Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-06

Date: August 16, 2016
To: AABB Members
From: Donna M. Regan, MT(ASCP)SBB – President
Miriam A. Markowitz – Chief Executive Officer
Re: Blood Center and Public Health Actions to Reduce the Risk of Zika Virus Transfusion Transmission

Summary

This Association Bulletin, developed by the AABB Transfusion-Transmitted Diseases Committee, is intended to supplement Association Bulletin #16-04, "Zika, Dengue, and Chikungunya Viruses," that provided information about:

- The potential for transfusion-transmitted Zika virus infections.
- The Food and Drug Administration (FDA) February 16, 2016 guidance document titled "Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus" available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf including the three recommendations listed below.
    - Recommendations for altering the donor history questionnaire for active or inactive areas to include Zika Additional Questions.
    - Recommendations to facilitate self-deferrals due to travel/residence, sexual contact or a Zika virus diagnosis or Zika-related symptoms.
    - Postdonation information (PDI) materials and recommendations for collection facilities and transfusion services in response to PDI received from donors.

This bulletin provides additional information on Zika virus including clinical outcomes following infection, reported cases of transfusion transmission and activities to be undertaken in response to the event of local transmission of Zika virus in the United States, or in advance in areas at perceived high risk for local transmission. It also 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 FDA guidance documents: http://www.cdc.gov/zika/geo/index.html. The CDC web site also provides information on Zika activity throughout the world.

This Association Bulletin contains recommendations including the:

- Availability and use of investigational blood donation screening tests for Zika virus.
- Use of licensed or investigational pathogen reduction technologies (PRT) for inactivating Zika virus.
- Actions following the recognition of local transmission as a result of voluntary investigational blood donation testing programs.
- Posting of data to the AABB Zika Virus Biovigilance Network.
    - Access to the AABB Zika Virus Biovigilance Network will be announced in a separate communication.

This bulletin contains minimal information for human cells, tissues, and cellular and tissue-based products (HCT/Ps). Current FDA recommendations are found in a March 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" available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf. 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 for distribution 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 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] Viral RNA has been recovered from urine, saliva, and breast milk, but transmission by these routes is unproven.[1] Transfusion transmission has been documented.[4-5]

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 15, 2016, active transmission has been reported in 56 (mostly tropical) areas, including 47 countries in the Americas, eight island countries in the Pacific, and Cape Verde off the Western coast of Africa in the Atlantic. http://www.cdc.gov/zika/geo/index.html.

In the United States, there have been numerous travel-associated cases; vectorial transmissions have been reported in the Commonwealth of Puerto Rico, the US Virgin Islands, American Samoa, and most recently in South Florida where, as of August 12, 2016, 28 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. http://www.cdc.gov/media/releases/2016/s0718-zika-utah-investigation.html. 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. [6]

Zika virus can be transmitted from an infected mother to the fetus during pregnancy and is responsible for fetal loss, microcephaly and other congenital neurological syndromes.[7] Microcephaly is one of the possible adverse outcomes among a spectrum of conditions that may be part of the congenital Zika virus syndrome. 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.[8]

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.[7]

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.[9] 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 of definite/probable cases, with 77 percent reporting rash during the first trimester, 18 percent during the second and 5 percent during the third trimesters. The finding of several newborn infants with abnormalities identified by neuroimaging despite normal-sized heads suggests that a strict definition of microcephaly for the congenital syndrome is too narrow.

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.[11] 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.[12] 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.[13] 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 post symptom onset despite RNA-negative findings in corresponding serum samples (in the same study, urine samples were RNA positive from 5-26 days).[14] 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.[15,16] 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.[17-21]

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.[22-24] For WNV, of 54 subjects followed for 3 months, 42 percent remained RNA positive in whole blood but not EDTA-plasma.[23]

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 $\log_{10}$ RNA copies/mL.[25] To date there are four probable cases of transfusion transmission from three Zika-infected donors in Brazil.[4,5] 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 to a female during pregnancy remain unknown.

Recent information related to blood safety is posted by the AABB on the Zika Virus web page at http://www.aabb.org/advocacy/regulatorygovernment/donoreligibility/zika/Pages/default.aspx, including a link to the "Tracking Zika Travel Notices" table to assist blood establishments responding to pre- and postdonation information, and donor eligibility and inventory management decisions.

In the United States (excluding territories), as of August 10, 2016, there have been 1955 travel-associated Zika virus infections, 22 sexually transmitted cases, one laboratory-acquired case, and one case reported to the CDC in a caregiver to an infected patient. As of August 15, 2016, in the absence of identifying any positive mosquitoes, 28 non-travel associated cases were confirmed in South Florida. http://www.floridahealth.gov/newsroom/all-articles.htm. As of August 2, 2016, Miami-Dade County has been identified on the CDC website as a Zika-virus-active area. In the

US territories, the case count includes 6587 locally acquired cases and 31 travel-associated cases. Six associated cases of Guillain-Barré syndrome have been reported on the CDC website in the United States (excluding territories) and 20 in US territories (http://www.cdc.gov/zika/geo/united-states.html). As of August 12, 2016, the U.S. Department of Health and Human Services has 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, where transmission has been confined to a very localized area in Miami-Dade County. http://www.floridahealth.gov/newsroom/all-articles.htm. However, other areas of Florida and 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 investigational nucleic acid test (NAT)-negative unit is used (see Section 1.3 below).

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 applications (IND) either using individual donation (ID)-NAT or a combination of minipool (MP)- and ID-NAT. Zika-virus-active areas are required to use ID-NAT if blood centers choose to perform investigational NAT. Other options in lieu of testing include use of investigational or licensed PRT (see below) or cessation of collections, as recommended by the February 2016 FDA guidance. 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 reactive rates reaching 1.8 percent of tested donations as of July 7, 2016.[26,27] In South Florida, where locally acquired cases have been confirmed, individual donation testing is also occurring. Also, some areas of the southern United States, not yet considered to be Zika active (but at higher risk for Zika virus spread due to the presence of the mosquito vector and the environmental conditions required for year-round mosquito breeding) have implemented investigational NAT. Consistent with WNV RNA donation screening assays, the investigational NAT assays for Zika virus have 95 percent lower limits of detection of less than 10 copies/mL.

The Intended Use statement of one of the two investigational tests 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 the IND holder (Hologic, Inc.) regarding the use of these tests. However, according to the March 2016 Guidance for Industry, the use of 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 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 while 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).[28] 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 demonstrated reflecting different platelet collection methods. (Cerus Corp., personal comm., 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).[25] 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 (e.g., riboflavin and UV light).[29] Those data demonstrate modest infectivity reductions for all four dengue types following treatment (<2 $\log_{10}$). FDA guidance permits the use of licensed or investigational PRT (should such be approved by FDA either for RBC or whole blood) in lieu of investigational blood donation screening or cessation of collections in Zika-virus-active areas.
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf.

A solvent/detergent-treated plasma product (Octaplas, manufactured by Octapharma in Vienna, Austria) is available in the United States. While data specifically showing its efficacy against Zika virus are not available, the FDA noted that "… ZIKV is likely cleared by the existing viral inactivation and removal methods that are currently used to clear viruses in the manufacturing processes for plasma-derived products. For example, these viral clearance steps for various products may include pasteurization, solvent/detergent (S/D) treatment and incubation at low pH..."
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf.

2.0 Definition of an area with active local vector-borne transmission (Zika-virus-active areas)

2.1 Zika-virus-active areas identified by clinical case reporting

The February 2016 FDA guidance provides recommended actions for blood establishments when Zika virus activity, as determined by state/local public health departments, is posted to the CDC "Areas with Zika" page for blood and tissue collection centers:

http://www.cdc.gov/zika/geo/index.html. The authority for designating an area as Zika virus active and reporting this to the CDC rests with state/local public health departments and not with CDC. At present there is no nationally mandated or uniform definition for states to use. Two proposed definitions for states to report Zika activity to the CDC to designate an area as active are listed below. States have the option to use either definition or to create their own.

- Two infections reported to and verified by a state public health department as non-travel- or sexual contact-related occurring within 14 days [as defined in the document from the Council of State and Territorial Epidemiologists (CSTE), "CSTE Proposal for Blood Bank Notification of Zika Virus Transmission Areas" (http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/PDFs/PDFs2/CSTEProposalforBloodBankNoti.pdf)].
- Two cases excluding travel or sexual contact occurring within 45 days [as described in the "CDC Draft Interim Zika Response Plan" (http://www.cdc.gov/zika/pdfs/zika-draft-interim-conus-plan.pdf)].

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. See Attachment #1.

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/geo/index.html), the area will be defined as Zika virus active, and blood establishments should follow the recommendations in the February 2016 FDA guidance.

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).

2.2 *Removing the designation of Zika-virus-active area*

In the February 2016 FDA guidance, no criteria were established for reversing the designation of an area of active transmission. However, information on reversing a designation of active area can be found in the section on "Discontinuing the Designation of a Zika Transmission Area" in the "CDC Draft Interim Zika Response Plan" (http://www.cdc.gov/zika/pdfs/zika-draft-interim-conus-plan.pdf), which provides:

> "States, with assistance from CDC as needed, should continue to assess the likelihood of ongoing local transmission, on at least a weekly basis, during mosquito season. The designation of a Zika transmission area will end (and the area will be removed from the interactive CDC map) on the CDC's "Areas with Zika" web page (http://www.cdc.gov/zika/geo/index.html) when no new cases of local Zika virus transmission are identified in or around the Zika transmission area for a period of 45 days, or when environmental conditions are not conducive to mosquito transmission. This timeline allows for three mosquito (extrinsic) incubation periods (the time from when a mosquito acquires Zika virus from an infected human to the time it is capable of

transmitting the virus to a new human host) and suggests that Zika virus transmission is no longer ongoing."

3.0 Zika virus investigational NAT

3.1 Considerations for implementation of Zika virus investigational NAT

Blood centers in high-risk areas (states of the southern United States where *A. aegypti* is active and environmental conditions support viral replication year-round) may consider implementation of Zika virus investigational NAT, even in the absence of local transmission, based on the following:

1. 80 percent of Zika-virus-infected individuals are asymptomatic, and the illness is generally mild compromising case ascertainment. Both observations reduce the sensitivity of clinical surveillance, so that reliance on the reporting of clinical cases to the public health department is not likely to be sensitive enough to detect the earliest time at which local mosquito-borne Zika transmission has occurred in a particular geographic area.
2. Zika viral RNA has been detected in asymptomatic blood donors.
3. Zika virus is most likely transfusion transmitted (four probable cases to date from Brazil).
4. Zika viral RNA may persist in plasma for 1-2 weeks. In whole blood (compared to plasma or serum), it may persist for 1-2 months, although it seems unlikely (based on experience with WNV) that a donation from an infected individual could transmit Zika virus infection during the latter part of that time.
5. IND applications are available from two NAT manufacturers.
6. Investigational NAT is not needed for collections that are treated with licensed or investigational PRT methods, the latter under an Investigational Device Exemption.

3.2 Overview of actions based on Zika virus investigational NAT

Additional actions to be taken in areas with Zika NAT-reactive blood donations are currently at the discretion of blood centers or within investigational protocols as this scenario has not been addressed in FDA guidance or by the CDC. One possible criterion that would trigger further action would be the detection of one NAT-repeat-reactive donation in which travel, sexual, or other non-vector person-to-person transmission has been excluded. Further actions include implementing investigational ID-NAT, expanding ID-NAT if a blood center is already testing to include a greater percentage of its collections; or, if performing MP-NAT (as currently allowed by one investigational protocol), converting to ID-NAT. Blood centers may also consider the implementation of PRT (licensed or investigational).

All Zika virus investigational NAT-reactive donations should be entered into the AABB Zika Virus Biovigilance Network that will contain a map indicating Zika virus investigational NAT-reactive donations and reports providing additional information. The information plotted on the United States map that is part of the Network will provide initial reactive results by residential zip code; the size of a given symbol will be proportional to the number of cases reported. Each Zika virus NAT-reactive notification to the Network will result in AABB sending a blast email

to all subscribers (ie, similar to the WNV notification process). Further information about the Network is provided in Section 3.3 below.

Once a donor is identified as having acquired a locally transmitted infection based on the blood center's evaluation of the donor's travel and excluding other risk factors, this information should be used to update information about this donor that was previously entered into the Zika Virus Biovigilance Network (ie, updating an initial reactive entry). Distinction of Zika-reactive donations in active (per the CDC website) vs inactive areas will be available in accompanying reports within the Network. State/local public health agencies will be notified by blood centers of blood donors testing reactive by investigational tests; as such, the public health agencies will likely conduct their own investigation, and if confirmed as local mosquito-borne transmission, the information will be forwarded to the CDC and potentially posted at the discretion of the state/local public health department using the appropriate geographic area (see Section 2.1 above) on the "Areas with Zika" web page for blood and tissue collection centers (http://www.cdc.gov/zika/geo/index.html).

Until the time that a specific geographic location has been identified as a Zika-virus-active area by the CDC, or FDA issues additional recommendations, blood centers should consider whether to use investigational donation testing results and/or individual clinical case reports to define the geographic area that they consider appropriate for further action. Blood centers that are already testing in a restricted geographic area may consider expanding their area and those that are not yet testing may consider test implementation. The decision for testing should be communicated to other blood centers that collect in contiguous or overlapping areas. The associated testing data for NAT-reactive donations submitted by blood centers will be found on the Zika Virus Biovigilance Network.

3.3 Immediate recommended actions following a Zika virus investigational NAT-reactive test result

This section applies to testing that is done at the discretion of the blood center whether or not collections occur in an area designated by the CDC as Zika virus active.

1. Notify the AABB Biovigilance Network site for 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; see Attachment #1. Consult the AABB Biovigilance Network for additional information. AABB will release the URL, for the Network, in a separate communication.
2. Enter the donor into the deferral and counseling protocol (and/or referral for evaluation and counseling).
3. Investigate the donor's recent travel/non-vector person-to-person exposure (independent of any public health investigation that may not be timely enough for appropriate actions on the part of collection facilities).
4. Notify the appropriate public health jurisdiction of an initial reactive result (noting that supplemental testing will follow); see Attachment #1.

5. Consult with public health agencies, and when additional information on risk factors is known, determine whether a geographic area should be reported by public health to the CDC to identify that area as Zika-virus-active based on investigational blood donation screening test results; see Attachment #1.
6. Perform supplemental testing consistent with methods specified in the respective IND protocols. 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. 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 4 weeks and notify consignee.
8. Monitor the donor over the next month for his or her clinical outcome.

3.4 Donor reentry

Blood centers should consult with their IND sponsors with respect to donor reentry.

3.5 Labeling

Multiple blood centers are testing for Zika virus RNA by NAT under IND applications allowed by the FDA. As part of the INDs, FDA requires that test-negative blood components be labeled as "negative for Zika virus by an investigational test," with this verbiage added to each test-negative blood product label (ie, ISBT 128 or equivalent label). The FDA has also recommended additional labeling (via a labeling supplement or modification of the *Circular of Information*) to state "Units labeled as negative for Zika virus RNA were tested with an investigational nucleic acid test (NAT) and found to be nonreactive."

3.6 Investigating a recipient exposure

AABB recommends that further evaluation should occur for recipients of prior donations (ie, those collected in the prior 4 weeks) from donors who test reactive on their current donation by a Zika virus investigational NAT assay and for both the donors and recipients when a recipient subsequently reports a Zika virus clinical diagnosis.

Recommendations for management of recipients of transfusions from donors who report PDI regarding a Zika virus diagnosis are contained in Association Bulletin #16-04; 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 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 4 weeks 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 negative investigational ID-NAT results will be cleared and thus eligible to donate. Implicated donors who test investigational NAT reactive should be deferred for 4 weeks 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.

4.0 Summary of variance requests granted by FDA to existing (February 2016) guidance

Variance requests may be submitted to the FDA to modify any step in an FDA guidance. Blood centers have been successful to date in obtaining the variances listed below. The actions described below cannot be taken until a blood center has received specific approval from the FDA to do so.

1. Zika-virus-active areas: For blood centers performing investigational ID-NAT or having implemented PRT, the requirement to implement two additional donor screening questions (ie, those related to the donor's sexual contacts and Zika-virus-related symptoms or a diagnosis in the donor) has been waived.
2. Zika-virus-active areas: If an entire state is posted to the "Areas with Zika" web page (http://www.cdc.gov/zika/geo/index.html) on the CDC website, but blood centers wish to apply blood safety interventions on a smaller geographic area, they can do so if they collaborate with the appropriate public health jurisdiction to define a more appropriate at-risk area.
3. Zika-virus-inactive areas: A blood center will be allowed to collect and release blood donations made by donors who otherwise would be temporarily deferred based on the answers to the Zika-virus-related travel questions, provided a sample from their donation tests negative by an investigational ID-NAT.

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

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/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 & tissue collection centers – resources
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

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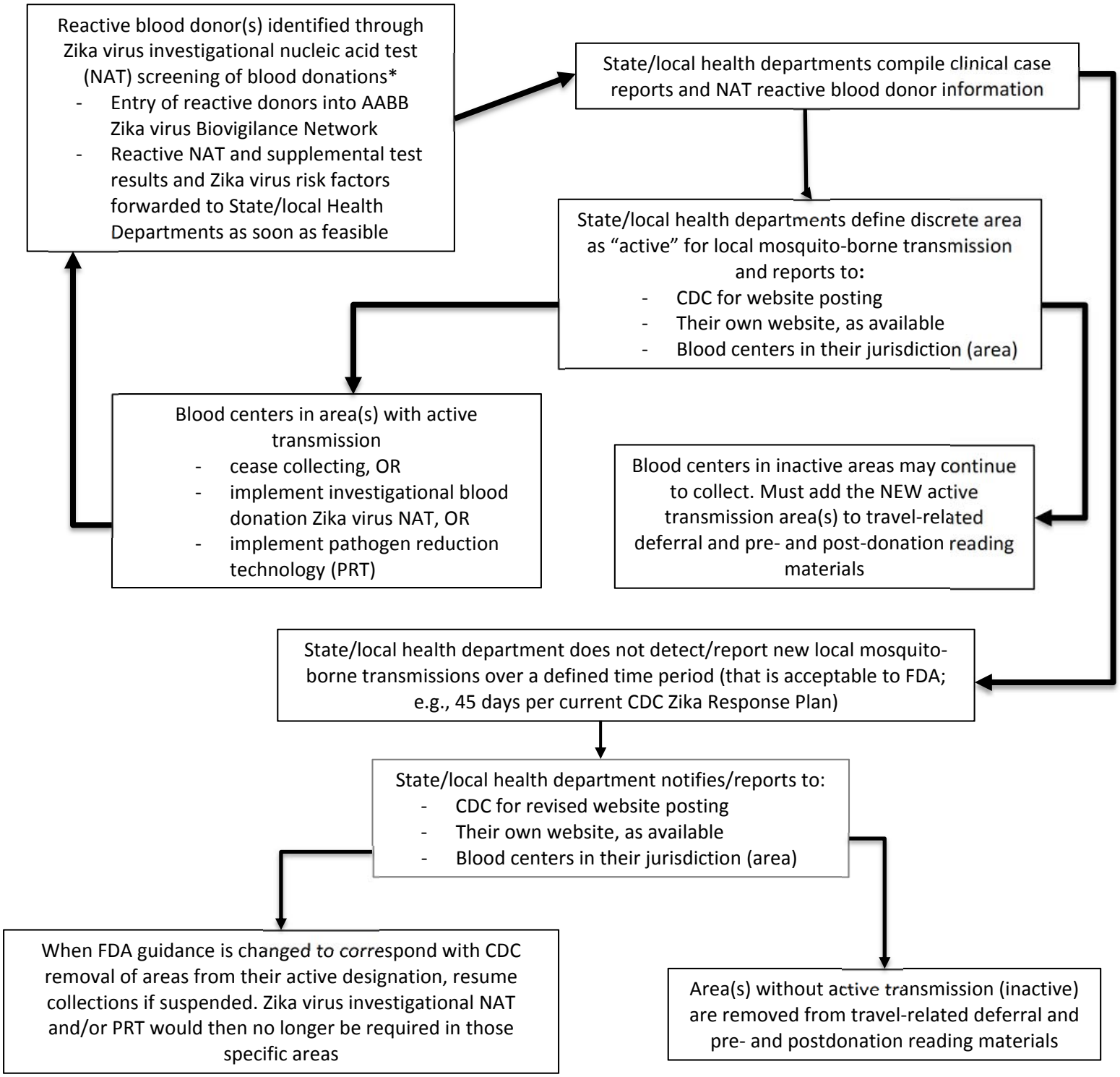
Attachment 1

Zika virus Reporting: Suggested interactions between Blood Centers and State/Local Public Health Departments including reporting by Blood Centers to the AABB Biovigilance Network



*Includes 1) proactive blood donor screening for all donors or for selected donors or 2) blood donor screening conducted in active areas (posted to CDC.gov)