Blood Products Advisory Committee Meeting
FDA White Oak Campus, Silver Spring, MD
March 20-21, 2019

Topic: Re-evaluation of Strategies to Reduce the Risk of Zika Virus (ZIKV) Transmission by Blood and Blood Components

Issue: FDA seeks advice from the Committee on whether testing blood donations for Zika virus (ZIKV) using minipool nucleic acid testing (MP NAT) with defined criteria to switch to individual donation testing (ID NAT) remains an appropriate strategy to reduce the risk of transfusion-transmitted ZIKV, or whether screening blood donations for ZIKV can be discontinued in some or all U.S. states and territories, now that local mosquito-borne transmission has subsided in the U.S. and abroad.

The BPAC will hear presentations on ZIKV epidemiology and the status of ZIKV in the U.S., on the U.S. experience with screening blood donations for ZIKV with MP NAT and ID NAT, and on possible donor screening options for ZIKV or their discontinuation.

Background:

A. ZIKV Epidemiology and Experience during Outbreaks

ZIKV is an enveloped, single-stranded RNA arbovirus in the *Flaviviridae* family (genus *Flavivirus)*, closely related to West Nile virus (WNV) and dengue virus (DENV). Like DENV and chikungunya virus (CHIKV), an alphavirus, ZIKV is primarily transmitted by *Aedes* mosquitos, most commonly *Aedes aegypti* (1).

Local transmission of ZIKV in the U.S. and its territories was reported in Puerto Rico in December 2015, in Florida in July 2016, and in Texas in November 2016 (2–4). In addition to vector-borne disease, ZIKV infection occurs through other routes of exposure, including perinatal, intrauterine, sexual, laboratory-acquired, and blood-borne transmission (1, 5–9). The number of clinical ZIKV disease cases in the U.S. peaked in July-August 2016 with over 5,000 cases reported in the U.S. states and over 36,000 in Puerto Rico (Figures 1 and 2) (4).

During recent ZIKV outbreaks, asymptomatic infection of blood donors has been documented and transfusion-transmission of ZIKV has occurred. At the peak of the 2016 outbreak in Puerto Rico, about 1.8% of blood donations were reactive for ZIKV by ID NAT (10,11). Three cases of probable ZIKV transfusion-transmission were reported in Brazil from two donors who had symptoms a few days after donating blood and whose retained serum samples subsequently were tested and found positive for ZIKV RNA (8,9). During the French Polynesian outbreak in 2013, a retrospective study identified 30 ZIKV RNA-reactive blood components that were transfused to 26 recipients, with follow-up completed on twelve of the patients (12,13). None of the

transfusion recipients in this report or other published cases to date developed ZIKV-related symptoms after transfusion.

The number of ZIKV cases has decreased substantially in 2017 and 2018, not only in the U.S. but also worldwide (4). Despite the dramatic decrease in reported cases, ZIKV prevalence and incidence in the U.S. and abroad is unpredictable, as is observed for other viruses transmitted by the same mosquito vectors as ZIKV. For example, about several hundred locally-transmitted (autochthonous) DENV disease cases have been reported over the last 9 years in 3 states, with considerable variability from year to year. In addition, autochthonous CHIKV disease has occurred sporadically in Florida and Texas in 2014-5.

B. FDA Policies to Address Transfusion Risk from ZIKV

FDA first issued guidance in February 2016, with recommendations specific to areas without or with active (local, vector-borne) transmission of ZIKV (14). Beginning in March 2016, Puerto Rico obtained blood and blood components from unaffected areas of the continental U.S. and in April 2016 initiated ID NAT under IND using the cobas Zika test.

FDA issued revised guidance in August 2016 to address the exceptionally urgent, uncertain, and evolving situation, taking into account the potentially severe consequences of ZIKV infection. FDA recommended universal ID NAT or pathogen reduction for indicated blood components (i.e., platelets, plasma) using a risk-based phased approach for implementation (15). At that time, there were over 8,000 cases of locally-acquired ZIKV infection in Puerto Rico, 2,245 travel associated cases in U.S. states, and 14 locally-acquired, mosquito-borne cases in Florida.

Nationwide and territorial implementation of universal ID NAT effectively intercepted over 400 potentially infectious units from asymptomatic blood donors in Puerto Rico and U.S. states between April 2016 and December 2017 (16). Subsequently, the ZIKV outbreak in Puerto Rico and affected U.S. states dramatically subsided by the end of 2017. Similarly, the number of ZIKV cases in Brazil and the Americas has significantly decreased (17).

On December 1, 2017, BPAC reviewed the available data on ZIKV blood donor screening and the evolving epidemiology in the U.S. and discussed alternatives to universal ID NAT to provide an adequate and appropriate safeguard against the current and future risk of ZIKV transmission through blood transfusion (18-23). BPAC unanimously determined that the incidence and prevalence of ZIKV did not support continued universal ID NAT in the U.S. or its territories. The committee, however, was also unanimous in its recommendation that blood establishments should not stop testing for ZIKV in the U.S. and its territories. A majority of the committee members supported the use of MP NAT year-round in all U.S. states and territories, with defined criteria to switch to ID NAT when local mosquito-borne ZIKV transmission is suspected or documented in a defined geographic collection area. Discussing additional testing options, the committee was split almost evenly on whether MP NAT should be discontinued completely in

states that lack the mosquito vector. The committee generally agreed that other donor screening options such as using ID NAT to test donors who report possible exposure to ZIKV through travel or sexual contact or providing ID NAT-negative blood components to selected patients based on clinical indications (e.g., pregnant women, intrauterine transfusion, neonates) were not feasible or acceptable.

Taking the BPAC discussion into consideration, FDA updated the testing recommendations in a revised final guidance in July 2018 (16). The current recommendations allow screening using either MP NAT or ID NAT, but require ID NAT when certain threshold conditions are met that indicate an increased risk of suspected mosquito-borne transmission in a defined geographic collection area.

As stated in the July 2018 guidance, FDA may update the recommendations as warranted, based on available epidemiologic and scientific evidence affecting the risk of ZIKV transmission by blood and blood components.

C. Current Status of ZIKV in the United States and its Territories

1. Clinical cases of ZIKV since 2016

Since the 2016 outbreak that recorded over 5,000 ZIKV disease cases in U.S. states and over 36,000 in Puerto Rico, the number of ZIKV cases decreased considerably in 2017 and 2018 (Figure 1) (4).

Based on final U.S. data reported by CDC's ArboNET for January 1, 2017 through December 31, 2017, states reported 452 symptomatic ZIKV disease cases of which 437 cases were in travelers returning from affected areas, 7 cases were acquired through presumed local mosquito-borne transmission in Florida (n=2) and Texas (n=5), and 8 cases were acquired through other routes. U.S. territories reported 666 symptomatic ZIKV disease cases, all except one acquired through presumed local mosquito-borne transmission (4).

The number of cases decreased further in 2018. Based on provisional U.S. data reported by CDC ArboNET as of January 2, 2019, in 2018 states reported 64 ZIKV disease cases in travelers returning from ZIKV-affected areas and territories reported 116 cases acquired through presumed local mosquito-borne transmission (4).

As of this writing (February 4, 2019), there are no active areas of ZIKV transmission in U.S. states; however, Puerto Rico and other U.S. territories are still identified on the CDC world map as areas with risk of ZIKV infection (https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika).

2. Rate of detection of ZIKV in blood donors since 2016

Based on final data reported by the AABB Zika Biovigilance network, there were 407 and 412 NAT-reactive donations for ZIKV in 2017 and 2018, respectively, with the highest density of reporting in Florida, Georgia and Alabama. AABB will provide detailed information about these data to the Committee. (24)

Discussion:

Consideration of Alternatives to Universal Donation Testing for ZIKV in the U.S.

Given the available information about the decline of ZIKV in the US and the Americas, FDA is re-evaluating its July 2018 recommendations on testing blood donations for ZIKV using MP NAT or ID NAT. (Use of an FDA-approved pathogen reduction system for plasma or platelet components would remain an acceptable alternative to testing donations for ZIKV and is not further discussed in this issue summary on testing options.)

FDA seeks advice from the Committee on the following testing strategies:

1. No policy change at this time; continue universal donation testing for ZIKV using MP NAT or ID NAT, as described in the July 2018 guidance, but reassess the policy periodically.
2. Discontinue testing in most states but maintain testing for ZIKV using MP NAT or ID NAT in certain states and territories that have had documented local mosquito-borne transmission of ZIKV (i.e., Florida, Texas, Puerto Rico, U.S. Virgin Islands); in states where the mosquito vector is present and that accounted for about 85% of ZIKV-reactive donations by travelers returning from ZIKV-affected areas during the 2016 outbreak (i.e., Florida, Texas, California, New York); and/or where there has been documented transmission of other *Aedes*-borne arboviruses (DEN, CHIK) (i.e., Hawaii, U.S. territories).
3. Eliminate all testing for ZIKV pending another significant outbreak in the United States or its territories.

FDA is not recommending predonation assessment for ZIKV risk factors, such as possible exposure to ZIKV through travel or sexual contact. Most infected persons and their sexual partners are asymptomatic and unaware that they have been infected. Further, as the outbreaks in the Americas have subsided, many countries no longer perform active ZIKV surveillance.

Option 1: No Policy Change at this Time

Continue universal testing for ZIKV using MP NAT or ID NAT as described in the July 2018 guidance, but reassess the policy periodically.

Pro:

- Provides nationwide monitoring for blood donors with asymptomatic infection resulting from all modes of ZIKV transmission (e.g., local vector-borne, sexually-transmitted and travel-related cases).

Con:

- Maintains a resource-intensive approach, placing burdens on the blood system in the face of significantly diminished or absent risk (25).

Option 2: Regional Testing for ZIKV with MP NAT or ID NAT

Discontinue testing in most states, but maintain testing for ZIKV using MP NAT or ID NAT in some, or all, of the following states or territories:

- **Florida, Texas, Puerto Rico, U.S. Virgin Islands** where documented local, mosquito-borne ZIKV transmission has occurred;
- **California and New York** where the mosquito vectors are present, and the states accounted for a significant proportion of the ZIKV-reactive donations from travelers returning from ZIKV-affected countries during the 2016 outbreak;
- **Hawaii, U.S. territories** where the mosquito vectors are present and documented transmissions of other *Aedes*-borne arboviruses (DEN, CHIK) have occurred

  Pro:
  - Reduces the volume of testing and alleviates burden in states with low or absent risk of mosquito-borne ZIKV transmission
  - Continues testing in areas of highest risk of ZIKV cases from local mosquito-borne ZIKV transmission and with high numbers of returning travelers.
  - Maintains capability to rapidly respond to re-emergence of ZIKV in U.S. states and local outbreaks

  Con:
  - Regional burden on the blood system for testing donations for ZIKV in the face of significantly diminished risk

- Will not detect an outbreak if one occurs in states that are not testing and will not detect ZIKV infections among returning travelers or sexual contacts in states that are not testing

Option 3: Eliminate All Testing for ZIKV in Areas with No Risk of ZIKV Infection

Eliminate all testing for ZIKV without re-introduction of donor screening for risk factors (e.g., travel) in areas with no risk of ZIKV infection, pending another outbreak in the United States.

Pro:

- Provides relief from ZIKV testing when ZIKV risk is substantially reduced or absent
- Increases the availability of resources for other blood safety initiatives

Con:

- Reduces preparedness against possible resurgence of the ZIKV epidemic
- Will not prevent transfusion transmission of ZIKV and poses risk of ZIKV complications among at risk patients (primarily pregnant women)

Questions for the Committee:

1. At this time, do the available data support continuing universal testing for ZIKV using MP NAT or ID NAT, as recommended in the July 2018 Final Guidance (no policy change at this time) (Option 1)?

2. If the answer to Q1 is "No," do the available data support a year-round regional testing strategy for ZIKV using MP NAT or ID NAT in at-risk U.S. states and territories (Option 2)?

3. If the answer to Q2 is "Yes," please comment on regional testing in the following states and territories:

    a. **Florida, Texas and Puerto Rico, U.S. Virgin Islands** where documented local, mosquito-borne ZIKV transmission has occurred

    b. **California and New York** where the mosquito vectors are present, and the states previously accounted for a significant proportion of the ZIKV-reactive donations from travelers returning from ZIKV-affected countries

    c. **Hawaii, U.S. territories** where the mosquito vectors are present and documented transmissions of other *Aedes*-borne arboviruses (DEN, CHIK) have occurred

4. If the answer to Q2 is "No," do the available data support the elimination of all testing for ZIKV without re-introduction of donor screening for risk factors (e.g., travel) in areas with no risk of ZIKV infection, pending another outbreak in the United States (Option 3)?

Summary Table of ZIKV Testing Options

Option	Recommendation	Arguments Pro	Arguments Con
1	No policy change (universal MP NAT with ID NAT trigger)	• Nationwide coverage against all modes of ZIKV transmission (e.g., local vector-borne, sexually transmitted- and travel-related cases)	• Maintains resource-intensive approach of MP NAT/ID NAT trigger strategy placing burden on the blood system in the face of significantly diminished or absent risk
2	Regional testing for ZIKV using MP NAT or ID NAT in at-risk states or territories; discontinue testing in all other states	• Reduces testing volume • Testing would continue in the areas with the highest risk of ZIKV • Maintains capability to rapidly respond to local outbreaks	• Maintains testing of blood in areas of the U.S. when there are no reported cases of ZIKV • Will not detect an outbreak if one occurs in states that are not testing and will not detect ZIKV infections among returning travelers or sexual contacts in states that are not testing
3	Eliminate all testing for ZIKV without re-introduction of donor screening for risk factors (e.g., travel) in areas with no risk of ZIKV infection, pending another outbreak in the United States	• Provides relief from ZIKV testing when risk is substantially reduced or absent • Increases the availability of resources for other blood safety initiatives	• Provides no safeguard against ZIKV transfusion transmission • Reduces preparedness against possible resurgence of the ZIKV epidemic

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Figure 1: Provisional data for laboratory-confirmed symptomatic Zika virus disease cases with illness onset in 2016-2018, reported to ArboNET by US states (excluding territories). https://www.cdc.gov/zika/reporting/case-counts.html

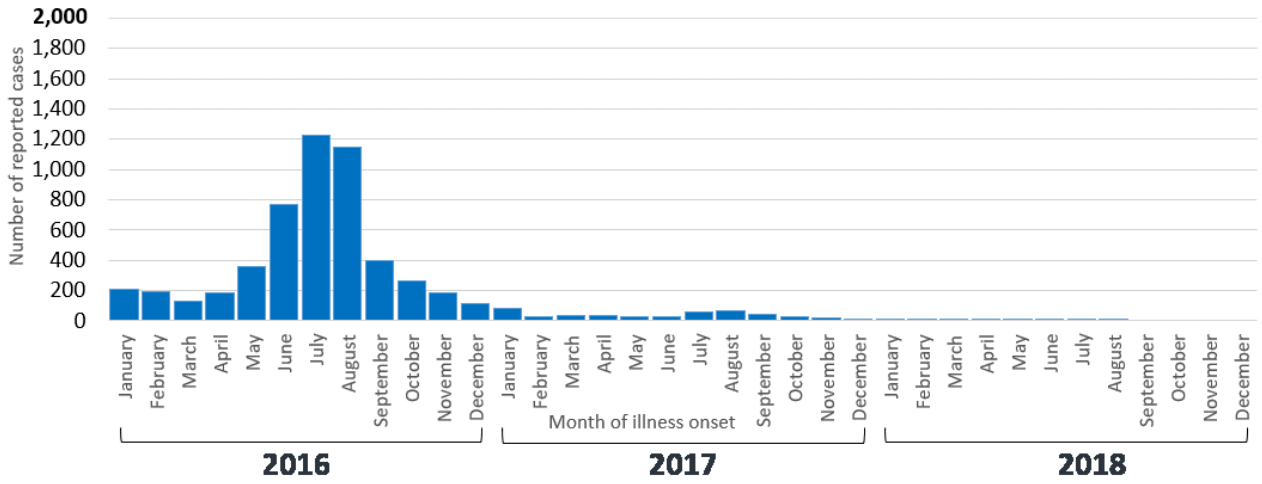

Figure 2: Laboratory-confirmed symptomatic Zika virus disease cases* with illness onset in 2016–2018, reported to ArboNET by territories – United States (provisional data as of October 3, 2018 https://www.cdc.gov/zika/reporting/case-counts.html