U.S. FOOD & DRUG ADMINISTRATION

Screening of Cord Blood Donors for Zika Virus Infection

Advisory Council on Blood Stem Cell Transplantation
September 10, 2019

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Office of Tissues and Advanced Therapies
CBER/FDA

Topics

- HCT/P Donor Eligibility Requirements
  (21 CFR part 1271, subpart C)
- Current FDA Recommendations for Identifying ZIKV Risk Factors for Donors of HCT/Ps
  - Guidance, Risk Communications, Zika Tests
- Summary

What are HCT/Ps?

- Human cells, tissues, and cellular and tissue-based products
  - Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient (§ 1271.3(d))

- Examples:
  - Musculoskeletal tissue
  - Cardiovascular tissue
  - Skin
  - Dura mater
  - Ocular tissue
  - Reproductive cells & tissues
  - Placenta/amnion
  - Cellular-derived therapeutic products (e.g. pancreatic islets, mesenchymal stem/stromal cells, fibroblasts)
  - Hematopoietic Stem/Progenitor Cells (HPCs) derived from peripheral or cord blood

HCT/P DONOR ELIGIBILITY REQUIREMENTS

Donor Eligibility

21 CFR 1271.45(b,c)

- A donor eligibility (DE) determination is based on screening and testing of HCT/P donors for relevant communicable disease agents or diseases (RCDADs)
- A DE determination is required for all HCT/P donors, except as provided in § 1271.90
- An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, except as provided in §§ 1271.60(d), 1271.65(b), and 1271.90

When is a Donor Eligible?

21 CFR 1271.50(b)

- Donor screening (described in § 1271.75) must indicate that the donor:
  - Is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases; and
  - Is free from communicable disease risks associated with xenotransplantation
- Donor testing results for relevant communicable disease agents (described in § 1271.80 and §1271.85) must be negative or nonreactive, except as provided in § 1271.80(d)(1)

Current RCDADs

Disease Agent or Disease	Applies to	Screening	Testing
HIV-1 and -2	All HCT/Ps	X	X
Hepatitis B Virus	All HCT/Ps	X	X
Hepatitis C Virus	All HCT/Ps	X	X
Syphilis	All HCT/Ps	X	X
TSE	All HCT/Ps	X	
Sepsis	All HCT/Ps	X	
Vaccinia (recent smallpox vaccination)	All HCT/Ps	X	
WNV	All HCT/Ps	X	X (seasonal, Living Donors)
ZIKV	All HCT/Ps	X	
HTLV-I and II	Viable, leukocyte-rich HCT/Ps	X	X
CMV*	Viable, leukocyte-rich HCT/Ps		X
Chlamydia trachomatis	Reproductive HCT/Ps	X	X
Neisseria gonorrhea	Reproductive HCT/Ps	X	X

*CMV is not an RCDAD. Donors of viable leukocyte-rich HCT/Ps must be tested for CMV, and positive test results must be communicated to the responsible physician.

Exceptions in 21 CFR Part 1271

- Use of HCT/Ps from an ineligible donor (§ 1271.65(b)):
  - Allogeneic use in a 1st or 2nd degree blood relative
  - Directed reproductive donors (§ 1271.3(l))
    - Donor of reproductive cells or tissue to a specific recipient, and who knows and is known by the recipient before donation
  - Urgent medical need (UMN) (§ 1271.3(u))
    - No comparable HCT/P is available, and the recipient is likely to suffer death or serious morbidity without the HCT/P

    Note: HPCs from ineligible donors that are intended for hematopoietic stem cell transplantation generally qualify for the UMN exception.

★Special labeling & notification requirements (§ 1271.65(b)(2)-(3))

HCT/P Regulatory Framework: Cord Blood

- Under the regulatory framework for HCT/Ps, minimally manipulated umbilical cord blood products for unrelated allogeneic use are regulated as biological products under Section 351 of the Public Health Service Act and the Food, Drug, and Cosmetic Act; and subject to premarket review requirements
- The requirements for Biological License Application (BLA) or use under an investigational new drug application (IND) became effective October 20, 2011*
- The donor eligibility requirements in 21 CFR part 1271 are applicable to donors of cord blood

- Cord blood BLA guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bla-minimally-manipulated-unrelated-allogeneic-placentalumbilical-cord-blood-intended-hematopoietic

HCT/P Regulatory Framework: Cord Blood

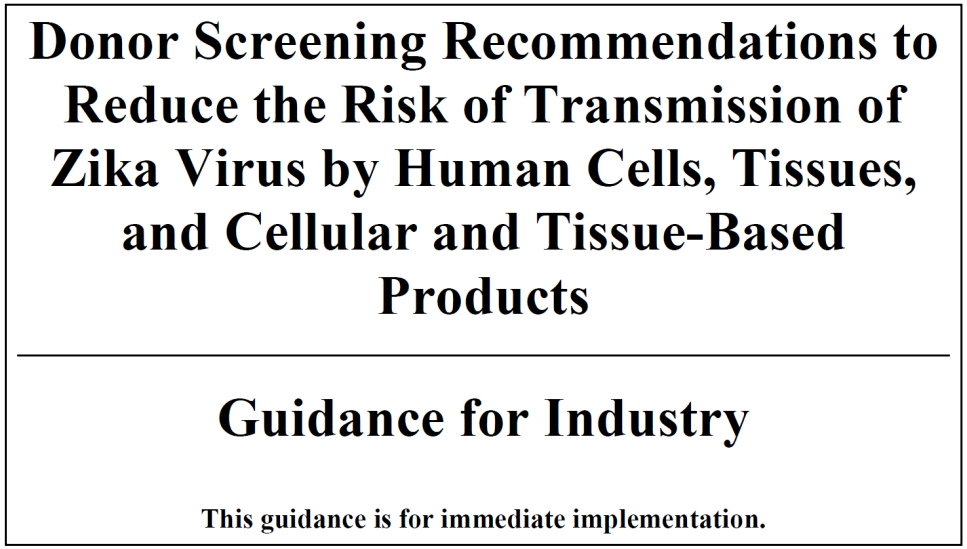
- Unlicensed cord blood units may be used under an IND because FDA recognized the importance of patients having continued access to the best matched available cord blood unit that may not meet all the licensure requirements but may be otherwise suitable for transplantation*

- Cord blood from ineligible donors may be used for hematopoietic stem cell transplantation under an IND (exception in § 1271.65(b)(1)(iii))

* Cord blood IND guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bla-minimally-manipulated-unrelated-allogeneic-placentalumbilical-cord-blood-intended-hematopoietic

ZIKV GUIDANCE AND RISK COMMUNICATION

ZIKV Guidance



Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products

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Guidance for Industry

This guidance is for immediate implementation.

- Published on March 1st, 2016:
  - Identified ZIKV as an RCDAD for all donors of HCT/Ps
  - Included recommendations for screening HCT/P donors for ZIKV
- Updated guidance document published in May 2018:
  - The update supports the continuation of recommendations to screen living donors of HCT/Ps for risks of infection with ZIKV based on geographic areas with risk

ZIKV-Guidance- May 2018

- Information updated by:
  - providing findings from more recent epidemiological studies including impact on public health;
  - reporting new data that informs the potential for transmission of ZIKV;
  - discussing the current status of availability of ZIKV tests;
  - updating sexual contact risk factors;
  - updating when an area is considered to have an increased risk for ZIKV transmission; and,
  - providing additional scientific references.

ZIKV Guidance – May 2018

Living donors of HCT/Ps should be considered ineligible if they have any of the following risk factors:

1. Medical diagnosis of ZIKV infection in the past 6 months.
2. Residence in, or travel to, an **area with an increased risk** for ZIKV transmission within the past 6 months.
3. Sex within the past 6 months with a **person** who is known to have either of the risk factors listed in items 1 or 2, above.

ZIKV Guidance – May 2018

Additionally, donors of umbilical cord blood, placenta, or other gestational tissues should be considered ineligible if the birth mother who seeks to donate gestational tissues has any of the following risk factors:

4. Medical diagnosis of ZIKV infection at any point during that pregnancy.
5. Residence in, or travel to, an **area with an increased risk** for ZIKV transmission at any point during that pregnancy.
6. Sex at any point during that pregnancy with a **person** who is known to have either of the risk factors listed in items 1 or 2, above.

ZIKV Guidance – May 2018

The following non-heart-beating (cadaveric) donors should be considered ineligible:

- Persons with a medical diagnosis of ZIKV infection in the past 6 months.

ZIKV Guidance – May 2018

- Appropriate testing measures to prevent the transmission of ZIKV through HCT/Ps are not available at this time
  - Currently available Nucleic Acid Tests (NATs) are designed to detect ZIKV RNA in plasma isolated from a donor blood specimen
  - Blood plasma NAT alone is not sufficient to determine whether a donor's HCT/Ps may be infected with ZIKV.
  - ZIKV is readily detected in HCT/Ps, such as semen and umbilical cord blood or other gestational tissues, after viral RNA is no longer detectable in plasma
- Appropriate screening measures exist so you must screen donors of HCT/Ps for risk factors for, and clinical evidence of, infection with ZIKV (§ 1271.75(a))

ZIKV Tests

- Viremia often resolves within 3-5 days after symptom onset (significant outliers have been reported)
- Currently, two ZIKV-NATs are available that have been licensed by FDA to detect ZIKV RNA in plasma specimens
  - High sensitivity
  - High specificity but false positives do occur
  - As disease incidence decreases, positive predictive value decreases and false positives increase despite high specificity
  - Tests package inserts explain that ZIKV RNA may persist in certain organs and tissues, as well as other body fluids, longer than it is detectable in plasma and serum
  - For this reason, FDA does not provide recommendations on testing HCT/P donors

Donor Testing

- If an HCT/P donor is tested with a ZIKV NAT assay:
  - Results are part of donor's relevant medical records
  - A donor with a reactive or positive test must be determined ineligible ((§ 1271.75(a)&(d))
  - Because ZIKV can be detected in some HCT/Ps after RNA is no longer in plasma; a nonreactive plasma NAT does not assure that recovered cells or tissues are not infected with ZIKV and a nonreactive test does not override any risk factors for ZIKV identified*
  - FDA continues to recommend screening HCT/P donors for ZIKV risk as stated in the current Zika guidance updated in May 2018, and to not rely on test results*

*Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products, Guidance for Industry. Published March 2016, Updated May 2018

Donor Testing

- FDA is committed to working with manufacturers interested in developing tests for HCT/P donors and will consider appropriate recommendations for use of such tests upon their availability

Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products, Guidance for Industry. Published March 2016, Updated May 2018

ZIKV Guidance – May 2018

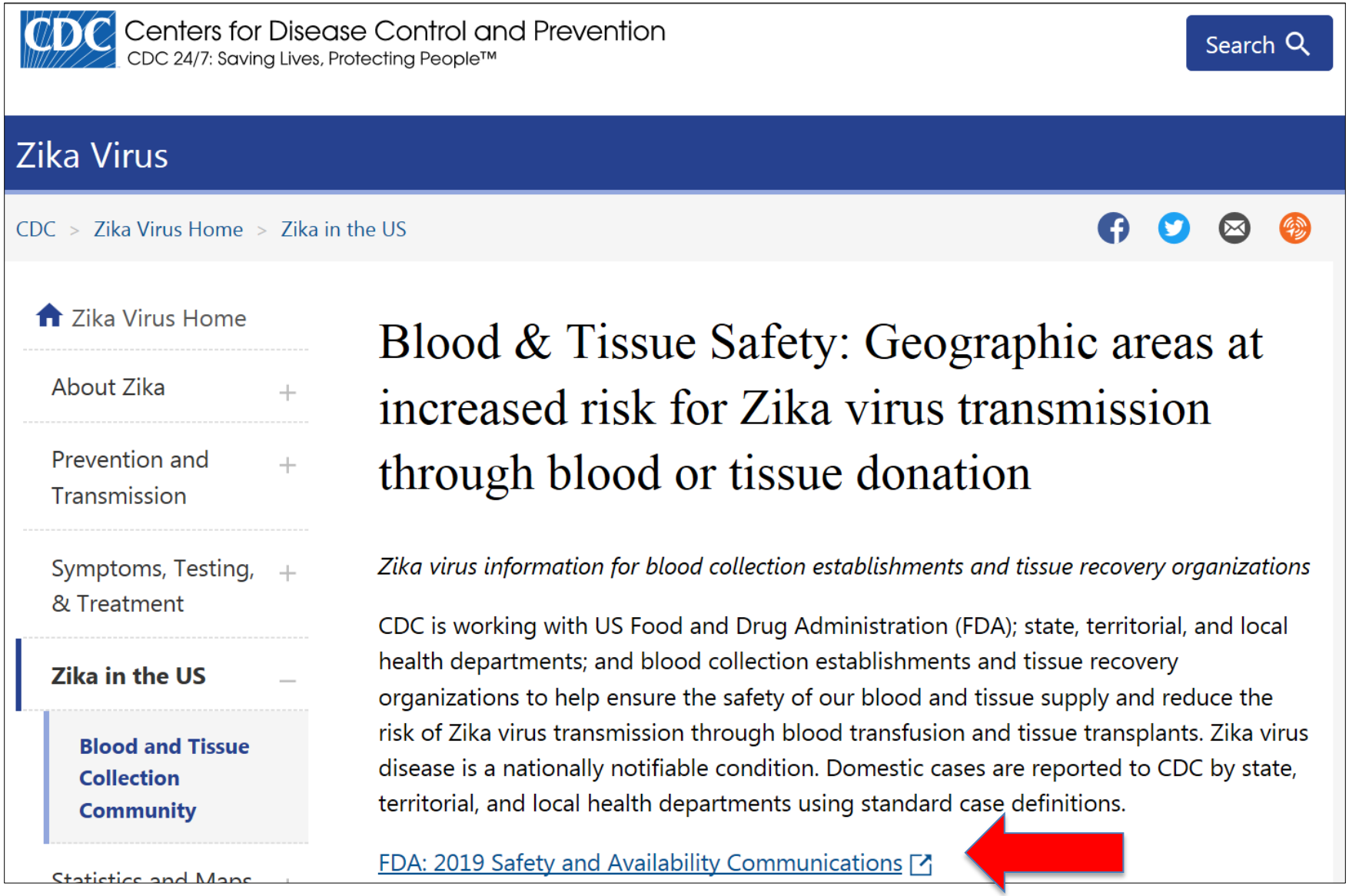
ZIKV Epidemiology

In general, an area is considered to have an increased risk for ZIKV transmission when locally transmitted, mosquito-borne ZIKV has been reported or the potential is suspected based on epidemiological evidence. See the Centers for Disease Control and Prevention (CDC) website for Blood and Tissue Safety:

https://www.cdc.gov/zika/areasatrisk.html

Note: Prior to May 2018, CDC website identified areas with "active ZIKV transmission"

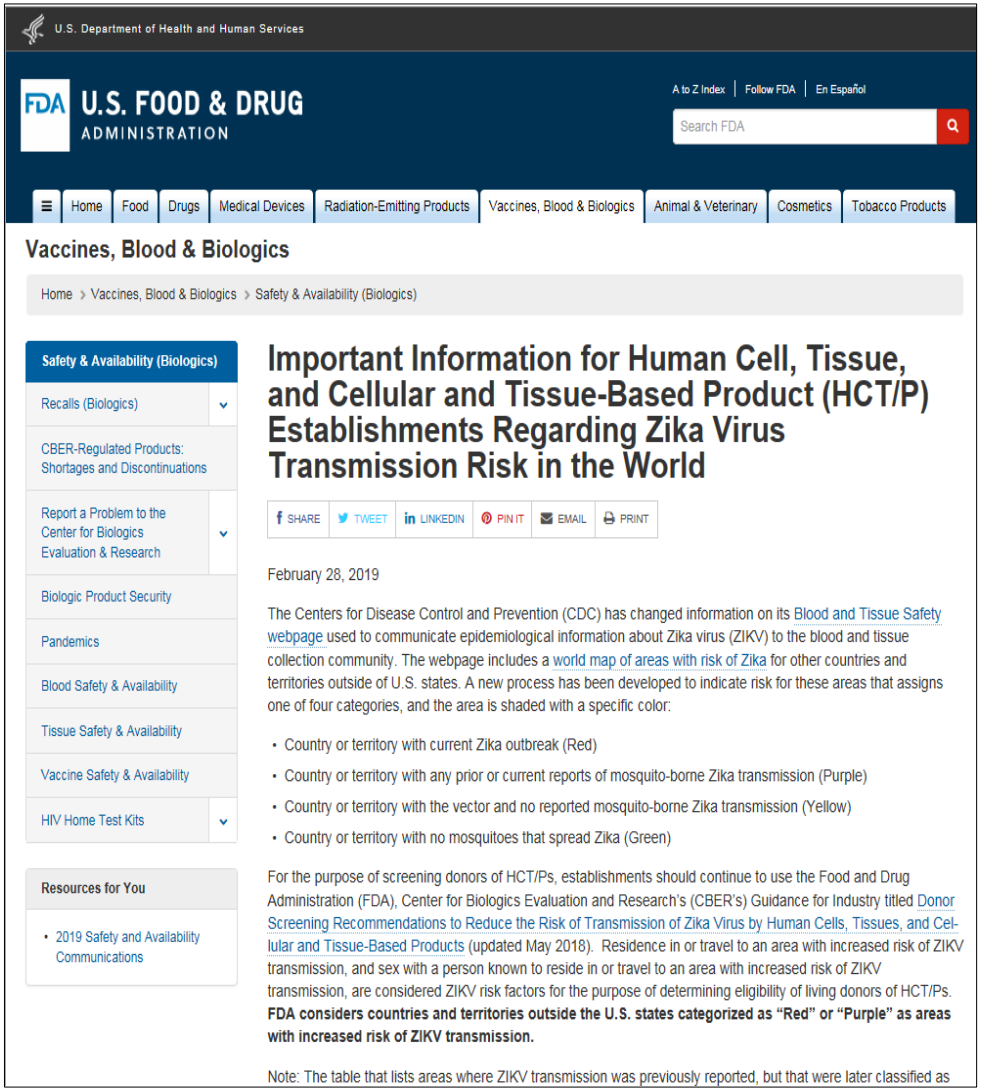
Website updated 2-28-2019



https://www.cdc.gov/zika/areasatrisk.html

FDA Safety and Availability Communication Related to ZIKV – February 2019

- A new process has been developed by CDC for the World Map to indicate risk for areas outside the US states. It assigns one of four categories, and the area is shaded with a specific color:
  - Country or territory with current Zika outbreak (Red)
  - Country or territory with any prior or current reports of mosquito-borne Zika transmission (Purple)
  - Country or territory with the vector and no reported mosquito-borne Zika transmission (Yellow)
  - Country or territory with no mosquitoes that spread Zika (Green)
- **FDA considers countries and territories outside the U.S. states categorized as "Red" or "Purple" as areas with increased risk of ZIKV transmission**



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Resources for You

- 2019 Safety and Availability Communications

Important Information for Human Cell, Tissue, and Cellular and Tissue-Based Product (HCT/P) Establishments Regarding Zika Virus Transmission Risk in the World

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February 28, 2019

The Centers for Disease Control and Prevention (CDC) has changed information on its Blood and Tissue Safety webpage used to communicate epidemiological information about Zika virus (ZIKV) to the blood and tissue collection community. The webpage includes a world map of areas with risk of Zika for other countries and territories outside of U.S. states. A new process has been developed to indicate risk for these areas that assigns one of four categories, and the area is shaded with a specific color:

- Country or territory with current Zika outbreak (Red)
- Country or territory with any prior or current reports of mosquito-borne Zika transmission (Purple)
- Country or territory with the vector and no reported mosquito-borne Zika transmission (Yellow)
- Country or territory with no mosquitoes that spread Zika (Green)

For the purpose of screening donors of HCT/Ps, establishments should continue to use the Food and Drug Administration (FDA), Center for Biologics Evaluation and Research's (CBER's) Guidance for Industry titled Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (updated May 2018). Residence in or travel to an area with increased risk of ZIKV transmission, and sex with a person known to reside in or travel to an area with increased risk of ZIKV transmission, are considered ZIKV risk factors for the purpose of determining eligibility of living donors of HCT/Ps. **FDA considers countries and territories outside the U.S. states categorized as "Red" or "Purple" as areas with increased risk of ZIKV transmission.**

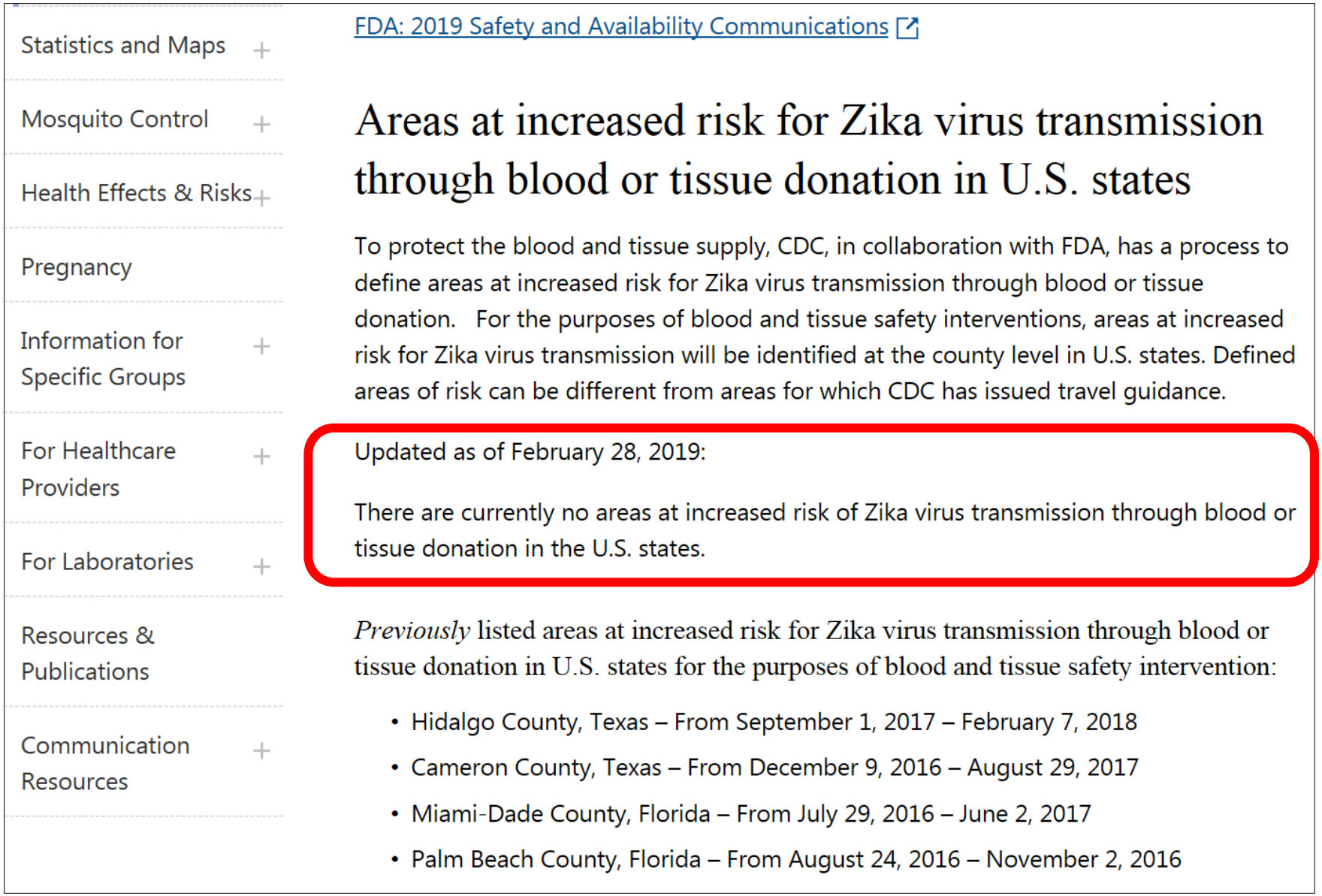
Note: The table that lists areas where ZIKV transmission was previously reported, but that were later classified as

https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm630269.htm

FDA Safety and Availability Communication Related to ZIKV – February 2019

Regarding references to use when screening living donors of HCT/Ps:

- First access the CDC webpage for Blood and Tissue Safety.
- **To evaluate domestic travel**, the "Areas at increased risk for Zika virus transmission through blood or tissue donation in U.S. states" is listed first and continues to be defined at the county level within a state. For the purpose of screening HCT/P donors, do not use other CDC webpages or maps for evaluating travel within the United States.
- **For evaluating travel to areas outside of the U.S. states**, use the link to the world map and consider countries and territories categorized as "Red" or "Purple" as areas with increased risk of ZIKV transmission. When an area outside the U.S. states becomes shaded as Red or Purple for the first time on the world map, that area and the date of the change will be posted on the Blood and Tissue Safety webpage.
- The CDC webpage for Blood and Tissue Safety should be monitored frequently for any updates.



https://www.cdc.gov/zika/areasatrisk.html

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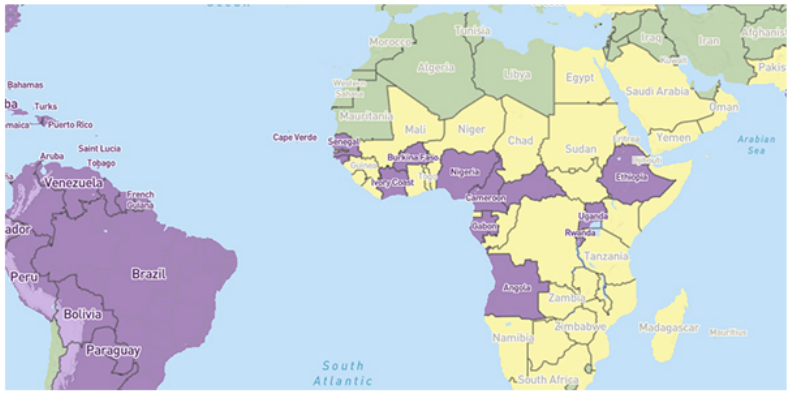
Areas with risk of Zika outside of U.S. states

Based on laboratory analyses and mathematical modeling, a conservative yet plausible estimate for introduction of Zika virus and substantive risk of exposure in North America, South America, Central America, and the Caribbean is January 1, 2014 (*1,2,3*). Furthermore, scientific evidence confirms Zika virus presence in some African and Asian countries for decades, in some cases dating back to the 1950's (*4,5,6*).

Please refer to the world map at this link for areas with risk of Zika outside of the United States:

The map categorizes countries in 4 shaded categories:

- Country or territory with current Zika outbreak (Red)
- Country or territory with any prior or current reports of mosquito-borne Zika transmission (Purple)
- Country or territory with the vector and no reported mosquito-borne Zika transmission (Yellow)
- Country or territory with no mosquitoes that spread Zika (Green)



For the purposes of blood and tissue safety intervention, the following list indicates the date an area's shade first became purple (or red if not previously purple) **after the map updates were introduced on February 28, 2019:**

None

References

1. Lednicky J, Beau De Rochars VM, El Badry M, et al. Zika Virus Outbreak in Haiti in 2014: Molecular and Clinical Data. Reithinger R, ed. *PLoS Neglected Tropical Diseases*. 2016;10(4):e0004687. doi:10.1371/journal.pntd.0004687.

https://www.cdc.gov/zika/areasatrisk.html

HCT/P DONOR SCREENING FOR ZIKV-SUMMARY

Summary

- There are currently no areas at increased risk of Zika virus transmission through blood or tissue donation in the U.S.
- Since the 2016 outbreak, the number of ZIKV cases has decreased in the U.S. and worldwide, however, ZIKV prevalence and incidence is unpredictable
- Cases involving travelers returning from affected areas and local mosquito-borne transmission continue to be reported https://www.cdc.gov/zika/reporting/2019-case-counts.html

Summary

- Appropriate testing measures to prevent the transmission of ZIKV through HCT/Ps, including cord blood, are not available at this time

- FDA continues to recommend screening living donors of HCT/Ps for risks of infection with ZIKV, including screening based on geographic risk areas (updated guidance-May 2018)

- Cord blood from ineligible donors may be used for hematopoietic stem cell transplantation under an IND (exception in § 1271.65(b))

Summary

- Although other information such as post donation follow-up on donor's health status may be helpful, it is unknown whether such measures would be adequate for preventing the transmission of ZIKV through HCT/Ps
  - Potential challenges: method of follow-up, adequate timeframe, feasibility of uniform implementation for all donors of gestational tissues, including cord blood

- Understanding of risks of HCT/Ps may evolve as more information about ZIKV becomes available

- FDA continues to consider recommendations as new information becomes available

Helpful Resources

- Tissue & Tissue Products Homepage
  - https://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm
- 21 CFR part 1271
  - http://www.ecfr.gov/cgi-bin/text-idx?SID=ae1deecc79a9f185d48af015ae277f5d&mc=true&tpl=/ecfrbrowse/Title21/21cfr1271_main_02.tpl
- Tissue Guidances – General List
  - https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances

Contact Information

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- **OTAT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
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ADDITIONAL SLIDES: ZIKV RESEARCH

Zika Virus and Tissue Tropism

- ZIKV RNA has been detected in:
  - Multiple tissues and fluids, including placenta (chorion and amnion), umbilical cord tissue, umbilical cord blood, semen[1-4]
  - Full-term placenta when infection occurred in 1st, 2nd, or 3rd trimester
  - Placentas of babies that appeared healthy at birth
  - Gestational tissues when maternal blood or plasma negative for ZIKV RNA
- Infectious virus isolated from placenta, amniotic fluid

1. Van der Eijk, et. al., *Miscarriage Associated with Zika Virus Infection*, N Engl J Med. 2016; 375:1002-1004.
2. Quicke, et. al., Zika Virus Infects Human Placental Macrophages. Cell Host Microbe. 2016; 20(1):83-90
3. Bhatnager J. et al. Zika Virus RNA Replication and Persistence in Brain and Placental Tissue. Emerg Infect Dis. 2017 Mar; 23(3): 405–414.
4. Benjamin, I, et al, Zika virus detected in amniotic fluid and umbilical cord blood in an in vitro fertilization-conceived pregnancy in Venezuela. Fertil Steril, 2017. 107(6):1319-1322.

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Companion Studies to Define the Distribution and Duration of Zika Virus in Non-Human Primates

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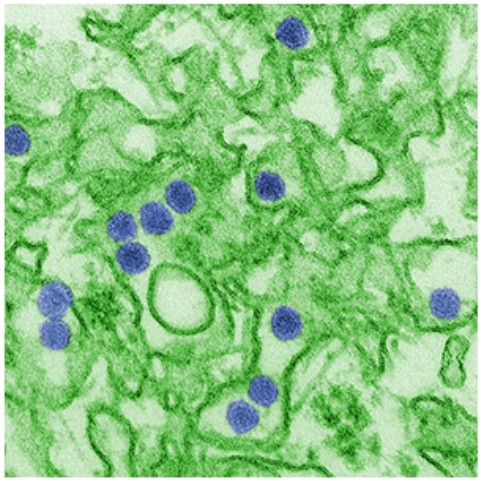
Background | Project Description | Project Outcomes | Additional Reading

Performer: University of California, Davis
Project leader: Koen Van Rompay, DVM, PhD
Contract value: $144,890
Project dates: October 2016 – April 2017



Background

Prior to 2015, Zika virus outbreaks had occurred in areas of Africa, Southeast Asia, and the Pacific Islands. However, in May 2015, the Pan American Health Organization (PAHO) issued an alert (PDF, 199 KB) regarding the first confirmed Zika virus infection in Brazil. Outbreaks are now occurring in many countries, including local transmission in parts of the continental United States.

Most people never know that they have been infected with Zika—in fact, four out of five patients with Zika virus infections are thought to have no symptoms at all. When symptoms do occur, the most common are fever, rash, joint pain, and conjunctivitis (red eyes). Even in those who develop symptoms, Zika illness is usually mild, with symptoms lasting from several days to a week.

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm537724.htm

Identification of Viral Resevoirs in Zika Virus Infected Macaques

- Companion Studies to Define the Distribution and Duration of Zika Virus in Non-Human Primates (University of California, Davis)
  - Project funded through the FDA Medical Countermeasures Initiative (MCMi) Regulatory Science Extramural Research Program
  - 4 pregnant rhesus macaques were inoculated intravenously and intraamniotically with a 2015 Brazilian strain of ZIKV during the 1st or 2nd trimester and euthanized near the end of gestation, except 1 animal whose fetus died 7 days post-inoculation (dpi)
  - Up to 38 different tissues were collected from each primate and tested for the presence of ZIKV RNA by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and/or qualitative transcription-mediated amplification (TMA)
  - Tissues with ≥ 3 $\log_{10}$ copies/gram tissue were further tested for presence of infectious ZIKV by plaque assay on Vero cells
  - Histopathological analysis by in situ hybridization (ISH) was performed on most RNA positive tissues using two sets of probes designed to hybridize the positive sense ZIKV RNA genome

http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm537724.htm

Identification of Viral Reservoirs in ZIKV Infected Macaques

- ZIKV RNA was detected in a number of tissues in pregnant rhesus macaques for more than 3 months after inoculation.
  - Infectious virus was also detected in placental tissues, amniotic fluid and the umbilical cord by plaque assay
  - Highest levels of virus in lymphoid tissue

1. Coffey LL. Et al. Zika Virus Zika Virus Tissue and Blood Compartmentalization in Acute Infection of Rhesus Macaques. PloS one. 2017; 12(1):e0171148.
2. http://wayback.archiveit.org/7993/20180126133803/https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM565405.pdf

Highlights from Non-Human Primate ZIKV Studies

- Nonpregnant female:
  - Ovary, vagina, cervix, uterus (4-8 days after IV inoculation with ZIKV) [1]
  - Cervix, uterus, vagina (~ 15 days after SC inoculation with ZIKV)[2]
  - Uterus and ovary (28 days after SC) [3]
  - Cervix, vagina, ovary, uterus (14 days after IV) [4]
  - Uterus, vagina (7 and 28 days after SC) [5]
- Pregnant female:
  - Ovary, umbilical cord, placenta, amniotic fluid (7-105 days after IV + IA) [6]
  - Amniotic fluid, decidua, placenta, uterus (37-124 days after SC) [7]
- Male:
  - Testes, prostate, seminal vesical (28 days after SC) [3]
  - Urethra, seminal vesicle (35 days after SC) [5]

NHP Study References

1. Carroll, T., et al., *Zika virus preferentially replicates in the female reproductive tract after vaginal inoculation of rhesus macaques*. PLoS Pathog, 2017. 13(7): p. e1006537.

2. Dudley, D., et al., *Infection via mosquito bite alters Zika virus replication kinetics in rhesus macaques*. bioRxiv, 2017.

3. Osuna, C.E., et al., *Zika viral dynamics and shedding in rhesus and cynomolgus macaques*. Nat Med, 2016.

4. Coffey, L.L., et al., *Zika Virus Tissue and Blood Compartmentalization in Acute Infection of Rhesus Macaques*. PLoS One, 2017. 12(1): p. e0171148.

5. Hirsch, A.J., et al., *Zika Virus infection of rhesus macaques leads to viral persistence in multiple tissues*. PLoS Pathog, 2017. 13(3): p. e1006219.

6. Coffey, L.L., et al., *Companion Studies to Define the Distribution and Duration of Zika Virus in Non-Human Primates*, in FDA MCMi Regulatory Science Extramural Research: Final Report. 2017. (https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm537724.htm)

7. Nguyen, S.M., et al., *Highly efficient maternal-fetal Zika virus transmission in pregnant rhesus macaques*. PLoS Pathog, 2017. 13(5): p. e1006378.