CDC's Response to **Zika**

IMPLEMENTING CDC GUIDANCE FOR INFANT NEUROIMAGING AND INFANT AND PLACENTAL ZIKA VIRUS TESTING

Based on Maternal Zika Virus Exposure and Laboratory Test Results

Notes: (1) This tool summarizes general CDC guidance for the following scenarios. Please consult CDC* or your state or local health department for case-specific questions. Health departments should adapt CDC guidance depending on local capacity and circumstances.

(2) In all cases, adverse pregnancy or birth outcomes should also be evaluated for other etiologies.

(3) Infant serum and urine should be tested for Zika virus by Zika NAT, and infant serum for Zika virus IgM antibodies. If CSF is obtained, it can also be tested. Please refer to the published guidance for more information.

(4) Pathology testing includes testing of formalin-fixed or formalin-fixed, paraffin-embedded placenta, umbilical cord, fetal membranes, and fetal or infant organ tissue (e.g., brain, spinal cord, eye) by ZIKV RT-PCR. Microscopic evaluation of fixed tissues is conducted in selected cases. IHC testing might be conducted on placental tissues up through the early second trimester, and on fetal and infant brain, eye, and spinal cord tissue. Please refer to the website for further guidance.

(5) Please note that a positive RT-PCR result from placental testing cannot distinguish between maternal and fetal infection. A positive RT-PCR result from the placenta can confirm maternal Zika infection but cannot be used to confirm congenital Zika infection in the infant/fetus. Negative RT-PCR results on placental tissue do not exclude maternal ZIKV since the duration of ZIKV persistence in the placenta is unknown and the samples evaluated may not reflect the placenta in its entirety.

Timing of Zika virus exposure† relative to timing of maternal specimen collection		**EXPOSURE† WITHIN ANY TIME PERIOD**		**ALL EXPOSURE† WITHIN 12 WEEKS OF SPECIMEN COLLECTION (I.E., EXPOSURE IS COMPLETELY WITHIN TESTING WINDOW§)**		
Test results and interpretation from maternal specimens (e.g.serum, urine, and whole blood) >>		**Recent ZIKV infection** NAT positive OR non-negative Zika IgM¶ **AND** Zika PRNT** ≥ 10, and dengue PRNT** < 10	**Recent flavivirus infection, specific virus cannot be identified**** non-negative Zika IgM¶ **AND** Zika PRNT** ≥ 10, and dengue PRNT** ≥ 10	**No evidence of ZIKV infection** Zika IgM negative OR non-negative Zika IgM¶ **AND** Zika PRNT** < 10	**Presumptive recent** ZIKV or flavivirus infection** non-negative Zika IgM¶ **AND** PRNT** pending	**Not tested**
Additional maternal testing on serum, urine, and whole blood >>		← **Additional maternal testing not indicated** →			**Additional Maternal Testing:** Follow up PRNT results, if indicated according to lab guidance. If maternal IgM is inconclusive, repeat IgM testing in accordance with EUA.	**Maternal Testing:** Recommended; specimens should be collected as soon as possible.
Pregnancy outcome	**Live birth with anomalies consistent with congenital Zika syndrome††**	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.
		Infant Laboratory Testing: Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Do not wait for maternal test results. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.
		Placental Pathology Testing: Not indicated; no added diagnostic value given known maternal ZIKV diagnosis.§§	**Placental Pathology Testing:** Should be considered to aid in maternal diagnosis.	**Placental Pathology Testing:** Fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid in maternal diagnosis.¶¶	**Placental Pathology Testing:** Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Pathology Testing:** Fix and store placenta until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.
	Live birth and phenotypically normal	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge.	**Neuroimaging:** Not indicated.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.
		Infant Laboratory Testing: Recommended; specimens should be collected within 2 days of birth.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth.	**Infant Laboratory Testing:** Not indicated.	**Infant Laboratory Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Infant Laboratory Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available.
		Placental Pathology Testing: Not indicated; no added diagnostic value given known maternal ZIKV diagnosis.§§	**Placental Pathology Testing:** Should be considered to aid maternal diagnosis.	**Placental Pathology Testing:** Not indicated.	**Placental Pathology Testing:** Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Pathology Testing:** Fix and store placenta until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.
	Infant death (following live birth)	**Pathology Testing:** Consider testing placental and infant tissues.***	**Pathology Testing:** Consider testing placental and infant tissues.***	**Pathology Testing:** Testing of placental and infant tissues not indicated.§§	**Pathology Testing:** Fix and store placental and infant tissues until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.	**Pathology Testing:** Fix and store placental and infant tissues until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.
	Pregnancy/fetal loss	**Pathology Testing:** Testing placental and fetal tissues can be considered.*** Consult CDC for specific guidance.*	**Pathology Testing:** Testing of placental and fetal tissues can be considered.*** Consult CDC for specific guidance.*	**Pathology Testing:** Testing of placental and fetal tissues not indicated.§§	**Pathology Testing:** Fix and store placental and fetal tissues until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.	**Pathology Testing:** Fix and store placental and fetal tissues until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.

Abbreviations: CT= Computed Tomography; EUA = Emergency Use Authorization; IgM = Immunoglobulin M; IHC = Immunohistochemistry; MRI= Magnetic Resonance Imaging; NAT = Nucleic Acid Test (includes rRT-PCR and RT-PCR); PRNT = Plaque Reduction Neutralization Test; rRT-PCR = Real-time Reverse Transcription-Polymerase Chain Reaction; RT-PCR = Reverse Transcription-Polymerase Chain Reaction; ZIKV = Zika virus.

* Please contact CDC Zika Pregnancy Hotline at 770-488-7100 or zikamch@cdc.gov for clinical questions. Please contact pathology@cdc.gov and eocevent189@cdc.gov for pathology-related questions and consultations.

† Possible Zika virus exposure is defined as travel to or residence in an area with risk of Zika and a Travel Notice or sex without a condom with someone who traveled to or lived in an area with risk of Zika and a Travel Notice.

§ Start and end date of exposure are both within the 12-week testing window.

¶ Non-negative serology terminology varies by assay and examples include positive, equivocal, presumptive positive, or possible positive results. For explanation of a specific interpretation and informaton on each assay, refer to https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika, under the "Labeling" bullet for the specific assay. Inconclusive maternal IgM specimens should be retested in accordance with EUA. If the inconclusive maternal IgM cannot be reconciled, refer to the relevant exposure category "Not tested" column, and base decision to test placenta on maternal and/or infant test results.

** Currently, PRNT confirmation is not routinely recommended for individuals living in Puerto Rico. In Puerto Rico, for "presumptive recent ZIKV" guidance, refer to the column for "recent ZIKV infection;" and for "presumptive recent flavivirus infection" guidance, refer to the column for "Recent flavivirus, specific virus cannot be identified."

†† Including but not limited to: microcephaly; structural brain anomalies (e.g., decreased brain volume, calcifications); posterior eye anomalies (e.g., chorioretinal scarring, optic nerve hypoplasia); contracture of one or more joints; and functional neurologic abnormalities (e.g., spasticity/hypertonia, dystonia/dyskinesia). For complete list of anomalies please check the CDC Zika virus pregnancy outcomes website: https://www.cdc.gov/zika/reporting/pregnancy-outcomes.html

§§ In exceptional circumstances, placental and/or fetal tissue testing may be considered in consultation with CDC at 770-488-7100 or pathology@cdc.gov and eocevent189@cdc.gov.

¶¶ If infant testing is done it should be performed before placental testing, if possible. If (1) infant NAT (rRT-PCR) is p ositive for Zika, or (2) infant IgM is Zika positive or equivocal AND infant or maternal PRNT is positive for Zika but negative for dengue, then there is limited utility of placental testing. If other infant test results are obtained, placental testing may provide another opportunity to identify maternal infection that would otherwise go unrecognized.

*** Testing of fixed placental and fetal tissues from pregnancy losses, and autopsy tissues from infant deaths, includes ZIKV RT-PCR and microscopic evaluation. IHC testing might be conducted on placental tissues up through the early second trimester, and on fetal and infant brain, eye, and spinal cord tissue. Testing for other etiologies might be pursued based on microscopic findings, or other clinical/epidemiologic history. For fetal or infant autopsy tissues, appropriate consent from the parents or guardian must be obtained by the healthcare provider prior to collection and submission of specimens to CDC for Zika virus testing.

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Implementing CDC Guidance for Infant Neuroimaging and Infant and Placental Zika Virus Testing Based on Maternal Zika Virus Exposure and Laboratory Test Results

Notes: (1) This tool summarizes general CDC guidance for the following scenarios. Please consult CDC*or your state or local health department for case-specific questions. Health departments should adapt CDC guidance depending on local capacity and circumstances.

(2) In all cases, adverse pregnancy or birth outcomes should also be evaluated for other etiologies.

(3) Infant serum and urine should be tested for Zika virus by Zika NAT, and infant serum for Zika virus IgM antibodies. If CSF is obtained, it can also be tested. Please refer to the published guidance for more information.

(4) Pathology testing includes testing of formalin-fixed or formalin-fixed, paraffin-embedded placenta, umbilical cord, fetal membranes, and fetal or infant organ tissue (e.g., brain, spinal cord, eye) by ZIKV RT-PCR. Microscopic evaluation of fixed tissues is conducted in selected cases. IHC testing might be conducted on placental tissues up through the early second trimester, and on fetal and infant brain, eye, and spinal cord tissue. Please refer to the website for further guidance.

(5) Please note that a positive RT-PCR result from placental testing cannot distinguish between maternal and fetal infection. A positive RT-PCR result from the placenta can confirm maternal Zika infection but cannot be used to confirm congenital Zika infection in the infant/fetus. Negative RT-PCR results on placental tissue do not exclude maternal ZIKV since the duration of ZIKV persistence in the placenta is unknown and the samples evaluated may not reflect the placenta in its entirety.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Timing of Zika virus exposure† relative to timing of maternal specimen collection		ALL OR PART OF THE EXPOSURE† OCCURRED MORE THAN 12 WEEKS PRIOR TO SPECIMEN COLLECTION (I.E., EXPOSURE† IS COMPLETELY OR PARTIALLY OUTSIDE TESTING WINDOW†††)		
Test results and interpretation from maternal specimens (e.g.serum, urine, and whole blood) >>		**No evidence of recent ZIKV infection** NAT negative **AND** Zika IgM negative§§§	**Presumptive recent ZIKV or flavivirus infection** non-negative Zika IgM¶ **AND** PRNT** pending	**Not tested**
Additional maternal testing on serum, urine, and whole blood >>		**Additional Maternal Testing:** Not indicated.	**Additional Maternal Testing:** Follow up PRNT results, if indicated according to lab guidance. If maternal IgM is inconclusive, repeat IgM testing in accordance with EUA.	**Maternal Testing:** Might be considered.†††
Pregnancy outcome	**Live birth with anomalies consistent with congenital Zika syndrome††**	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.
		Infant Laboratory Testing: Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Laboratory Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.
		Placental Pathology Testing: Fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid maternal diagnosis.¶¶	**Placental Pathology Testing:** Can be considered to aid maternal diagnosis. Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Pathology Testing:** Fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid maternal diagnosis.¶¶
	Live birth and phenotypically normal	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge.	**Neuroimaging:** Head ultrasound recommended, should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.
		Infant Laboratory Testing: Should be considered¶¶¶; specimens should be collected within 2 days of birth.	**Infant Laboratory Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Infant Laboratory Testing:** Should be considered¶¶¶; specimens should be collected within 2 days of birth.
		Placental Pathology Testing: If infant testing is performed, fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid maternal diagnosis.¶¶ Consult CDC if infant testing is not performed.*	**Placental Pathology Testing:** Can be considered to aid maternal diagnosis. Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Pathology Testing:** If infant testing is performed, fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid maternal diagnosis.¶¶ Consult CDC if infant testing is not performed.*
	Infant death (following live birth)	**Pathology Testing:** Consider testing placental and infant tissues.***	**Pathology Testing:** Consider testing placental and infant tissues.*** Can consider fixing and storing placental and infant tissues until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Pathology Testing:** Consider testing placental and infant tissues.***
	Pregnancy/fetal loss	**Pathology Testing:** Testing of placental and fetal tissues can be considered.*** Consult CDC for specific guidance.*	**Pathology Testing:** Testing of placental and fetal tissues can be considered.*** Can consider fixing and storing placental and infant tissues until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Pathology Testing:** Testing of placental and fetal tissues can be considered.*** Consult CDC for specific guidance.*

Abbreviations: CT= Computed Tomography; EUA = Emergency Use Authorization; IgM = Immunoglobulin M; IHC = Immunohistochemistry; MRI= Magnetic Resonance Imaging; NAT = Nucleic Acid Test (includes rRT-PCR); PRNT = Plaque Reduction Neutralization Test; rRT-PCR and RT-PCR = Real-time Reverse Transcription-Polymerase Chain Reaction; RT-PCR = Reverse Transcription-Polymerase Chain Reaction; ZIKV = Zika virus.

* Please contact CDC Zika Pregnancy Hotline at 770-488-7100 or zikamch@cdc.gov for clinical questions. Please contact pathology@cdc.gov and eocevent189@cdc.gov for pathology-related questions and consultations.

† Possible Zika virus exposure is defined as travel to or residence in an area with risk of Zika and a Travel Notice or sex without a condom with someone who traveled to or lived in an area with risk of Zika and a Travel Notice.

††† If maternal testing is performed >12 weeks after exposure and/or symptom onset, a negative Zika IgM or NAT result does not rule out recent maternal ZIKV infection because IgM antibody and viral ribonucleic acid levels decline over time.

§§§ If PRNT testing also performed and is negative, please refer to 'No evidence of ZIKV infection' column in the 'All exposure within 12 weeks of specimen collection' section of this table.

¶ Non-negative serology terminology varies by assay and examples include positive, equivocal, presumptive positive, or possible positive results. For explanation of a specific interpretation and informaton on each assay, refer to https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika, under the "Labeling" bullet for the specific assay. Inconclusive maternal IgM specimens should be retested in accordance with EUA. If the inconclusive maternal IgM cannot be reconciled, refer to the relevant exposure category "Not tested" column, and base decision to test placenta on maternal and/or infant test results.

** Currently, PRNT confirmation is not routinely recommended for individuals living in Puerto Rico. In Puerto Rico, for "presumptive recent ZIKV" guidance, refer to the column for "recent ZIKV infection;" and for "presumptive recent flavivirus infection" guidance, refer to the column for "Recent flavivirus, specific virus cannot be identified."

†† Including but not limited to: microcephaly; structural brain anomalies (e.g., decreased brain volume, calcifications); posterior eye anomalies (e.g., chorioretinal scarring, optic nerve hypoplasia); contracture of one or more joints; and functional neurologic abnormalities (e.g., spasticity/hypertonia, dystonia/dyskinesia). For complete list of anomalies please check the CDC Zika virus pregnancy outcomes website: https://www.cdc.gov/zika/reporting/pregnancy-outcomes.html

¶¶ If infant testing is done it should be performed before placental testing, if possible. If (1) infant NAT (rRT-PCR) is positive for Zika, or (2) infant IgM is Zika positive or equivocal AND infant or maternal PRNT is positive for Zika but negative for dengue, then there is limited utility of placental testing. If other infant test results are obtained, placental testing may provide another opportunity to identify maternal infection that would otherwise go unrecognized.

¶¶¶ Infant testing should be considered because recent maternal ZIKV infection is not ruled out by negative maternal NAT or IgM, or when maternal testing has not been performed. Specimens should be collected soon after birth, as Zika RNA and IgM antibodies decline over time.

*** Testing of fixed placental and fetal tissues from pregnancy losses, and autopsy tissues from infant deaths, includes ZIKV RT-PCR and microscopic evaluation. IHC testing might be conducted on placental tissues up through the early second trimester, and on fetal and infant brain, eye, and spinal cord tissue. Testing for other etiologies might be pursued based on microscopic findings, or other clinical/epidemiologic history. For fetal or infant autopsy tissues, appropriate consent from the parents or guardian must be obtained by the healthcare provider prior to collection and submission of specimens to CDC for Zika virus testing.