Zika and the Blood Supply

A Work in Progress

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- Zika virus can be transmitted by transfusion, but the harm caused to recipients is not clear in most cases. It is very likely that the virus could also be transmitted by transplanted organs. Sensitivity to the risk from transfusion is elevated by consideration of possible severe neurologic damage in fetuses. Strategies for dealing with transfusion risk vary with the presence of Zika in the region. In nonendemic areas, risks can be reduced by excluding donors who have exposure through travel or sexual contact with someone at risk. In both endemic and nonendemic areas, the risk can be further reduced by nucleic acid testing of donors, or pathogen reduction of platelet and plasma products. The real risk to the population depends on the frequency of infection as well as the efficacy of these interventions. The interventions chosen will depend on the risk assessment for any situation; in the United States at this time, a combination of travel deferrals, testing, and, to a lesser extent, pathogen reduction is being used, but universal testing of US blood donors under investigational use has been mandated by the US Food and Drug Administration, beginning with states most at risk of local transmission. Canada is largely using travel deferrals. A precautionary approach may be taken; however, a formal decision-making framework has been suggested. The situation globally is clearly very fluid, as the epidemic continues to spread and we continue to learn how to best protect recipients of blood and transplants.


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This article discusses off-label products from Roche Molecular Systems (Pleasanton, California) and Hologic/Grifols (Hologic, Marlborough, Massachusetts; Grifols, Emeryville, California). These products have not been approved by the US Food and Drug Administration and are currently being evaluated under an Investigational New Drug (IND) Application. Dr Rossmann is a Principal Investigator on the Roche Molecular Systems study, A Prospective Study to Evaluate the Specificity of the cobas R Zika test for use with the cobas R 6800/8800 System for the Screen of Blood Donations for the Presence of Zika Virus RNA. Dr Katz has no relevant financial interest in the products or companies described in this article.

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The classic transfusion-transmitted infections (TTIs), hepatitis B, human immunodeficiency virus (HIV), and hepatitis C, are chronic infections transmitted person-to-person by a set of well-understood routes and behaviors. As such, we have attempted for years to reduce their impact on blood safety by donor behavior screening, examination, and testing.1 In contrast, the threat of acute arboviral infections to transfusion safety was not appreciated until after the introduction of West Nile Virus (WNV) into the United States in 1999. It spread widely in the Western Hemisphere during several years, and in 2002 a model was published suggesting a risk of transfusing blood from viremic donors.2 At almost the same time, a case report described both transmission of WNV by transfusion from an asymptomatic donor to a trauma victim and then from that patient/organ donor to several recipients through the transplanted organs.3,4 The blood community, in collaboration with test manufacturers and the US Food and Drug Administration (FDA), responded to WNV with donor deferrals for symptoms, product quarantines and, most effectively, the development and deployment of blood donor nucleic acid testing (NAT) for WNV RNA, less than 1 year after recognition of the first transmissions.5 Subsequently, dengue, chikungunya, and Zika viruses have been evaluated as possible threats to transfusion safety.6 Zika virus has engaged the transfusion medicine community during 2016 because of its explosive spread in the Americas, and because it has been associated with serious morbidity. Zika virus fulfills the major criteria for suspicion that it may be a TTI: (1) the agent can be present in the blood of a healthy donor, (2) the agent is infectious by the parenteral route, (3) the agent survives modern processing and storage conditions for blood components, and (4) the agent causes recognizable and significant morbidity.

Most Zika virus infections (≈80%) are asymptomatic,7 but infection of pregnant women is causally associated with serious congenital injury of the fetus and newborn,8 and a broader group of patients may develop Guillain-Barré syndrome.9 The risk of these serious outcomes has provoked aggressive responses from both the AABB10,11 and the FDA.12-15

VIROLOGY AND DISTRIBUTION

Zika is a flavivirus related to dengue virus at the sequence level. It is enveloped with a 10.7-kb, positive-sense RNA genome. The virus was isolated from a febrile rhesus macaque in 1947 during yellow fever surveillance studies in the canopy of the Zika forest in Uganda. It is
Zika was subsequently recovered from *Aedes africanus* mosquitoes. Multiple species of *Aedes* support replication of Zika and may contribute to the enzootic maintenance of infection: their relative roles in transmission to and among humans are unknown, but *Aedes aegypti* (the most important vector for dengue, chikungunya, and yellow fever) is thought to be the major vector in the Americas. *Aedes albopictus*, *hensilii*, and *polyynesians* are also known to be able to transmit Zika virus.17 Monkeys and humans appear to be the only vertebrate hosts for Zika in nature, in contrast to WNV, whose amplification in diverse migratory bird populations contributed to its explosive spread in the Americas after its introduction in 1999.

Pathogenicity, as a febrile rash illness, was recognized later, in sporadic infections in Africa and South Asia.18 The infection was felt to be trivial, and extensive research waited for the explosive outbreaks in the Federated States of Micronesia (Yap Island) and French Polynesia, characterized by serologic (not necessarily clinical) attack rates of 73% and 66%, respectively.7,19 during the 2007 and 2013–2014 epidemics. Later, an association with Guillain-Barré syndrome was established in French Polynesia that saw a 20-fold increase in cases associated with the Zika epidemic.9,20

Introduction into the Americas occurred in 2013 according to molecular clock data,21 but the disease was not identified clinically until 2015, in Brazil.22 Even when the large Brazilian outbreak was recognized, interest was initially tempered by the assumed mild nature of the clinical infection. This changed in fall 2015, when temporal and geographic associations of the epidemic with an increased rate of microcephaly in infants born to infected pregnant women were recognized.23 These observations were subsequently extended to multiple countries.24 Since establishing itself in Brazil, Zika has spread to a large number of countries in Latin America and the Caribbean.25 Cases in US states to date (October 12, 2016) include 3807 travel-associated cases, 32 sexual transmissions, a single laboratory-acquired infection, and 128 local vector-borne transmissions. In US territories, there have been 25 871 locally acquired infections (25 355 in Puerto Rico) and 84 travel cases. The primary vector *A aegypti* is present in the southern tier of states especially, whereas *A albopictus* can be found even further north in the continental United States.27 Unfortunately, we are not entirely sure of the current distribution of these vectors because surveillance is incomplete. The presence of vectors and the historical occurrence of limited outbreaks of dengue and chikungunya in the continental United States and Hawaii, also spread primarily by *A aegypti*, have raised concern about autochthonous vector-borne Zika infection with subsequent transfusion transmission from asymptomatically infected blood donors.28–30 Local vector-borne transmission of Zika has occurred in very restricted areas in South Florida,31,32 the Florida Department of Health reports 153 cases as of publication, but many of the infected individuals were asymptomatic and found only in surveillance. The index patient was infected during travel to an endemic country. In response to the investigations in South Florida, the FDA advised US blood centers on July 27, 2016, to begin application of requirements in prior guidance (see below).33

**NONVECTOR TRANSMISSION**

In addition to vector-borne infection, Zika is transmitted sexually (32 US cases reported to the Centers for Disease Control and Prevention [CDC] to date), primarily from infected males but at least once from an infected female, vertically from mother to fetus, and by accidental laboratory exposure.35 Zika virus has been detected in breast milk,36 and saliva,37 but the clinical relevance of these observations is unclear. There are reports from Utah of apparent Zika transmission to a family member/caregiver of a patient, infected during travel to an endemic country, who had a very high titer of virus.38,39

**MICROCEPHALY**

Conclusive evidence demonstrates that Zika virus is transmitted from an infected mother to the fetus during pregnancy and causes fetal loss, microcephaly, and other congenital neurologic syndromes.8 Microcephaly is only one among a spectrum of adverse outcomes that characterize the congenital Zika virus syndrome.40 Zika viral RNA has been recovered from amniotic fluid, placenta, and fetal brains; in vitro, Zika virus impairs growth in human neurospheres and brain organoids, models for the neurotropism of this virus.41 Of 7830 suspected cases of congenital Zika virus syndrome reported in Brazil, investigations of 1501 live-born infants were completed by the Ministry of Health as of February 27, 2016; a total of 602 cases (40%) were classified as definitely or probably Zika virus associated.40 Several newborn babies with abnormalities were identified by neuroimaging despite normal-sized heads, demonstrating that microcephaly is only one manifestation of the congenital Zika syndrome. A case control study from Rio de Janeiro showed that fetal abnormalities occurred in 12 of 42 Zika virus–positive women studied, with infections acquired during all 3 pregnancy trimesters.42 Fetal abnormalities varied by week of gestation as identified by ultrasound; pathologic change during embryogenesis occurred at the earliest stages, but central nervous system abnormalities and most notably intrauterine growth restriction occurred at later gestational ages. A subsequent report suggests that the association of infection with microcephaly is highest in the first trimester and lower in the second and third trimesters.43 In light of these observations, long-term follow-up of infants born to infected mothers is needed to fully characterize the spectrum of congenital Zika infection and to assess the risk of transmission, via vector-borne or other routes, including transfusion, during the second and third trimesters, and the risk to neonates and infants with developing central nervous systems. The frequency of microcephalic infants among mothers infected during the first trimester was estimated at 0.95% in a retrospective study in French Polynesia.44 A much larger study in Bahia, Brazil, estimated this rate as ranging from 0.88% to 13% depending on the underlying estimates of infection rate and the accuracy of identification of the disease.45 Several cases of Zika-related microcephaly have been identified in the continental United States, with all attributed to travel-associated maternal infection.

**TRANSFUSION RISK**

In French Polynesia, 2.8% of otherwise qualified (ie, asymptomatic) blood donors had circulating viral RNA by polymerase chain reaction.46 This observation first raised the issue of transfusion transmission of Zika virus. Transmissions to 4 recipients from 3 blood donors, who were well on
the day of donation but who subsequently reported illness consistent with Zika virus infection, have appeared in various media. Two transmissions to 3 recipients have been published from Brazil.46,47 None of the recipients had signs or symptoms that could be credibly related to Zika infection. These observations have resulted in consideration of how to mitigate the risk of TTI from blood donors.

Zika plasma viremia is believed to last 1 to 2 weeks, consistent with WNV and dengue, which are both flaviviruses, and chikungunya, an alphavirus. A review and pooled analysis of 22 symptomatic Zika cases projected viral clearance in 95% of patients by 19 days (95% confidence interval, 13–80 days).48 Zika virus RNA appears to persist for a longer interval in whole blood compared with serum or plasma; follow-up testing of 5 individuals yielded detectable RNA in whole blood from 5 to 58 days after symptom onset despite RNA-negative findings in corresponding serum samples.49 Also, urine samples in this study were RNA positive from 5 to 26 days. It is well documented that Zika virus and RNA persist in urine and semen longer than in plasma. After 5 days, 82% of clinical cases remained RNA positive from urine but not serum.50 Zika RNA (not culturable virus) detection in semen for up to 188 days after symptom onset has been reported from returning travelers.51–53 The clinical significance of this persistence is unknown, but similar findings with WNV have not been associated with late transfusion transmissions from blood donors who have negative plasma RNA in routine donor screening.54 The persistence of Zika virus RNA in urine and other tissues likewise has unknown significance but has led, out of precaution, to relevant standards for organ and tissue donors.14

The risk of collecting a Zika viremic blood donation in the United States is the sum of the risks of viremia in asymptomatic donors infected during travel to epidemic foci, plus that from asymptomatic donors infected by autochthonous mosquito-borne infection, plus that from asymptomatic sexually infected donors and from other rare routes of transmission (eg, to caregivers). Accurate models of this aggregate risk are not yet available in the absence of an understanding of critical model parameters. Although it is clear that approximately 80% of infections are subclinical, incomplete ascertainment and reporting of clinical illness means that we cannot really make any precise extrapolation to the total number of infected donors. Further, early case report data cited above suggest that a substantial proportion of TTIs may be asymptomatic, so the clinical burden from transfusion may be difficult to recognize. Early models have been put forward, as discussed below.

A total of 56 cases of possible autochthonous vector-borne transmission are being investigated in South Florida at the time of this writing.31,55 These cases are associated with some risk that donor infection and asymptomatic viremia will pose a risk for transfusion transmission. Data on vector-borne dengue and chikungunya infections in the United States, viruses transmitted by the same Aedes vectors, should be informative about the characteristics of Zika transmission. Sporadic small outbreaks of chikungunya and dengue are well documented in Florida, Texas, and Hawaii, but sustained transmission is not generally recognized.29–31 This is probably due to demographic and epidemiologic circumstances that do not obtain in areas sustaining explosive epidemics. These variables include population densities, vector densities, mosquito surveillance and control strategies, and the presence of infrastructure, such as screens and air conditioning, that reduces population exposure to infected vectors, even when they are present. In 2014, local spread of chikungunya was identified in South Florida, where a total of 12 locally acquired cases were recognized (in the context of 2799 cases in the United States associated with travel to areas with epidemic chikungunya).29 No local transmission has subsequently been described. Most recent dengue cases in the continental states were acquired elsewhere by travelers or immigrants, but there has been some activity in Hawaii, Florida (especially Key West), and Texas (especially the Rio Grande Valley). By far the largest recent outbreak is in Hawaii, where 264 cases were reported between September 11, 2015, and March 17, 2016.50

Transfusion transmission of chikungunya has never been reported. Recognition of transfusion-transmitted dengue is rare, but it appears that it is often subclinical and may occur more often than is recognized. In a linked donor-recipient study during a large epidemic in Brazil, more than 0.5% of donors were viremic, and 16 viremic units were given to 16 susceptible recipients, resulting in 6 possible or probable TTIs. The infected transfusion recipients could not be distinguished clinically from uninfected controls.56 The very limited data available for Zika transmission in Brazil seem to be consistent with the dengue experience that clinical morbidity is not universal when exposure via transfusion occurs.

**RISK MITIGATION STRATEGIES**

When the public thinks of blood safety, the first question often is: “Aren’t you testing for that?” In fact, testing is only one of several strategies that can be used to reduce the risk of a TTI. Several other approaches are available and may be easier to implement quickly, may be more effective, or may be more cost-effective. Many agents can be addressed through a combination of activities.

**Conservative Transfusion**

When discussing adverse effects from transfusion it is worth noting the obvious fact that the safest transfusion is the one that is not given. Decreasing blood use in the United States is well documented.57 This seems primarily in response to the demonstration, in many studies, that clinical outcomes with conservative transfusion appear equivalent to those with liberal transfusion,58 but economic considerations may also have contributed. Unnecessary transfusion causes unnecessary risks and costs, regardless of the safety of the transfused product.

**Donor Education and Recruitment**

Appropriate education and recruitment are the cornerstones of transfusion safety in those cases where relevant data exist. In these circumstances, centers can provide donors with information that identifies their risk of infection based on demographics, behavior, and/or clinical signs and symptoms of infection. Such education can occur at the time of recruitment, or more specifically at the time and point a donor presents to donate. Self-deferral criteria for donors according to risk of Zika exposure include travel to regions with local vector-borne transmission (including areas of the United States where state and local public health authorities have declared the occurrence of local mosquito-borne transmission and notice has been posted by the CDC), sexual exposure to at-risk and infected partners, and
information about symptoms that suggest Zika infection. These approaches have the advantage of being capable of rapid implementation, even in the tightly regulated current good manufacturing practices environment at blood centers. Disadvantages include poor predictive value, resulting in the deferral of many donors who are not at real risk, and the difficulty of quantifying rates of self-deferral, and especially of classifying them as appropriate or inappropriate.

**Donor Questionnaire**

The formal donor history is a second opportunity to elicit such risks and allows quantification of the donor loss. Amending the donor history questionnaire is a complicated process in the highly regulated environment of the donor room and the current good manufacturing practices environment of blood centers. It involves drafting and evaluation of candidate questions for accuracy and understanding, training of personnel, and revisions to standard operating procedures and computer systems, with appropriate formal validations at each step. Consequently, this approach takes longer than the implementation of donor education materials. Survey research on almost 50,000 donors suggests that 28-day deferrals for travel to areas outside the United States and Canada in the Western Hemisphere, including areas where Zika is being actively transmitted, should result in the loss of approximately 2.23% of winter and 1.17% of summer donors. This proportion varies and is higher in southern states, especially their border areas, where travel to Latin America and the Caribbean is more common.

**Donor Physical Examination**

For Zika, the infected donor would be most likely to be detected, if at all, by the presence of a fever or rash. Because donors are asked not to donate unless they feel “healthy and well,” the examination is unlikely to detect many donors who would otherwise be accepted. The donor physical examination is generally of greater utility to protect donor health—for example, the detection of unrecognized hypertension—than for transfusion safety, where the focus is on stigmata of injection drug use, which is not relevant to Zika.

**Postdonation Information**

Donors are routinely encouraged to contact their blood center if they recall relevant information after donating or when illness develops in the period immediately following their donation. They are now informed specifically of the need to contact their collector if they receive a Zika diagnosis after donation. Receipt of this postdonation information allows the collector to withdraw untransfused components and to assess any need to notify the transfusion service and/or transfusing physicians about a need to evaluate recipients of implicated components.

**TESTING FOR ZIKA**

Immediately after WNV transmission by transfusion was recognized, the critical characteristics of acute arboviral infection kinetics were described: a short incubation period; and appearance, then clearance of virus and viral nucleic acid from plasma coincident with development of antibody responses that appear rapidly and persist beyond any reasonable estimate of infectivity. Accordingly, NAT, not serology, was immediately recognized as the preferred method of testing when donor screening was needed. To support the volume of testing needed and to conserve resources, minipool NAT, as used for HIV and hepatitis C since 1999, was used for WNV screening. In this method, samples from a number of donors (6–16, generally) are combined for initial screening, and the constituent individual donations are tested only if the pool is positive. This method is much less costly than individual tests, but some sensitivity is lost. With the recognition that breakthrough transmissions can occur from low-level, seronegative viremias missed in minipool NAT, strategies were developed to convert from minipool to individual donor screening NAT (ID-NAT) when WNV activity is demonstrated in a geographic region. In the United States, 2 manufacturers provide all donor NAT. Roche Molecular Systems (Pleasanton, California) uses real-time reverse transcription-polymerase chain reaction–based assays, and Hologic (Marlborough, Massachusetts), in partnership with Grifols (Emeryville, California), uses transcription-mediated amplification. Both have developed assays for Zika, although both are on testing instruments and with reagents not currently approved or in routine use in the United States. Investigational nucleic acid tests for blood donation screening were made available for voluntary implementation under investigational new drug exemptions (INDs), either using ID-NAT or a combination of minipool NAT and ID-NAT under appropriate epidemiologic circumstances, in March 2016. Zika virus active areas (US areas with mosquito-borne transmission) are required to suspend collection or to use ID-NAT.

Consistent with WNV RNA donation screening assays, the investigational NAT assays for Zika virus have 95% lower limits of detection of less than 10 copies per milliliter. The Intended Use statement of investigational tests may include “other living donors,” a term used by the FDA to differentiate donors of hematopoietic progenitor cells and some other human cells, tissues, and cellular and tissue-based product donors (referred to as HCT/Ps in FDA guidance) from blood donors. Diagnostic (as opposed to donor screening) assays for RNA and immunoglobulin (IgM) are available under Emergency Use Authorization.

Blood donation testing using ID-NAT was implemented for collections in Puerto Rico, a Zika virus active area, under the Roche IND in early April 2016, with weekly reactive rates during June 2016 exceeding 1% of tested donations. In addition, some areas of the southern United States not yet considered Zika active (but at higher risk for Zika virus spread because of the presence of the mosquito vector and persistence for long periods of suitable environmental conditions for mosquito breeding) have voluntarily implemented investigational NAT. To date, 0 of 79,000 donations from the Houston area have been confirmed positive in individual donation testing. With the recognition of local mosquito-borne Zika transmission in South Florida in late July, testing at the ID level was started there. Several unconfirmed reactive donations, primarily from Florida, are being investigated further at the time of this writing.

Donations reactive on IND RNA testing are discarded and components from prior donations within 28 days of the positive test are recalled if untransfused. Recipients of any such units are to be investigated for evidence of transfusion transmission.

Testing carried out under the IND protocol allows cost recovery by blood centers. It is critical that blood centers and the customer hospitals be in close communication regarding
the risk of active Zika transmission and the risk–benefit of voluntary donation screening, because costs may be incurred. Additionally, testing only in certain areas may lead to “mixed” inventories, with some units being tested and others not. Hospital transfusion services and their computer support may find such situations problematic. Transfusion services may choose to use tested units only in high-risk situations, such as transfusions to pregnant women or intrauterine transfusions, but such situations are not well defined.

Pathogen Reduction

A pathogen reduction technology licensed in the United States for transfusable plasma and apheresis platelets (INTERCEPT Blood System, Cerasorb Corporation, Concord, California) is effective in inactivating Zika virus as assessed by in vitro infectivity assays (>6.5 log_{10} in plasma). Similar findings in apheresis platelets have been presented (>4.2 to 6.8 log_{10} reduction of infectious virus) that are dependent on the platelet collection method.65 In corresponding RNA detection assays, greater than 10 log_{10} reduction of Zika virus RNA is observed in plasma; this would represent a margin of safety of 3 to 5 log_{10} with INTERCEPT treatment compared with reported viral copy numbers for RNA-positive donors in French Polynesia (mean, 4.85 log_{10} with 6.91 log_{10} as the highest reported value).66 These reductions are consistent with those reported for other arboviruses using the same technology. The FDA guidance permits the use of licensed or investigational pathogen reduction in lieu of cessation of collections or of investigational blood donation screening in Zika virus active areas. Lesser reductions have been presented for an alternative pathogen reduction process.67

Guidance Documents

The February 2016 FDA Guidance requires the following15:

1. Potential donors with travel to areas with local Zika transmission (including in the United States) are asked to self-defer for 4 weeks after the end of their potential exposure. Presenting donors are provided with a list of such areas and formally deferred for 28 days, well beyond the maximum duration of plasma viremia.
2. Donors with a Zika infection diagnosis are deferred for 4 weeks following complete resolution of their illness.
3. Sexual partners of males who received a Zika diagnosis, or were at risk for Zika infection, during the 3 months before an attempted donation are deferred for 4 weeks after the last such sexual contact.
4. Otherwise acceptable donors are informed to call their blood collection facility if they subsequently realize they should have self-deferred or been deferred based on such exposures, regardless of the presence or absence of symptoms, or if they have a diagnosis of Zika.

In late August 2016, the FDA revised this guidance and required testing of all donations collected in the United States and its territories with an investigational ID-NAT for Zika virus under an IND application or, when available, a licensed test. The option to use pathogen reduction was included as an alternative for those products (platelets, plasma) for which a licensed system is available. Blood collectors in states and territories with locally acquired Zika cases (at the time of guidance publication, these were Florida and Puerto Rico) were to implement such testing immediately. Eleven other states—because of their proximity to areas with locally acquired cases or because of an epidemiologic link, such as a high number of travel cases—were to implement this recommendation no later than 4 weeks after issue, that is, late September 2016. These states are Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina, and Texas. All other states are to implement the recommendations “as soon as feasible,” but within 12 weeks of the guidance issue date. Blood collectors who implemented such testing no longer had to apply the travel deferrals previously required.

This guidance requires substantially more testing than has been previously performed for any pathogen in an individual–donation format rather than a pooled format. This requires additional resources. Implementation within the specified timeline will pose operational challenges.

Scope of Risk Reduction Needed

It is possible to select Zika risk-reduced blood products only for certain recipients, or, alternatively, to use testing only for certain donors, such as those who have recently traveled to a risk area. Both approaches were in use by various collectors and hospitals prior to the latest FDA guidance. This is similar to the selective use of donor cytomegalovirus testing or application of gamma irradiation to components destined for patients recognized to be at risk for transfusion-associated graft-versus–host disease. The only recipient group that has been definitively identified as needing risk-reduced products is pregnant women, but this spectrum of risk is not fixed.

TRANSPLANTATION AND TISSUES

The apparent persistence of Zika virus in tissues other than blood has led the FDA to issue guidance for HCT/Ps that is different from those for blood.14 These rules cover many types of tissues, including skin, ocular tissue, reproductive cells and tissues, and cells derived from peripheral or cord blood. The guidance, issued March 1, 2016, for immediate implementation, identified Zika as a relevant communicable disease agent or disease. It defined as ineligible any living donor who had, within the past 6 months, a medical diagnosis of Zika virus infection, or residence in or travel to an area with active Zika virus transmission within the past 6 months, as well as sex within the past 6 months with a male who is known to have either of the preceding risk factors. Additionally, the donor of any gestational tissues (including umbilical cord blood) is ineligible if she has received a medical diagnosis of Zika virus at any point during that pregnancy; if she has resided in or traveled to an area with active Zika virus transmission at any point during that pregnancy; or if she has had sex at any point during that pregnancy with a male who has either had a medical diagnosis of Zika virus or has residence in or travel to an area with active Zika virus transmission. Cadaveric (non–heart-beating) donors are ineligible only if they have had a medical diagnosis of Zika virus in the past 6 months. It is important to note that the “ineligible” donor may be used in a number of circumstances when no comparable tissue or transplant from an eligible donor is available and the recipient is likely to suffer death or serious morbidity without the tissue, that is, when there is “urgent medical need.” The scarcity of organs for transplantation...
and the necessity of very close HLA matching for some types of transplant means that products from “ineligible” donors are used more frequently than a similar blood product would be. Special labeling is required for these products. The National Marrow Donor Program has instituted a special questionnaire to determine whether donors of hematopoietic progenitor cells are eligible; considering the importance of HLA matching for allogeneic transplants, ineligible donors may be used if the transplant center determines it is appropriate (ie, that benefit outweighs risk). Similar changes have been made to screening procedures for solid organ transplants.68

If Zika establishes local transmission over any substantial geographic area, problems arise for not only organ transplants from the area, but cord blood and other types of tissue banking activities. In light of unknown risk and absent adequate testing strategies, cord blood banks may have to suspend activities for a period. This is an area of active discussion with the FDA.69 In general, similar approaches to organ and tissue safety have been taken by the European Union, although more NAT testing of affected tissues and donors is proposed.70

APPROACHES TO RISK

Precautionary Principle

In evaluating a new threat to blood and tissue safety, the United States does not formally use a risk analysis or decision-making framework, but acts with a more precautionary approach. The precautionary principle is a theoretical one, most commonly discussed as applied to environmental issues, that states that if the harm to the public is unknown or something is not known to be safe or there is not scientific consensus, it shall be regulated as though it were dangerous. Thus, for example, we do not wait for demonstration of harm from transmission by transfusion of the Zika virus, but take steps in advance to avoid this, assuming such transfusion would be dangerous. This approach is undoubtedly related to the very painful history of the transfusion transmission of HIV in many countries in the 1980s, and is in contrast to a more formal, risk-based process that has been used elsewhere.

Risk-Based Decision Making

In the United States, transparent, formal risk analysis is not necessarily undertaken before FDA guidance regarding blood safety is considered.21 The FDA’s Zika guidelines have been issued as final, with no formal risk assessment included and without public consultation with the blood community or other stakeholders. Interventions involving considerable donor losses due to travel deferrals and/or considerable expense for testing are being implemented rapidly, based in large part on the agency’s insistence that the steps it has dictated are justified by the risk being mitigated. The blood community has developed, and advocates the public application of, a risk-based decision-making framework to rationalize these processes, making specific reference to using a broad societal perspective to consider interventions affecting a wide variety of stakeholders both from within and outside the transfusion medicine “silo.”22 This framework is sensitive to multiple contexts: the nature of the risks being considered, evolving technology, ethical issues, and competition for economic resources. Monte Carlo simulations performed by investigators at Héma–Québec and Canadian Blood Services suggest that the risk of travel-acquired (as opposed to local) donor viremia will be less than 1 in 200,000,000 with a 21-day deferral after Canadian travel to a destination with rates of Zika infection consistent with those being reported in Brazil. Applying US-specific model parameters yields a risk of 1 in 565,000 with no travel deferral and 1 in 66,700,000 with a 21-day deferral.23 If one assumes it likely that serious clinical morbidity will be confined to pregnant women being transfused early in pregnancy, the clinical risk is less than these estimates. Another model, for Australia, estimates the risk of collecting a viremic donation from a female donor infected by sexual transmission from a male partner (V. Hoad and A. Keller, written communication, February 2016). Their point estimate is 1 in 9,370,000, with a risk of symptomatic infection in the transfusion recipient of 1 in 46,800,000 and a risk of severe developmental abnormality of 1 in 1,874,000,000 in a baby born to a mother infected by transfusion during pregnancy. Such models must be refined in the future as the epidemic evolves and more precise estimates of appropriate inputs become available.

Although the risk-based decision-making framework was developed specifically for blood-collecting organizations to systematize the processes of issue identification, risk assessment, stakeholder engagement, risk communication, and decision-making, it should be adaptable to the public policy realm. Its objectives are straightforward: (1) optimal blood safety, recognizing that elimination of all risk is not possible from the standpoints of both blood supply adequacy and costs; (2) appropriate resource allocation in proportion to the magnitude and seriousness of the risk and the effectiveness of the interventions to reduce risk; and (3) explicit assessment and incorporation of the social, economic, and ethical factors that should affect decisions about risk.

CONCLUSIONS

The situation of Zika in the United States and world is changing daily, as are our knowledge and evaluation of transfusion and transplant risk. An active dialogue between all affected parties and regulators is necessary to assure the optimal outcome of a safe and adequate supply for blood, tissue, and transplant recipients.

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