI provided the necessary administrative support. HHS laboratories funded their own research, and test manufacturers funded their testing of panel samples. For non-HHS laboratories, a supplement to the ongoing NHLBI Retrovirus Epidemiology Donor Study (REDS)-II research program was granted to support the work of the central laboratory and non-HHS laboratories involved in the procurement and testing of biospecimens. The REDS-II data coordinating center provided the necessary independent statistical expertise.

An assessment of EID risk in the context of blood safety requires answering three basic questions: Is the infectious agent present in blood donors? Is it transfusion

transmitted? And if so, does it have a clinical impact? The SRWG first evaluated all relevant literature, including all XMRV-related reports, animal studies, and observational studies evaluating if associations existed between CFS or ME or prostate cancer and transfusion history. After this review, the SRWG decided to concentrate on answering the first question—is XMRV in the blood supply? To that end, the SRWG focused on evaluating assays to identify and quantify viral NAs and antibodies to establish the prevalence of XMRV infection among blood donors. Three studies were conducted, and results were disseminated as soon as they became available to all relevant stakeholders through presentations, webinars, and publications.

Phase I to III blood XMRV SRWG studies and timeline

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As part of the blood XMRV SRWGs task to design and coordinate research studies to evaluate whether XMRV poses a threat to blood safety, a literature review and three laboratory studies—Phases I to III—were performed. A careful review of the current state of epidemiologic knowledge on potential association of prostate cancer and/or CFS with receipt of prior blood transfusions, revealed little to no association. Four relevant studies on the potential association of blood transfusions with cancer were identified (reviewed by Simmons et al.[61]). Although not conclusive, there was little evidence of an association between blood transfusions and prostate cancer. In contrast, far less was known about the potential association between CFS or ME and transfusion history. Only one peer-reviewed study could be identified[62] where blood transfusions were mentioned in relation to a cluster of CFS cases. In this instance, it was reported that none of the cases had received transfusions. Thus, the SRWG concluded that there was no published evidence of an epidemiologic link suggesting transfusion transmission of agents linked to either prostate cancer or CFS.

The SRWG included several laboratories with assays to detect NA from XMRV and other related MLVs, including laboratories that previously published on the detection of such viruses in blood donors and other healthy populations,[43,47] as well as those that had failed to detect the viruses in any population.[52,63] Thus, it was decided that in the initial Phase I studies, the SRWG would compare the sensitivities of these assays using analytical panels. The panels consisted of XMRV-infected cells (22Rv1 cells) or supernatant from those cells, diluted in WB or plasma respectively to mimic potential clinical samples. No gross differences between the sensitivities of the participating assays for detecting viral NA were observed for the two analytical panels.[61,64] Thus, the differences in detection of NA by groups that did not detect virus in clinical samples could not be explained by a lack of sensitivity.[52,63] In addition, a number of the other participating laboratories used these assays in subsequent studies that failed to detect XMRV or other MLVs in blood donors[64,65] or other populations such as patients with CFS or prostate cancer.[60,66] Although the Phase I study was not designed to examine assay specificity, in general there were no concerns in terms of false-positive results.[61,64]

Two pilot studies of clinical samples from CFS patients previously described as XMRV positive[43] were performed in Phase II. The first study was unblinded and designed to identify the best sample type (WB, plasma, PBMNCs) and processing methods. The results were inconsistent and thus a second, blinded study was performed using samples from four patients with CFS who had previously tested XMRV positive and a healthy control individual previously demonstrated to be XMRV negative. Four laboratories performed NA detection, while two studied serologic responses. The majority of laboratories (three of four) were unable to detect any evidence of XMRV or MLV NA in any of the samples, and one of the laboratories failed to detect any serologic response. The fourth NA laboratory was unable to report results due to an internal error in sample processing. The final serologic laboratory reported three of four patients with CFS to be seropositive for XMRV. The control was also found to be positive, despite previously being pedigreed as negative.

The SRWG Phase III study assessed 15 purportedly XMRV- or MLV-positive samples and 15 negative controls. In addition to the NAT performed on all three blood components, serologic and virus culture assays were also performed on plasma.[67] Samples and controls were divided and distributed to nine independent laboratories for blinded testing. Six of seven laboratories performing NAT found no positive clinical samples. The seventh found three positive samples—one from the XMRV or MLV clinical sample set and two from the negative controls, but phylogenetic analysis suggested that all of these sequences likely arose from 22Rv1 contamination (P. Kellam and S. Hué, unpublished analysis). Among the two laboratories that were able to report virus culture results, one found no positive samples, and the second reported the presence of XMRV in 40% of negative controls, compared with 20% of clinical samples. Among the four laboratories that conducted serology testing, two reported no positive samples, and the others found an even distribution of positive samples among negative and positive controls. In addition, there was no correlation between which samples the two laboratories found to be positive, despite the fact they were running the same assay. On the basis of these results, the SRWG noted that no laboratory demonstrated reproducible detection of XMRV or MLV and that available assays could not reproducibly detect virus or antibodies in samples from patients previously characterized as positive. The Working Group thus concluded that

routine screening of blood donors for XMRV or other MLVs is not warranted.[67]

Since this work was published, several additional publications have reported no signs of XMRV in human blood donors[64,65,68,69] and additional publications have found no association between XMRV and CFS,[70,71] as well as further evidence that detection of XMRV in clinical samples is the result of contamination from multiple sources.[60] These reports eventually led to retractions of the two articles that reported detection of XMRV in CFS patients and control donors.[43,47]

Discussion points

1. Although several articles have shown no evidence of XMRV or MLV in human blood samples and no association between XMRV and CFS or prostate cancer, several questions are unresolved. For example, it is not clear why the detection rates in CFS samples in the two original articles observing an association[43,47] are vastly different from those in controls (although the theory that repeated sample handling of the CFS patient samples, collected in some cases decades earlier than negative controls, seems likely).
2. It is not clear whether the original studies tested cases versus controls in a blinded fashion.
3. While there is no evidence XMRV ever entered the human population, the creation of XMRV through passage of human tissue in mice does illustrate that novel threats could come not only from cross-species transfer of an agent, but also from agents generated in the laboratory.
4. The response to XMRV occurred rapidly and deliberately with respect to blood safety.

OTHER AGENTS OF POTENTIAL CONCERN

The horizon

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The classic paradigm of emerging threats to the blood supply assumes that an agent can cause persistent, asymptomatic infections in donors and that an infected donor can continue to make many infectious blood donations. Likewise, experiences with HIV and HCV have led many to assume that the next threat will spread by parenteral contact and be associated with risk behaviors. Recent agents, such as WNV and dengue, are vector borne, cause transient infections, and would cause a substantial number of transfusion-transmitted cases only if infection was highly prevalent. Moreover, the risk of infection with these agents depends more on where someone lives or travels. Potential transfusion-transmissible agents that require further investigation might be discovered through repository studies or viral discovery programs without being associated with any known disease; from agents associated with clinical disease, but not proven to be transfusion transmitted at the time they are discovered; or from zoonotic agents, such as the virus underlying SARS, that are spread to humans.

Although there was no evidence to establish that the SARS virus was transmissible by transfusion, the blood safety community mobilized when the outbreak first occurred. Likewise, there has been no evidence that recent measles outbreaks are transmitted by transfusion, but there has been enough concern for a working group to issue a fact sheet. Although arboviruses such as WNV can cause human disease and be transmitted by transfusion, the risk for such transmission will depend on their outbreak potential, and because they have complicated epidemiologies such potential cannot be predicted. Retroviruses are of particular concern because of their potential for latent infection and mutagenicity. In addition, transfusion bypasses the body's natural defenses and therefore can be a highly efficient route of transmission. Thus, even low concentrations of pathogen can be transmitted based on the volume of blood transfused. Moreover, many recipients are often immunosuppressed and can therefore develop severe clinical disease if infected.

Retrospective analyses of the response to HIV and HCV, along with concerns about public perceptions, have led to a reset of the threshold for action in responding to potential threats to the blood supply. Now, even a theoretical risk will trigger assessment and possible action. It is widely recognized that such precautionary thresholds might result in actions that will not have been indicated when complete information is available.

The AABB EID group has published a review of 68 agents in **TRANSFUSION** and updated its Web information sheets to facilitate decision making in response to an emerging threat.[34] The committee has also prioritized agents into four groups based on public health or regulatory concern and on the amount of scientific or epidemiologic evidence of blood safety risk. In addition, an expert group working with Canadian Blood Services has published a model of the risk of an emerging pathogen entering the blood supply.[72] This model predicts a prevalence rate of 4.5 per 10,000 donors (range, 1-8) for a chronic agent like HIV and 2.5 per 10,000 (range, 0.7-7.5) for an acute agent such as WNV. The model also suggests a risk period, defined as the time from the pathogen entering the blood supply to the time of effective intervention, of about 1.5 years (range, 1-2 years) for acute agents and 5 years (range, 3-10 years) for chronic agents.

In light of these concerns, case investigations including lookback, traceback, and outbreak investigations, surveillance (of organ transplant recipients and other populations at high risk for symptomatic transfusion-transmitted infection), data monitoring, and further modeling of risk are needed to evaluate emerging agents.

Animal inoculation experiments can relate levels of viremia or parasitemia to infectivity during different stages of infection, and in vitro studies can assess viability of organisms in stored blood components. NHLBI has established five linked donor–recipient repositories, and several other donor-only or recipient-only repositories are available.[73] Testing of frozen repositories with donor–recipient linkage can help to evaluate transfusion transmission and provide a historical perspective on prevalence and incidence, but these repositories are usually limited to particular geographic catchment areas and time periods, and recipient enrollment and sample collection are difficult and expensive. Therefore, prospective testing of donor cohorts is valuable.

The evaluation of emerging threats faces new challenges. Discovery programs using sensitive molecular technologies will identify new agents, some of which might appear in asymptomatic donors and have no known disease associations. Other agents discovered in this manner might be associated with disease, even though causation has not yet been proven. Stakeholders in blood safety and public health will have a mandate to maintain surveillance efforts and possibly to further investigate these agents. Animal models such as humanized mice will show infectious agent or disease transmission, but this transmission might be secondary to extensive manipulation and therefore might not be reflective of actual risk. In other cases, transfusion transmission might be theoretically possible, but the likelihood very low. Infrastructure and detailed planning processes can address these scenarios, and potential approaches might differ by scenario. Whether a general action plan can be created and tailored to an emerging threat, whether such a plan should be international, and which entities should assume responsibility are not clear, nor is it clear whether the NHLBI-funded REDS-III project or other organizations should develop a toolbox to aid in planning or whether such toolboxes already exist. Research areas such as pathogen inactivation or reduction technologies might need more attention.

TASK FORCE DISCUSSION: LESSONS LEARNED AND FUTURE RESPONSE STRATEGIES

The first challenge to addressing the implications of EIDs is identifying which agents can be transmitted. Agents whose primary transmission is inhalation or ingestion may also be transmitted by injection, including transfusion. National and international public health infrastructures focus on more common means of transmission.

Once the possibility that an agent may be transmitted by transfusion emerges, the public health and blood transfusion communities respond, relying on the experience gained over the past three decades. Blood safety experts have learned the importance of engaging all stakeholders early on in a collaborative process. They have developed an in-depth knowledge of the laboratory, animal infectivity, and epidemiologic study tools at their disposal and have developed infrastructures and resources that can be drawn upon.

The blood safety community has a variety of risk-reduction approaches, including 1) introduction of specific donor deferral criteria; 2) implementation of sensitive screening tests; 3) limiting production of blood components or derivatives likely containing the agent; 4) discontinuing collection of blood in specific geographic regions, as feasible, where the agent may be spreading; 5) improved adherence to evidence-based, conservative use of blood and components; and 6) the implementation of pathogen reduction methods.

Inherent uncertainties include identifying which EIDs pose a threat to blood safety and managing risks based on imperfect tests and incomplete data. Reducing these unavoidable uncertainties would improve future response strategies. The task force focused on several approaches: strategies to enhance early recognition of a potential threat, development of a "formalized" risk assessment and management action plan (and associated set of tools) that can be triggered as soon as a new threat is identified, structuring and coordinating additional basic and translational research to identify and better understand potential EID threats and assess risks, and the importance of training future experts.

Strategies that would allow for early recognition of a potential threat to the blood supply

When the study by Lombardi and colleagues[43] was published, stakeholders quickly took action because they recognized, early on, the potential implications of XMRV. Although several publications had previously associated XMRV with prostate cancer, recognition of XMRV as a potential threat to the blood supply was not triggered until the *Science* study noted the presence of XMRV in the blood of 3.7% of healthy controls and the more widespread recognition that XMRV was a retrovirus that—if confirmed to be present in blood—had the potential to establish a chronic asymptomatic carrier state similar to that seen with HIV and human T-lymphotropic virus.

Using XMRV as an example, the task force participants noted that current infectious disease alert systems (in this case, publication of an article and a related commentary in a prestigious journal) should be refined. The triggers for response to potential threats remain ad hoc and inconsistent, and although informatics methods are in place to identify these threats, what brings an agent to the forefront remains poorly defined. Software and global programs are available for horizon scanning, but these

systems do not have a module for blood safety; finally, it is unclear what criteria short of demonstrated transfusion transmission are relevant. Scientific publications can trigger the recognition of a potential threat, but because newly discovered agents may be patented and mitigating threats to the blood supply can be lucrative, some investigators might be led to suggest blood screening that is otherwise inappropriate. Journals such as *Science* have triggers to ensure that appropriate people have been alerted before an article is published, but this plan is in place only for findings that could be applied to bioterrorism threats. Publication of information in a more obscure journal could have resulted in a substantial delay in recognition of public health implications.

It is important to have a coherent approach to identifying and responding to potential brewing controversies that would affect an evaluation of whether or not a new EID agent is a threat. Although many were concerned about how the findings of Lombardi and coworkers were presented, those concerns were overshadowed by the finding of XMRV in almost 4% of healthy controls. Although such concerns were expressed via the Internet (as were preliminary results from other negative studies), it took time for such comments to appear in high-profile scientific journals; in the interim, the blood safety community was faced with the inability to fully evaluate these concerns until their publication.

The task force suggested the following strategies to enhance early recognition or dismissal of a new threat:

1. Create an alert system for journals to communicate with blood safety authorities about potential threats to the blood supply, before an article is published.
2. Develop a process to more quickly release information about emerging scientific controversies relevant to blood safety.
3. Include blood safety in existing public health and bioterrorism horizon-scanning systems.

Development of a "formalized" risk assessment and management action plan (and associated set of tools) that can be triggered as soon as a new threat is identified

The blood safety community is responsible for developing and initiating a risk assessment and management action plan once a new EID threat has been identified. A checklist (or decision tree) similar to that used by the Federal Aviation Administration in responding to emergencies was suggested. Such a plan must be developed simultaneously with efforts to corroborate the initial findings; development of the plan should also at least consider situations when inaction is actually the best course. An action plan can include triggers and decision points to guide theoretical actions, but these triggers could simply provide impetus for further consideration. For example, with the H1N1 influenza epidemic, decision trees were established, and stakeholders reconvened and considered potential actions each time a threshold or trigger was approached. Action plans should be flexible, because each infectious agent is different, and one response does not fit all situations. Moreover, in many cases, such as that with XMRV, critical elements of a checklist, such as the epidemiology of an agent or its association with disease, might not be known to guide next steps.

The response to XMRV illustrates the benefits of a coordinated response. A more formalized process, where all stakeholders, including representatives from the blood safety community, convene in an emergency operations center and determine scientific priorities, would ensure that blood safety is considered and optimally addressed in parallel with other epidemic response priorities. Although such processes do occur, they tend to be ad hoc and should be made more systematic.

Infrastructure to enable effective research responses exists, but is rarely tailored to the agent of interest and may not be known to those responsible for reacting to the early stages of concern. Blood donor issues in the context of disaster planning exist within the American Red Cross and America's Blood Centers, which have well-developed networks of contacts to call on in response to a threat. Much of this infrastructure is informal and remains strong only as long as experts involved in prior EID responses are engaged, active funded programs (such as the NIH-funded REDS program) are in place, and personal and institutional memory of previous experiences, such as those with HIV and HCV, exists. A formalized, systematized infrastructure could minimize the consequences of transitions in expertise and leadership and a fading collective memory. Such an infrastructure must have flexibility to respond to various circumstances.

The task force suggested the following to aid in the development of optimized risk assessment and management action plans:

1. Create action plans with clearly defined stakeholders, decision trees, and thresholds for action. These triggers can cause stakeholders to convene and consider proposed actions in light of existing and evolving evidence and craft a coherent plan for action.
2. Include blood safety when prioritizing issues in response to emergencies, epidemics, or pandemics.
3. Develop a "formalized" process that identifies existing infrastructures and resources, including networks of contacts with diverse expertise that need to be accessed or engaged should a new threat emerge.

Structuring and coordinating additional basic and translational research to identify and better understand potential EID blood safety threats and assess risks

Basic research is needed to understand whether a potential EID infects humans, the nature of the immune response in humans, the agent's animal reservoir, tissue tropism infectivity and transmissibility, where the agent will be found, whether and how long the agent survives in blood components and under what storage conditions, whether the agent is transmitted by transfusion, and if transmitted, the disease penetrance and short- and long-term clinical consequences of infection in blood recipients. Such research informs recognition of a potential threat, triggers or thresholds for action, and decisions about who should be responsible for each action. Virus discovery research programs are also beneficial as they can establish a background atlas of viruses present in the blood supply.

As illustrated by the XMRV experience, corroboration of reports indicating that an EID may be a threat by separate independent laboratories is a top priority. Large donor and donor–recipient repositories are valuable resources to evaluate transfusion transmission risks.

Optimal support of such research is complex. Existing programs that are capable of addressing public health risks are extremely valuable. The usual funding mechanisms of government agencies, such as NIH R01 grants, are slow. Recognition of a public health threat should trigger the activation of rapid funding mechanisms and/or the ability to redirect existing research program funds toward data collection, specimen banking and testing, and formal risk assessment. Mechanisms are needed to support researchers to redirect their laboratories toward addressing potential threats without risks of negative consequences to their careers and the core long-term research focus of their laboratories. The relevant DHHS agencies—NIH, CDC, and FDA—should work together to create a coherent approach to flexible funding mechanisms and identification of existing programs that can be utilized or reprogrammed as needs arise. State agencies should be involved as needed in these processes.

Newly created "rapid response" funding mechanisms would allow for flexibility and should involve the biotechnology and diagnostic industry and FDA as early as possible to enable rapid development and approval of tests and address proprietary interests. Nongovernmental, nonprofit, and private organizations can move quickly and are often best at establishing key collaborations with relevant industry partners who develop serologic and NAT screening tests. Intramural research programs at NIH and CDC have been instrumental in responding to previous threats.

The task force suggestions to facilitate EID risk assessment research included:

1. Establish processes to corroborate initial findings in separate, independent laboratories, simultaneously with the mobilization of responses.
2. Establish mechanisms to rapidly support assessments of an agent's prevalence, infectivity, associations with disease, survival in blood components, transfusion transmission capability, and removal by pathogen reduction.
3. Create or strengthen links among large recipient databases, donor–recipient repositories, and bioinformatics to track transfusion exposures and associated disease outcomes.
4. Trigger the activation of alternative rapid funding mechanisms and/or the ability to redirect existing research program funds toward data collection, specimen banking, and risk assessment if a public health threat is recognized.
5. Foster collaboration with biotechnology and diagnostics industry such that tools are available for large-scale research studies and prospective screening of blood donors, if warranted.

The importance of training future experts

One of the very highest priority items identified is training future blood safety experts. Those now entering the field have not lived through the HIV, HBV, and HCV epidemics. Formalizing and documenting existing informal response infrastructure, as accomplished by this task force report, will provide a record of a fading collective memory. The blood safety community must engage junior investigators to actively participate and to take leadership roles in future responses to EIDs.

The task force suggested that the blood safety community should:

1. Formalize and document the existing informal response infrastructure to help mitigate the effects of a fading collective memory.
2. Engage junior investigators to actively participate in responses to EIDs, including assuming leadership roles in and formalizing all aspects of the EID response effort in both government and the broader scientific and blood safety community.

Next steps

In the months after this workshop, AABB (through the EID group of its Transfusion-Transmitted Disease Committee responsible for the EID supplement[34]) agreed to lead an effort to formulate and manage such a risk assessment. The critical components outlined in this article will be integrated, for example, horizon scanning, outlines for

appropriate research studies (e.g., repository, prospective questionnaire, recipient tracing), interventions that would need to be considered, pilot studies, international participation, funding as needed, and integration into blood center operations. The involvement of individuals with a focus for planning the future is necessary to meet the major themes: recognition, risk assessment development, research, and training future experts.

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The following observed the discussions held by the task force: Amy Dockser Marcus, Writer, Wall Street Journal; Barbara R. Jasny, PhD, Deputy Editor for Commentary, Science/AAAS.

CONFLICT OF INTEREST

The authors do not have any conflict of interest with the contents of this paper.

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