IMPLEMENTING CDC GUIDANCE FOR CLINICAL MANAGEMENT AND EVALUATION OF INFANTS BORN TO MOTHERS WITH POSSIBLE ZIKA VIRUS EXPOSURE DURING PREGNANCY; AND TESTING OF PLACENTAL, FETAL, OR INFANT AUTOPSY TISSUES(1, 2)

Notes: 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.

INFANT OR FETUS WITH CLINICAL FINDINGS CONSISTENT WITH CZS (3)				
Maternal Zika virus laboratory results and interpretations (4)	WITH maternal laboratory evidence of possible Zika virus infection during pregnancy (4)		No maternal laboratory evidence of possible Zika virus infection during pregnancy (4,5)	
	Acute Zika virus infection	Zika or flavivirus infection, timing cannot be determined	>12 weeks after exposure/symptoms (7) and either maternal testing negative, or mother not tested (8)	Maternal testing ≤12 weeks after exposure/ symptoms (7) negative (9)
LIVE BIRTHS				
Clinical evaluation and management	At birth: standard evaluation. (10) Infant Zika virus laboratory testing: NAT on serum and urine, consider CSF; IgM on serum, consider CSF. (11,12) By one month: head ultrasound, comprehensive ophthalmologic exam, automated ABR. Refer to developmental specialist, early intervention, and family support services; consider other consultations (e.g., genetics, ID, neurology). (13)			
Testing of placental tissues	Not indicated. (14)	Should be considered to aid in maternal diagnosis. (15)		Not indicated.
PREGNANCY LOSS OR INFANT DEATH FOLLOWING LIVE BIRTH				
Testing of fetal and placental tissues	May be considered to aid in fetal diagnosis.	May be considered to aid in fetal and maternal diagnosis.		Not indicated.
Testing of infant autopsy and placental tissues	Should be considered to aid in infant diagnosis.	Should be considered to aid in infant and maternal diagnosis.		Not indicated.

Abbreviations: ABR=Auditory Brain Stem Response, CSF=Cerebrospinal Fluid, CZS= Congenital Zika Syndrome, EEG= Electroencephalogram, ID=Infectious Disease, IgM=Immunoglobulin M, IHC=immunohistochemistry, NAT=Nucleic Acid Testing, PRNT= Plaque Reduction Neutralization Test, RNA=ribonucleic acid, RT-PCR= Reverse Transcriptase Polymerase Chain Reaction

(1) Zika virus testing on formalin-fixed, paraffin embedded tissue specimens is conducted at CDC's Infectious Diseases Pathology Branch (IDPB) and includes Zika virus RT-PCR on placental and fetal/ infant tissues. Zika virus IHC may be performed on placental specimens into the second trimester, fetal tissues from any gestational age, and infant autopsy tissues.

(2) Placental tissues include placental disc, umbilical cord, and fetal membranes. Zika virus RNA can be focal within placental tissues, and testing of three sections of placenta, one section of umbilical cord, and one section of fetal membrane is recommended (https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html). For pregnancy losses and infant deaths, submission of fetal or infant autopsy tissues, if available, in addition to submission of placental tissues, is preferred, but if not available will not preclude placental testing.

(3) Clinical findings consistent with CZS include severe microcephaly, decreased brain tissue with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures such as clubfoot or arthrogryposis, and hypertonia restricting body movement soon after birth. Additional findings are described at https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-syndrome-birth-defects.html.

(4) Maternal laboratory evidence of possible Zika virus infection during pregnancy includes the following test result interpretations (described at https://www.cdc.gov/mmwr/volumes/68/rr/rr6801a1.htm): Acute Zika virus infection; Zika virus infection, timing of infection cannot be determined; Flavivirus infection, specific virus cannot be identified, timing of infection cannot be determined; Presumptive Zika virus infection, timing of infection cannot be determined; Presumptive flavivirus infection, specific virus cannot be identified, timing of infection cannot be determined. DOES NOT INCLUDE: Insufficient information for interpretation; No laboratory evidence of Zika virus infection.

(5) For infants with clinical findings consistent with CZS with maternal testing pending; consider collecting, fixing, and storing placental tissues until results are available. Do not wait for maternal test results, but instead proceed with infant clinical management and testing.

(6) For infants without findings consistent with CZS with maternal testing pending and maternal specimen was collected within 12 weeks of all exposure, consider collecting, fixing, and storing placental tissues, and collecting and storing infant serum and urine. Once available, maternal test results should guide further management according to this framework.

(7) Symptoms of Zika virus disease include acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis.

(8) All or part of possible maternal Zika virus exposure, or symptom onset, occurred >12 weeks before maternal serum specimen was collected.

(9) Includes pregnant women with negative Zika virus NAT and negative Zika virus IgM ≤12 weeks after symptom onset or exposure.

(10) Standard evaluation at birth includes a comprehensive physical exam, including growth parameters; newborn hearing screen at birth, preferably with automated ABR; developmental monitoring and screening using validated screening tools recommended by the American Academy of Pediatrics (https://www.aap.org/en/patient-care/screening-technical-assistance-and-resource-center/); and vision screening as recommended by the American Academy of Pediatrics Policy Statement "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians" (https://publications.aap.org/pediatrics/article/137/1/e20153596/52809/Visual-System-Assessment-in-Infants-Children-and).

(11) CDC interim infant testing guidance recommends that Zika virus testing should be performed on CSF if it is/was collected for other reasons. Since there are reports of congenital Zika virus infection in which CSF was the only sample testing positive, healthcare providers should consider obtaining CSF for Zika virus RNA and IgM antibody testing in infants with clinical findings of possible congenital Zika syndrome but whose initial laboratory tests are negative on serum and urine.

(12) Because levels of Zika virus RNA and IgM antibodies decline over time, laboratory testing of infants should be performed as early as possible, preferably within the first few days after birth, although testing specimens within the first few weeks to months after birth might still be useful.

(13) Consultations with specialists may include: ID specialist for evaluation for other congenital infections (e.g., toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes simplex virus) and assistance with Zika virus diagnosis, testing, and counseling; neurologist by age 1 month for comprehensive neurologic examination and consideration for other evaluations such as advanced neuroimaging and EEG; ophthalmologist for comprehensive eye exam by age 1 month; clinical geneticist for confirmation of the clinical phenotype and evaluation for other causes of microcephaly or congenital anomalies; early intervention and developmental specialists; family and supportive services. Additional possible consultations, based on clinical findings of the infant include endocrinologist for evaluation of hypothalamic or pituitary dysfunction and consideration for thyroid testing; lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist for evaluation for dysphagia and man agement of feeding issues; orthopedist, physiatrist, or physical therapist for the management of hypertonia, clubfoot or arthrogrypotic-like conditions; pulmonologist or otolaryngologist for concerns about aspiration.

(14) Placental testing does not routinely provide additional diagnostic information in the setting of a maternal or infant diagnosis of acute or confirmed congenital Zika virus infection, respectively.

(15) Placental testing is not indicated for the subset of women with maternal laboratory test interpretation "Zika virus infection, timing cannot be determined" whose only possible exposure to Zika occurred during this pregnancy, as the positive Zika virus IgM and PRNT results likely represent acute Zika virus infection during pregnancy when compared with women whose positive serologic results may reflect an infection prior to pregnancy.

(16) Contact CDC's Infectious Diseases Pathology Branch at pathology@cdc.gov for case-specific questions.

(17) Persons with ongoing possible Zika virus exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk of Zika virus transmission.

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(6) For infants without findings consistent with CZS with maternal testing pending and maternal specimen was collected within 12 weeks of all exposure, consider collecting, fixing, and storing placental tissues, and collecting and storing infant serum and urine. Once available, maternal test results should guide further management according to this framework.

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