Transfusion Safety in the 21st Century: How Tightly Should the Blood Community Close the Window(s)?

Louis M. Katz
Mississippi Valley Regional Blood Center, Davenport, Iowa

(See the article by Rios et al., on pages 1300–8.)

HIV was present in 1.1% of transfused blood during the early 1980s in some communities [1]. Perceived shortcomings in the response of the blood community, regulators, and public health authorities led to an exceptionally precautionary approach to transfusion-transmitted infections [2]. In return for unprecedented protection of transfusion recipients, blood donors have since been subjected to behavioral interrogation and testing, which uses 9 assays for 6 transfusion-transmissible infections, with great success.

Behavioral deferrals (blood donor deferrals for high-risk behaviors) are surrogates, usually developed in the absence of acceptable laboratory tests, and they are blunt instruments. Still, for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV), donor recruitment and interviewing reduce the prevalence of infection in donations from first time blood donors by ~80% [3], compared with the US population. Behavioral deferrals are retained after test deployment as a layer of protection against false-negative test results, test errors, and erroneous component distribution. Residual transmission still occurs, and the lack of positive and negative predictive value for donor history causes donor loss and confusion, which are potent stimuli for test development. Food and Drug Administration (FDA)–approved donor tests are among the most sensitive and specific serological tests available in any venue. By 1993, the estimated risks of missing a potentially infectious donation during the seronegative window, with tests for HBV surface antigen (HBsAg) with anti-HB core antigen, anti-HCV antigen, and/or anti-HIV antigen, fell to one in 63,000, one in 103,000, and one in 493,000, respectively [4]. Tests for human T lymphotropic virus types I and II and syphilis are also required; tests for West Nile virus (WNV) and Trypanosoma cruzi have been voluntarily adopted.

In 1996, despite clinical trials involving >500,000 donors that failed to demonstrate yield of additional infected blood donors compared with antibody assays [5, 6], HIV p24 antigen testing was required for all US blood donations [7, 8], a policy exemplary of the risk aversion dominating transfusion medicine with respect to infectious diseases. Direct viral detection was being used because of its promise to close the seronegative window between HIV infection, infectivity, and the evolution of a detectable antibody response. Nucleic acid amplification tests (NATs) were developed at the same time, after studies of multiple closely spaced samples in seroconversion panels from paid plasma donors showed NAT to be more sensitive during acute infection than antibody (and antigen) detection [9, 10]. The Commissioner of Food and Drugs urged their development in 1994, and their use was subsequently required by European manufacturers of plasma derivatives (e.g., clotting factors and intravenous immunoglobulins), to whom US blood centers provide recovered plasma. In 1999, with sufficient automation to support the throughput needed for donor screening, unlicensed polymerase chain reaction and transcription-mediated amplification assays for HIV and HCV were implemented under Investigational New Drug (IND) exemptions from the FDA [11–13]. Testing minipools (MP-NAT) of aliquots from 16–24 donations allowed the processing of millions of donations annually and the discontinuation of p24 testing, while providing adequate sensitivity for the high viremia characteristic of HIV and HCV infections prior to seroconversion. Serologic analysis continued for the detection of chronic infections. The modeled risks from these 2 viruses are now around 1 in 2 million donations [14]. HBV NAT is not widely used because contemporary HBsAg assays approach the sensitivity of MP-NAT [15], anti-HB core antigen testing.
can detect occult HBV, the incidence of HBV is falling in the United States [16], and because of the perception that, for most recipients infected by transfusion, morbidity from HBV infection is modest.

All this was a prologue to the events that occurred around Labor Day in 2002, when WNV was transmitted from a blood donor to an organ donor and then to the organ recipients, [17]. Ultimately, there were 23 transmissions from 16 blood donors reported that year [18]. In the face of a rapidly evolving North American epidemic, the urgent collaboration of the blood community, test manufacturers, public health authorities, and the FDA to protect blood recipients was the most effective partnership since transfusion became common. Donors with nonspecific symptoms consistent with West Nile infection were deferred until well, and certain products thought to be at high risk for infection were withdrawn from inventories. Applying an understanding of clinical WNV infection, viral dynamics, and the immune response, there was consensus within weeks that clinical signs and symptoms and serologic analysis were unlikely to interdict most viremic donor blood. MP-NAT offered operationally feasible, sensitive, and specific detection of the quick-clearing, acute viremia associated with the humoral immune response and could be adapted to the HIV and HCV platforms that are already used or in development. With the commitment of blood collectors and test manufacturers to implement WNV NAT rapidly, a regulatory route for the widespread use of unlicensed tests was provided via FDA-approved IND protocols. By July of 2003, virtually the entire US blood supply was being tested with 1 of 2 prototypes (both of which were subsequently licensed) as another seasonal epidemic of human WNV infection accelerated. Since then, more than 2000 viremic blood donors have been reported to the Centers for Disease Control and Prevention’s ArboNet [19], and because a single donation is processed into multiple components, many additional risky transfusions have been avoided.

Retrospective testing of individual donation aliquots (ID-NAT) from areas with MP-NAT positive donors in 2003 confirmed that WNV viremia is often of low titer, raising concern about the sensitivity of MP-NAT for this subset of donors [20, 21]. Approximately half of the viremic donors in these studies were identified only with ID-NAT; of these, 85%–93% were antibody positive. Eleven transmission incidents were recognized as arising from the 2003–2006 transmission seasons, when around 50 million blood components were transfused. Because of viremia missed by MP-NAT and additional transmission incidents, the blood community devised voluntary minimum triggers to switch from MP-NAT to ID-NAT as early as 2004, while shepherding limited laboratory capacity [22, 23], and encouraged close communication among neighboring facilities to detect WNV activity in overlapping regions. The first triggers were identification in a blood region of >1 positive MP result in a rolling 7 day period, combined with a rate >1 in 1000 donations. During 2006, there were 2 transmissions from a single donor recognized by using these triggers [24]. None were reported during 2007. Further analyses during 2007 confirmed that the rate criterion was insensitive and operationally problematic, and it has been dropped [25]. Blood regions currently trigger the switch to ID-NAT by using either 1 or 2 positive MP results, depending on capacity and local WNV activity. How is this discrepancy between undetected donor viremia and the paucity of transfusion transmission in the context of using triggered ID-NAT reconciled? How should it inform ongoing efforts to mitigate WNV risk?

First, the infectivity of blood from the bulk of donors with low-level viremia after the onset of antibody production has been questioned; there is only 1 report of transmission by seropositive (for IgM only) blood [26]. Busch et al. [27] have estimated from follow-up of infected donors that from 2003–2005, approximately 1330 seropositive, viremic units of blood components were transfused in the United States, during which time there were no reports of transmission in the presence of antibody. In this issue of the Journal, Rios et al. [28] have demonstrated that as many as half of seropositive donations that were missed during MP-NAT, including plasma from subjects with viremia below the level of quantitation, contain WNV that is infectious for Vero cells and/or monocyte-derived macrophages. They conclude correctly that antibodies do not uniformly protect susceptible cells from infection in vitro, and that viral RNA in the presence of antibody needs further investigation as a transmission risk. A conclusion the authors avoided was that more ID-NAT is required to further close the WNV transmission window.

There are few data that tell us whether the pathogenesis of infection or the innate and adaptive immune responses after intravascular inoculation are qualitatively or quantitatively altered, compared with the pathogenesis and responses resulting from peripheral inoculation, resulting in viral clearance or requiring a higher inoculum to establish infection. Viral load decreases even prior to seroconversion in infected donors; this decrease is associated with increases in markers of interferon–mediated innate immunity [29], and these innate immune responses may affect the infectivity of stored, viremic blood components. The infectious dose of WNV in a blood unit is unknown and may be high enough that current MP-NAT is sensitive enough to protect most recipients, even in the absence of passively transfused antibody.

The authors note that surveillance for transfusion-transmitted WNV is passive, so it is likely that residual transmission occurs in the absence of case reports. Most vectorborne WNV infections are asymptomatic. Most recipients infected by transfusion become ill, but when illness occurs, it is often nonspecific and unrecognized. When neuroinvasive disease
occurs and is recognized, the association with blood will be missed if clinicians do not routinely inquire about recent transfusion. That said, the use of MP-NAT in tandem with ID-NAT in accordance with current triggers renders transmission by transfusion rare.

How much effort and what quantity of resources should we expend in closing the remaining window? A 2008 WNV draft guidance from FDA would recommend year-round WNV NAT and says that “as reagent availability increases, technology advances, and personnel and logistical issues related to blood donor screening diminish, ID-NAT for all blood and blood components, using a licensed NAT year-round may become feasible and practical” (emphasis added) [30, p. 5]. It goes on to propose tightening the minimal trigger to a single positive MP result in a given region and recommends retrospective testing of archived individual aliquots when the use of ID-NAT cannot be triggered within 24 h of the positive MP result [30].

Year-round screening is already performed in the United States because since 1999, the WNV season appears to have lengthened, and isolated human infections occur in late fall and early spring [31]; also, blood center computer systems generally do not support intermittent or selective donor testing. The former reason for year-round screening is paradigmatic of our inability to define acceptable risk in the blood community, and the latter reason reflects a low tolerance for variation in blood centers with respect to the opportunities for error it presents.

Those who collect blood know they must remedy the shortcomings of information systems in anticipation of an answer to the question of “how safe is safe enough?” While cost-effectiveness analyses do not by themselves answer that question, they can provide perspective. Two groups have assessed the cost-effectiveness of WNV donor testing [32, 33], and the results suggest that even the current strategy of year-round MP-NAT and triggered ID-NAT is an order of magnitude more costly than the “acceptable” range of $50,000-$100,000 per quality-adjusted life year. This is consistent with the very high incremental cost-effectiveness of both HIV and HCV MP-NAT [34]. The argument that “there is something about blood” is used to explain and justify blood safety standards that are much more rigorous than those for other medical interventions [35].

The FDA’s mission is to protect the safety, purity, and potency of the blood supply, not to control the resources consumed in the effort to prevent every instance of transfusion-transmitted infection. That said, institutionalizing a requirement for year-round testing, increasing the stringency of triggering criteria, and advocating for year-round WNV ID-NAT when health care resources are limited is not rational public health administration, even when we believe infectious WNV is present in the antibody-positive components we miss. Such proposals should trigger wide discussion outside the blood community–FDA axis about risk, acceptable risk, resource allocation, and benefits. Creating a test for an infection picks the “low-hanging fruit.” Addressing the much more common, serious, and noninfectious hazards that are often unrecognized among the complications of an illness serious enough to justify transfusion and changing the transfusion thresholds that physicians use are more difficult tasks, but may have larger payoffs.

We have not dealt consistently with risks that are of much greater magnitude than residual WNV transmission, including transfusion-associated acute lung injury, transfusion-associated circulatory overload, putatively injurious immunomodulation, mistransfusion, and overtransfusion, in part because of the focus on rare episodes of infectious disease transmission. The response to transfusion-transmitted WNV demonstrates internalization of the lessons of HIV infection and the ability to react to emerging infections (perhaps until robust pathogen reduction technologies for blood constitute a proactive response). An effort to rationalize transfusion safety modeled on efforts from more integrated healthcare systems in Canada and the European Union [36] is being piloted. “Hemovigilance” is a surveillance and control initiative piggybacked on the National Healthcare Safety Network infrastructure that many readers of this journal have leveraged to address health care–associated infections [35]. We hope that applying consensus definitions of events of interest in a nationwide, confidential, voluntary, and nonpunitive surveillance system will facilitate evidence-based allocation of resources to the mitigation of the most important risks of transfusion—if a broad constituency can decide “how safe is safe enough?”

References

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