



Advancing Transfusion and
Cellular Therapies Worldwide

Association Bulletin #16-07

Date: September 28, 2016
To: AABB Members
From: Donna M. Regan, MT(ASCP)SBB – President
Miriam A. Markowitz – Chief Executive Officer
Re: Updated Recommendations for Zika, Dengue, and Chikungunya Viruses

Summary

This Association Bulletin, developed by the AABB Transfusion Transmitted Diseases Committee and reviewed and approved by the AABB Board of Directors, is intended to supersede Association Bulletins #16-06 “Blood Center and Public Health Actions to Reduce the Risk of Zika Virus Transfusion Transmission” and #16-04 “Zika, Dengue, and Chikungunya Viruses.” The intent of this new bulletin is to clarify and update information and AABB recommendations in light of the Food and Drug Administration (FDA) guidance documents “[Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus](#),” published February 16, 2016 (February guidance), and “[Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components](#),” published August 26, 2016, (August guidance) classifying Zika virus as a relevant transfusion-transmitted infection (RTTI). This bulletin describes recommended actions before and after the implementation of the FDA recommendations contained in the August guidance, which are likely to be implemented under varying timetables by different blood centers based on the FDA recommendations. In addition, this bulletin provides recommendations on posting of data to the AABB Zika Virus Biovigilance Network. To access the AABB Zika Virus Biovigilance Network, click here: <http://www.aabb.org/research/hemovigilance/Pages/zika.aspx>

This bulletin also:

- Provides additional information on Zika virus including clinical outcomes following infection and reported cases of transfusion transmission.
- Discusses designation of an area as “active” following the recognition of reported cases of local mosquito-borne transmission in the United States as reported by the Centers for Disease Control and Prevention (CDC) on the “Areas with Zika” web page for “blood and tissue collection centers” available through the URL published in the February guidance document: <http://www.cdc.gov/zika/geo/index.html>. The CDC subsequently updated its web pages to provide information for “blood and tissue collection centers” at <http://www.cdc.gov/zika/areasatrisk.html>. The CDC website also provides information on Zika activity throughout the world. The designation of “active areas” is relevant only to blood centers that have not yet implemented the August guidance.

- Provides information and recommendations on postdonation information (PDI) relevant to Zika, dengue, and chikungunya viruses
- Contains minimal information for human cells, tissues, and cellular and tissue-based products (HCT/Ps). Current FDA recommendations are found in the March 7, 2016 FDA guidance document titled “[Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products](#)” This guidance identifies Zika virus as a relevant communicable disease agent or disease as defined in 21 CFR Part 1271.

Association Bulletins, which are approved by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and AABB recommendations. No new standards are proposed.

1.0 Background

1.1 Epidemiology and clinical outcomes

Zika, a flavivirus, is transmitted by *Aedes* mosquitoes, most commonly by *A. aegypti*. This same vector transmits dengue and yellow fever viruses (other flaviviruses) and chikungunya virus (an alphavirus). Another potential vector widely distributed in the United States that may transmit Zika virus is *A. albopictus*. Other routes of Zika virus transmission include intrauterine, perinatal, and sexual routes. Sexual transmission has been predominantly from infected males, but female-to-male transmission has been recognized.¹⁻³ As of August 26, 2016, a total of 17 studies or reports have been published on sexual transmission of Zika virus.⁴ Viral RNA has been recovered from urine, saliva, and breast milk, but transmission by these routes is unproven.¹ Transfusion transmission has been documented.⁵⁻⁶

Zika virus was first reported in Africa in 1947 from nonhuman primates, and subsequently from humans in Africa and Asia. It spread further to cause epidemics in the Pacific starting in 2007 on Yap Island in Micronesia, and an epidemic followed in 2013 in French Polynesia and other Pacific islands. In May 2015, Zika virus was recognized in Brazil and local mosquito-borne transmission has later been reported in numerous countries and territories in the Western Hemisphere including Mexico and almost all countries in the Caribbean and Central and South America.¹ As of August 31, 2016, active transmission has been reported in 58 areas, including 48 countries in the Americas, eight island countries in the Pacific, Cape Verde off the Western coast of Africa in the Atlantic, and Singapore (<http://www.cdc.gov/zika/areasatrisk.html>). Of note, as documented by the World Health Organization, 13 countries/territories have had evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases in 2016, or with the outbreak terminated.⁷ However, it is possible that reemergence of Zika virus infection may occur in other countries in Asia.

In the United States, there have been several thousand travel-associated cases (<http://www.cdc.gov/zika/geo/united-states.html>). Vectorial transmissions have been reported in the Commonwealth of Puerto Rico, the US Virgin Islands, American Samoa, and in South Florida where, as of September 19, 2016, 85 non-travel cases have been confirmed. An apparent

person-to-person (non-sexual) transmission in Utah has been reported in a caregiver to a Zika patient.⁸ In about 80 percent of individuals, infection with Zika virus is asymptomatic; in the remaining 20 percent, a mild febrile illness consisting of rash, joint pain, muscle pain, conjunctivitis, and headache are most commonly described.¹ However, in adults, severe complications including Guillain-Barré and other neurological syndromes have been reported.⁹ As of August 31, 2016, 18 countries/territories have reported Guillain-Barré associated with Zika virus infection.⁷

Zika virus can be transmitted from an infected mother to her fetus during pregnancy and is responsible for fetal loss, microcephaly, and other congenital neurological syndromes.¹⁰ Microcephaly is one of the possible adverse outcomes among a spectrum of conditions that may be part of the congenital Zika virus syndrome. As of August 31, 2016, 20 countries/territories have reported microcephaly or other Zika-virus-related congenital defects.⁷

Zika virus RNA has been recovered from a number of tissues including amniotic fluid, placenta, and fetal brains; in vitro, Zika virus impairs growth in human neurospheres and brain organoids, a model for the neurotropism of this virus.¹¹

Microcephaly associated with Zika virus infection in pregnant women was first described in Brazil. It is characterized by a very small skull in the affected fetus or neonate that results from interruption of growth of the brain tissue, accompanied by destruction of existing tissue, calcifications, severe cortical malformations, ventriculomegaly, cerebellar hypoplasia, and abnormal hypodensity of white matter. Through rigorous analyses, congenital Zika virus infection has been demonstrated to be the causal agent of this specific, rare phenotype of microcephaly.¹²

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; 602 (40 percent) were classified as definite or probable cases.¹³ Reported rash during pregnancy (especially early pregnancy) was positively associated with a smaller head circumference and poor survival; rash was reported in approximately 40 percent of the 183 pregnant women who delivered infants with definite/probable Zika-virus-related defects, with 77 percent reporting rash during the first trimester, 18 percent during the second trimester, and 5 percent during the third trimester. The finding of several newborn infants with abnormalities identified by neuroimaging despite normal-sized heads suggested that a strict definition of microcephaly for the congenital syndrome is too narrow. In another study, radiologic imaging of 438 fetuses or neonates in northeastern Brazil having suspected central nervous system impairment or having mothers who experienced a rash during pregnancy revealed brain abnormalities including ventriculomegaly and abnormalities to the corpus callosum and the cerebral cortex. Although most fetuses showed a reduced head circumference, others had a normal head circumference despite severe ventriculomegaly. Intracranial calcifications were most commonly seen at the gray matter–white matter junction and basal ganglia. The skull frequently had a collapsed appearance with overlapping sutures and redundant skin folds and, occasionally, intracranial herniation of orbital fat and clot in the confluence of sinuses.¹⁴

A case-control study from Rio de Janeiro showed that fetal abnormalities in 12 of 42 Zika-virus-positive pregnant women studied occurred with infections during all three pregnancy trimesters. Fetal abnormalities, as identified by ultrasound, varied by week of gestation at the time of infection; 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.¹⁰ 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.¹⁵ The frequency of microcephaly among infants of mothers infected during the first trimester was estimated at 0.95 percent in a retrospective study in French Polynesia and, in a much larger study in Bahia, Brazil, from 0.88 percent to 13 percent depending upon the underlying estimates of infection rate and the accuracy of identification of the disease.^{15,16} Several cases of Zika-related microcephaly have been identified in the continental United States, all attributable to maternal infections acquired in other countries (<http://www.cdc.gov/zika/geo/pregnancy-outcomes.html>).

1.2 Transfusion transmission concerns

It is believed that Zika virus RNA can be detected in plasma for 1-2 weeks, consistent with that of West Nile virus (WNV, another flavivirus) and dengue and chikungunya viruses. A systematic review and pooled analysis of 22 symptomatic Zika cases projected RNA clearance in 95 percent of affected patients in 19 days, with a 95 percent confidence interval of 13-80 days.¹⁷ A recent observation of unknown clinical significance is the longer persistence of Zika virus RNA in whole blood compared to serum; ie, in this study, follow-up testing of five individuals yielded detectable RNA in whole blood from 5-58 days after symptom onset despite RNA-negative findings in corresponding serum samples (in the same study, urine samples were RNA positive from 5-26 days).¹⁸ Previously, it has been well documented that Zika viremia and RNA persist in urine and semen longer than in plasma. After 5 days, 82 percent of clinical cases remained RNA positive from urine but not serum, resulting in recommended changes to guidance for diagnostic testing.^{19,20} Zika virus RNA detection in semen for 62-188 days has been reported in returning travelers, but attempts at virus isolation from these RNA-positive samples failed to demonstrate infectivity.²¹⁻²⁵

Recovery of Zika virus RNA for longer periods in whole blood vs serum or plasma is consistent with recovery reported for both WNV and dengue viruses.²⁶⁻²⁸ For WNV, of 54 subjects followed for 3 months, 42 percent remained RNA positive in whole blood but not EDTA-plasma.²⁷

The potential for transfusion transmission of Zika virus was suggested in 2014 during the French Polynesian outbreak when it was found that 2.8 percent of asymptomatic blood donors tested positive for Zika viral RNA; positive donors had a mean viral load of 4.85 log₁₀ RNA copies/mL.²⁹ To date, there are four probable cases of transfusion transmission from three Zika-infected donors in Brazil.^{5,6} All three donors reported PDI compatible with an arboviral illness that was subsequently diagnosed as Zika virus infection. None of the four recipients who acquired transfusion-transmitted Zika developed symptoms attributable to the infection; however, the consequences of a transfusion-transmitted infection to a female during pregnancy remain unknown.

AABB has posted recent information related to blood safety on the Zika Virus web page (<http://www.aabb.org/advocacy/regulatorygovernment/donoreligibility/zika/Pages/default.aspx>), including a link to the “Tracking Zika Travel Notices” table to assist blood centers responding to pre- and postdonation information, with regard to donor eligibility and inventory management decisions.

In the United States (excluding territories), as of September 14, 2016, there have been 3132 travel-associated Zika virus infections, 26 sexually transmitted cases, one laboratory-acquired case, and one case reported to the CDC in a caregiver to an infected patient.⁸ As of September 19, 2016, 85 non-travel associated cases were confirmed in South Florida (<http://www.floridahealth.gov/newsroom/2016/09/091916-zika-update.html>). On August 2, 2016, Miami-Dade County was identified on the CDC website as a Zika-virus-active area; subsequently, Palm Beach County was added. In the US territories as of September 14, the case count included 17,694 locally acquired cases and 65 travel-associated cases. Eight associated cases of Guillain-Barré syndrome have been reported on the CDC website in the United States (excluding territories) and 34 in US territories (<http://www.cdc.gov/zika/geo/united-states.html>). On August 12, 2016, the US Department of Health and Human Services declared a public health emergency for Puerto Rico in response to Zika virus <http://www.phe.gov/preparedness/Pages/default.aspx>.

At this time, the only state with confirmed local mosquito-borne transmission of Zika virus is Florida. However, other states in the southern United States may be considered at higher risk than the rest of the nation due to the presence of the mosquito vector and environmental conditions favoring transmission. At present, the risk of Zika virus transfusion transmission in the United States should be considered exceedingly small and is even smaller when a Zika virus investigational nucleic acid test (NAT)-negative unit is used.

1.3 Zika virus blood safety interventions

Investigational NAT for blood donation screening for Zika virus developed by two NAT manufacturers (Roche Molecular Systems and Hologic, Inc.) are available under investigational new drug (IND) applications. Consistent with WNV RNA donation screening assays, the investigational NAT assays for Zika virus have 95 percent limit of detection of less than 10 copies/mL.

The FDA August guidance provides recommendations for investigational individual donor NAT (ID-NAT) testing in all 50 states with variable implementation timelines described. Other options in lieu of testing include use of investigational or licensed pathogen reduction technology (PRT) (see below). Blood donation screening using investigational ID-NAT was implemented for collections in Puerto Rico, a Zika-virus-active area, under the Roche IND in early April 2016 with reactive rates reaching 1.8 percent of tested donations as of July 7, 2016.³⁰⁻³¹ In Florida, where locally acquired cases have been confirmed, investigational ID-NAT started in late July. Also, investigational NAT has been initiated in 10 states in the southern United States and Hawaii ahead of the timeline recommended in the August guidance. As of September 10, 2016, only Florida has reported confirmed-positive Zika virus infection in blood donors.

The Intended Use statement of the Hologic test includes “other living donors,” a term used by the FDA to describe donors of hematopoietic progenitor cells and some other HCT/Ps. HCT/P centers may wish to contact Hologic, Inc. regarding the use of these tests. However, according to the March 7, 2016 FDA Guidance, investigational NAT for Zika virus cannot be used to determine donor eligibility for HCT/P products

(<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf>). If performed, the results of all tests on the donor should be included in the accompanying records; the product(s) is not permitted to be labeled as Zika virus negative. Establishments should follow the labeling requirements in 21 CFR 1271, as well as any additional HCT/P labeling instructions set forth by the IND study protocol. As a precautionary note, it should be recognized that although a negative NAT result for Zika virus in a plasma sample may apply to peripheral blood progenitor cells, such a result may not reflect Zika virus levels in other HCT/P products, such as cord blood, tissues, or semen.

Diagnostic assays for RNA and IgM are available under Emergency Use Authorization (EUA) and are described on FDA’s EUA web page

(<http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmlegalregulatoryandpolicyframework/ucm182568.htm>).

A PRT licensed for plasma (INTERCEPT, Cerus Corporation) has been shown to be effective in inactivating Zika virus to the limit of detection as assessed by in-vitro infectivity assays ($>6.5 \log_{10}$ in plasma).³² Similar findings using the same technology were presented for apheresis platelets; ie, inactivation to the limit of detection, ≥ 4.2 - $\geq 6.8 \log_{10}$ reduction of infectious virus, with the range reflecting different platelet collection methods. (Cerus Corp., personal communication, June 10 2016.) In corresponding RNA detection assays, RNA \log_{10} reduction of Zika virus in plasma of $>10 \log_{10}$ RNA copies suggests a margin of safety of 3-5 \log_{10} as the result of INTERCEPT treatment when compared to reported viral loads for RNA-positive donors in French Polynesia (mean 4.85 \log_{10} ; 6.91 \log_{10} as the highest reported value).²⁹ These reductions are consistent with those observed for other arboviruses using the same technology. There are no other published or presented data available on Zika virus and PRT; however, for dengue virus, a closely related flavivirus, inactivation data have been published for another PRT technology (eg, riboflavin and ultraviolet light).³³ Those data demonstrate modest infectivity reductions for all four dengue types following treatment ($< 2 \log_{10}$).

2.0 Highlights of FDA recommendations contained in the August 26, 2016 guidance

Under an alternative procedure approved by the Director of the Center for Biologics Evaluation and Research, FDA has named Zika virus infection as a RTTI that, by definition, requires testing and other measures to further protect the safety of the blood supply. FDA has issued new recommendations that apply to Whole Blood and blood components but that do not apply to Source Plasma because viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of Zika virus. FDA also noted that solvent/detergent treatment is highly effective in clearing lipid-enveloped viruses in plasma-derived products. NOTE: A transfusable plasma product, available in the United States, manufactured using the solvent/detergent process is Octaplas (Octapharma, Vienna, Austria).

2.1 FDA Recommendations for enhanced safety procedures:

For all donations collected in the United States and its territories, FDA recommends:

- Testing for Zika virus using ID-NAT under an approved IND application until a licensed test is available; or
- Implementing PRT as an alternative to testing for:
 - platelets and plasma using an FDA-approved pathogen reduction device as specified in the Instructions for Use of the device; and
 - whole blood or red blood cells when an FDA-approved pathogen reduction device becomes available (as an alternative to testing all donations). Use of investigational PRT under an investigational device exemption may be permitted.

2.2 Implementation of donor testing

Zika virus-active-areas – Blood centers that collect Whole Blood and blood components in areas with one or more reported locally acquired mosquito-borne cases of Zika virus should implement the recommendations immediately or cease blood collection until testing or the use of PRT is implemented. When the guidance was issued on August 26, 2016, this applied to Florida and to Puerto Rico.

Areas not yet Zika virus active – The FDA recommends an implementation schedule that first targets states they have determined to be at greatest risk (these are Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina, and Texas). FDA recommended that blood centers in those states begin investigational ID-NAT within four weeks after the date of publication of the August 26, 2016 FDA guidance. These states were selected for earlier implementation based on their proximity to areas with locally acquired mosquito-borne cases of Zika virus or because of other epidemiological linkage to Zika virus, such as the number of travel-associated cases reported in a state. For all other states and US territories, FDA recommends implementing testing within 12 weeks of the date of publication of the August 26, 2016 FDA guidance.

2.3 Donor educational materials and donor health history screening

Following the implementation of donor testing and/or PRT as recommended in the August guidance, blood centers may discontinue:

- Providing Zika-related donation educational material to donors.
- Screening donors for Zika virus risk factors.

2.4 FDA recommendations for donor deferral

Blood centers should defer a donor for 120 days if:

- the donor has a reactive ID-NAT result, based on the date of testing or resolution of any symptoms, whichever is longer. The donor should be notified and counseled regarding the deferral and a possible Zika virus infection.

the donor volunteers a recent history of Zika virus infection, based on the date of resolution of symptoms or the date of a positive viral test, whichever is longer.

2.5 Labeling and product management

FDA recommended in the August guidance that blood centers update the circular of information to reflect that Zika virus ID-NAT was performed using an investigational or licensed test.

NOTE: Blood components must be labeled according to instructions provided in the specific IND protocol. The International Council on Commonality in Blood Banking Automation (known as ICCBBA) has released new ISBT-128 codes to assist with product labeling (<https://www.iccbba.org/about-iccbba/announcements/general-announcements/special-testing-general-database>).

Although not discussed in the August guidance, there will be an interval after the implementation of investigational testing when hospital transfusion services will have a mixed inventory of tested and untested products. This interval will be days for platelets, weeks for liquid RBCs and months or longer for frozen products. There is no FDA recommendation for the recall and destruction of untested products collected in a Zika-virus-inactive area. Transfusion services may consider triaging units tested by investigational NAT to those perceived to be at the highest risk from transfusion-transmitted Zika virus. Examples might include pregnant transfusion recipients, fetal recipients of intrauterine transfusions, neonates, and infants.

2.6 Quarantine and consignee notification

Following an ID-NAT-reactive test for Zika virus, FDA recommends that blood centers:

- Identify blood and blood components collected from that donor in the 120 days prior to the reactive donation.
- Quarantine and retrieve such affected prior collections.
- Notify the transfusion service of affected collections and, if transfused, advise the transfusion service to inform the transfusion recipient's physician of record.

2.7 Blood center reporting to FDA

All blood centers should update their annual reports to indicate the date of implementation of SOPs revised on the basis of the August 26, 2016 FDA recommendations.

3.0 Definition of an area with active local vector-borne transmission (Zika-virus-active areas identified by clinical case reporting) for use with February guidance

For blood centers that have not yet implemented the FDA recommendations contained in the August guidance, the February guidance provides recommended actions for blood centers when Zika virus activity, as determined by state/local public health departments, is posted to the CDC website. Current information for "blood and tissue collection centers" is found at <http://www.cdc.gov/zika/areasatrisk.html>.

There is currently no public health definition of a Zika-virus-active area that explicitly includes investigational blood donation screening results. Nevertheless, such results should be reported to

public health departments for further investigation and possible incorporation into state-specific algorithms for determining Zika-virus-active areas.

When a threshold is reached and the area is posted to the “Areas with Zika” page for “blood and tissue collection centers” on the CDC website (<http://www.cdc.gov/zika/areasatrisk.html>), the area will be defined as Zika-virus-active.

The geographic boundary of a Zika-virus-active area will be determined by the state/local public health department (an area of local transmission could be defined as a state, county, municipality, or cluster of zip codes).

4.0 Additional recommendations relevant to biovigilance and donor follow-up, PDI, and investigation of possible transfusion-related exposures

4.1 Actions recommended by AABB following a Zika virus investigational NAT-reactive test result

1. Notify the AABB Biovigilance Network site of initial reactive test results. The [AABB Zika Virus Biovigilance Network](#) will operate in a manner similar to that for WNV. Collection and testing facilities will need to assign staff responsible for information entry related to test results and other requested donation and donor data. Consult the AABB Biovigilance Network for additional information:
<http://www.aabb.org/research/hemovigilance/Pages/zika.aspx>.
2. Investigate the donor’s recent travel history and possible non-vector person-to-person exposure (independent of any public health investigation that may also occur).
3. Investigate the donor’s clinical history including the date of resolution of any reported symptoms; this information is important in deciding when the donor becomes eligible to donate.
4. Notify the appropriate public health jurisdiction of an initial reactive result and that additional information may be forthcoming.
5. Perform supplemental testing and donor follow-up consistent with methods specified in the respective IND protocols.
 - a. Methods include repeat primary NAT on an independent sample from the index plasma component, or alternate NAT and IgM antibody testing with plaque reduction neutralization testing (PRNT) in order to determine the antibody specificity, performed on the index sample or follow-up sample.

It should be noted that the results from PRNT may not be definite or clearly interpretable in persons with previous exposure to flaviviruses, especially dengue viruses.
 - b. When a determination of the donor’s infection status can be made, blood centers should update entries made on the [AABB Zika Virus Biovigilance Network](#) site allowing the most specific data to be available to the blood community.
6. Directions for sample collection and shipment to laboratories performing additional testing should be defined in investigational protocols.
7. Perform product quarantine and retrieval of in-date products donated in the prior 120 days and notify consignees.

8. Monitor the donor over the next month for his or her clinical outcome or as specified in the IND protocol.

4.2 Postdonation information relevant to Zika, dengue, and chikungunya viruses

AABB *Standards for Blood Banks and Transfusion Services* (Standard 5.3.4) requires that donors be provided written information regarding the importance of alerting their collection facilities if they become ill after donation. With regard to arboviruses (eg, Zika, dengue, and chikungunya viruses, as well as WNV), it is important that blood centers encourage donors to report signs, symptoms and diagnoses that could affect the status of units in inventory or that could require consignee notification. For dengue and chikungunya viruses, reporting PDI is important in the absence of deferral for a travel history, testing for these agents, or application of PRT.

With the implementation of ID-NAT for Zika virus or PRT, there is no longer a specific FDA recommendation to take further action for donors who report two or more symptoms suggestive of Zika virus infection (eg, fever, rash, joint or muscle pain, conjunctivitis, and headache) as part of PDI. Blood centers may choose to request the reporting of these symptoms of infection to the blood center if developed by the donor in the 2 weeks following donation so an appropriate evaluation of the suitability of the donation and eligibility of the donor may be considered.

The August guidance recommends a 120-day deferral for a donor who volunteers a recent history of Zika virus infection (see Donor Deferral above). In accordance with the August guidance, if PDI indicates a confirmed diagnosis of Zika virus infection, in-date products within the prior 120 days must be removed and consignees notified of any products collected in the prior 120 days. This does not apply to recovered plasma. Similarly, donors of such products would be deferred for 120 days after the resolution of symptoms. With regard to PDI related only to symptoms, each blood center will need to make its own evaluation as to the time intervals for consignee notification and donor deferral.

4.3 Investigating a possible transfusion-related Zika virus exposure

AABB recommends that further evaluation should occur for recipients of prior donations (ie, defined by FDA as those collected in the prior 120 days) from donors whose current donation tests reactive by a Zika virus investigational NAT assay and for both the donors and recipients when a recipient is reported to have a clinical diagnosis of Zika virus infection.

Recommendations for management of recipients of transfusions from donors who report PDI regarding a Zika virus diagnosis are described above; such recipients should be followed and offered testing (investigational ID-NAT or diagnostic assays allowed by EUAs; see below).

Testing of recipients and their associated donors should include both investigational ID-NAT and diagnostic IgM antibody assays, followed by PRNT, if IgM reactive, with the cautions noted above with respect to the interpretation of PRNT results, especially in those persons with prior dengue virus infections. If consistent with investigational protocols and if available, investigational ID-NAT should be performed; otherwise, Zika NAT and IgM diagnostic assays

cleared under EUA should be considered. Zika virus IgM assays should be those that are approved under EUA for diagnostic use. Although NAT reactivity may be of shorter duration in plasma vs whole blood or other body fluids, the enhanced sensitivity of the investigational ID-NAT assays (which are currently allowed only for plasma) justify the use of these sample types. Many of the diagnostic assays allowed under EUA are expected to have expanded claims for other body fluids including urine.

Donor and recipient samples from the index event (if available), as well as follow-up samples should be tested. Follow-up samples should be collected as soon as feasible following the notification of a recipient complication or transfusion of a component from a prior donation from a Zika-reactive donor (this is limited to components from units collected within 120 days of the reactive test result). In the event that a recipient with or without an implicated donor is found to be Zika-reactive (NAT and/or IgM), the state/local public health laboratory should be informed as it may wish to conduct a further investigation.

Associated donors with nonreactive investigational ID-NAT results will be cleared and thus eligible to donate. Implicated donors who test investigational NAT reactive should be deferred for 120 days from the reactive test date and cleared for future donation if a subsequent sample tests Zika-ID-NAT negative by one of the two investigational tests. The IgM status of the donor is used for diagnostic purposes and does not influence the donor's eligibility.

Zika Resources

FDA

February 2016 guidance document for blood donors

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf>

March 2016 guidance document for HCT/P donors

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf>

August 2016 guidance document for blood donors

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf>

Emergency Use Authorization web page

<http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmlegalregulatoryandpolicyframework/ucm182568.htm>

CDC

Areas at Risk posted for Blood and Tissue Collection Centers

<http://www.cdc.gov/zika/areasatrisk.html>.

<http://www.cdc.gov/zika/geo/index.html>.

Zika virus home page; contains the CDC Draft Interim Zika Response Plan

<http://www.cdc.gov/zika/index.html>

Web page for Zika virus case counts in the United States

<http://www.cdc.gov/zika/geo/united-states.html>

Zika virus information for blood and tissue collection centers

<http://www.cdc.gov/zika/blood-tissue-collection-centers.html>

AABB

Zika Virus web page, including a link to Tracking Zika Travel Notices table

<http://www.aabb.org/advocacy/regulatorygovernment/donoreligibility/zika/Pages/default.aspx>

AABB Zika Virus Biovigilance Network

<http://www.aabb.org/research/hemovigilance/Pages/zika.aspx>

ICCBBA

<https://www.iccbba.org/about-iccbba/announcements/general-announcements/special-testing-general-database>

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