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Interim Guidance for the Evaluation and Management of Infants With Possible Congenital Zika Virus Infection — United States, August 2016

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Updated Recommendations for the Initial Laboratory Testing and Evaluation of Infants With Possible Congenital Zika Virus Infection

Infant Diagnostic Testing

Laboratory testing for congenital Zika virus infection is recommended for infants born to mothers with laboratory evidence of Zika virus infection, and for infants with findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal testing results (Figure). Laboratory evidence of maternal Zika virus infection includes Zika virus RNA detected in any maternal clinical specimen by rRT-PCR and positive Zika virus IgM with confirmatory neutralizing antibody titer for Zika virus or flavivirus, not otherwise specified. Zika virus rRT-PCR testing should be performed on both infant serum and urine, and Zika virus IgM enzyme-linked immunosorbent assay (ELISA) should concurrently be performed on infant serum. If cerebrospinal fluid (CSF) is obtained for other studies, rRT-PCR testing for Zika virus RNA and Zika virus IgM should be performed on CSF. Laboratory testing should be performed on infant specimens; cord blood is not recommended because it can yield false positive results through contamination with maternal blood and might also yield false negative results.[21] Infant laboratory testing for Zika virus should be performed within the first 2 days after birth; if testing is performed later, distinguishing between congenital, perinatal, and postnatal infection will be difficult. If the timing of infection cannot be determined, infants should be managed as if they have congenital Zika virus infection.

A Zika rRT-PCR positive result in an infant sample confirms the diagnosis of congenital Zika virus infection (Table 1). Zika virus IgM detected in an infant, without detectable Zika virus RNA, should be interpreted as probable congenital Zika virus infection. The plaque reduction neutralization test (PRNT) measures virus-specific neutralizing antibodies and is used to confirm the specificity of the IgM antibodies against Zika virus and rule out a false positive IgM result[20] If the infant's initial sample is IgM-positive, but PRNT was not performed on the mother's sample, PRNT should be performed on the infant's initial

sample. However, PRNT cannot distinguish between maternal and infant antibodies. Because of this, it might be necessary to wait until the child is at least age 18 months, when maternal antibodies are expected to wane, to confirm congenital infection. PRNT should be performed on a sample collected from a child aged ≥18 months whose initial sample was IgM positive if Zika-specific neutralizing antibodies were detected by PRNT on either the infant's or mother's sample. If the infant's initial sample is negative by both IgM ELISA and rRT-PCR but clinical concerns remain (e.g., microcephaly with negative evaluation for other known causes), PRNT at age 18 months can be considered. If PRNT results at 18 months are negative, the child is considered to not have congenital Zika virus infection. If PRNT results are positive, congenital Zika infection is presumed, but postnatal infection cannot be excluded, especially for children living in an area with active Zika virus transmission.

In many cases, infant laboratory testing results will not be available before hospital discharge. In these cases, infants should be presumed to have congenital Zika virus infection until test results are available. For the purposes of this guidance, infants with confirmed or probable Zika virus infection should be managed in the same manner.

Detection of Zika virus RNA in the placenta can confirm the presence of maternal infection, but cannot distinguish between maternal and congenital infection. For circumstances in which maternal testing was not previously performed, performed more than 12 weeks after exposure,[22] or was not definitive (e.g., flavivirus not otherwise specified),[20] a positive placental rRT-PCR result can confirm maternal Zika virus infection. Based on unpublished CDC data, placentas from mothers with Zika virus infection during pregnancy can have detectable Zika virus RNA at the time of delivery, regardless of the timing of maternal infection. Clinical implications for an infant with Zika virus RNA detected in the placenta, in the absence of laboratory evidence of Zika virus in the infant, are unknown.

Limited data are currently available regarding perinatal Zika virus transmission.[23] Guidelines for evaluation and management of infants and children with postnatally acquired Zika virus disease[1] will be updated as more information is available.

Clinical Evaluation of Infants

Infants born to mothers with laboratory evidence of Zika virus infection should receive a comprehensive physical examination, including precise measurement of head (occipitofrontal) circumference,* length and weight, assessment of gestational age, and examination for neurologic abnormalities and dysmorphic features (Table 2). A postnatal head ultrasound should be performed on all infants born to mothers with laboratory evidence of Zika virus infection before discharge from the hospital, including those infants with normal prenatal ultrasound findings, because some abnormal findings associated with congenital Zika syndrome might not be readily apparent on prenatal ultrasounds. All infants should receive a hearing screen per universal screening recommendations before hospital discharge. Infants with laboratory evidence of congenital Zika virus infection should be referred for a comprehensive ophthalmologic exam and evaluation of hearing by ABR

testing before 1 month of age. Other evaluations should be performed as clinically indicated.

Infants with negative IgM and negative rRT-PCR testing born to a mother with laboratory evidence of Zika virus infection should receive routine care, including monitoring of head circumference at every well child visit and age-appropriate developmental screening.[24] Health care providers should report information on pregnant women in the United States and the U.S. territories with laboratory evidence of Zika virus infection and their infants (regardless of infant test results) to state, tribal, local, or territorial health departments for inclusion in the U.S. Zika Pregnancy Registry (http://www.cdc.gov/zika/hc-providers/registry.html), or the Puerto Rico Zika Active Pregnancy Surveillance System (ZAPSS) (http://www.cdc.gov/zika/public-health-partners/zapss.html).

For all infants with abnormal findings consistent with congenital Zika syndrome, an extensive evaluation is recommended (Box 2). Transfer to a facility with access to pediatric subspecialty care might facilitate this evaluation. However, the decision should not be based solely on the presence of maternal Zika virus infection during pregnancy. Health care providers should consider both the immediate needs of the infant and the potential negative impact of possible separation from his or her family. The recommended evaluation includes a complete blood count and metabolic panel, including liver function tests, a comprehensive examination by an ophthalmologist, ABR testing, and consideration of advanced neuroimaging in consultation with a neurologist. In addition, infants should be evaluated for other causes of microcephaly or intracranial calcifications, including genetic conditions and other congenital infections.

Infants born to mothers with risk factors for maternal Zika virus infection (travel to or residence in an area of Zika virus transmission or sex with a partner who traveled to or resided in such an area) and for whom maternal testing was not performed before delivery, should have a comprehensive physical examination, including standardized measurement of head circumference. Maternal diagnostic testing should be performed,[20,22] and testing of the placenta for Zika virus PCR should be considered (http://www.cdc.gov/zika/hcproviders/test-specimens-at-time-of-birth.html); infant testing should be performed if maternal testing is consistent with laboratory evidence of Zika virus infection. If an infant appears clinically well, further evaluation, including head ultrasound, ophthalmologic assessment, and infant laboratory Zika virus testing, can be deferred until maternal test results are available. However, if there is concern about infant follow-up, head ultrasound, ophthalmologic assessment and infant Zika virus testing should be performed before hospital discharge. CDC recommends standard precautions in all health care settings to protect both health care personnel and patients from infection with blood-borne pathogens, including Zika virus.[25]

Although Zika virus has been detected in breast milk,[26] no cases of Zika virus infection associated with breastfeeding have been reported, and current evidence suggests that the benefits of breastfeeding outweigh the theoretical risks of Zika virus transmission. All women with Zika virus infection during pregnancy should be encouraged and supported to breastfeed their infants, regardless of infant Zika virus testing results.

Outpatient Management of Infants With Laboratory Evidence of Zika Virus Infection and Abnormalities Consistent With Congenital Zika Syndrome

The care of infants with abnormalities consistent with congenital Zika syndrome requires a multidisciplinary team and an established medical home to facilitate the coordination of care, which is critical to ensuring that these infants receive necessary testing and consultations (Box 3), and that abnormal findings are detected and appropriately addressed.[27] If abnormalities are noted on prenatal evaluation, counseling specific to congenital Zika syndrome should occur during pregnancy, preferably with the involvement of obstetric and pediatric providers. Before the infant's discharge from the birth hospital, follow-up appointments with specialists and services recommended during initial evaluation should be made. Consideration should be given to using preexisting coordinated multidisciplinary care clinics.

Infants should receive routine preventive pediatric health care, including regularly scheduled immunizations.[24] Families of infants with congenital Zika syndrome should receive information that includes discussion of concerns for development, function, feeding and growth, and prognosis. Standardized measurement of growth parameters, including head circumference, weight, and length, should occur regularly through the first year of life.

Breastfeeding should be encouraged and supported for nutrition and enhanced bonding. Primary care providers should assess the infant for evidence of feeding difficulties and refer for consultations related to lactation, occupational therapy, speech therapy, nutrition, and/or gastroenterology for poor suck, swallowing dysfunction, gastroesophageal reflux, and aspiration. Swallowing dysfunction might not be evident initially and feeding should be monitored closely.

A neurologic examination should be performed at age 1 month and 2 months by a primary care provider and subsequently as needed depending on the infant's clinical status. If not already initiated, neurology referral should occur for evaluation of any abnormalities, including sleep problems and excess irritability. If the ophthalmology exam performed within the first month of life was normal, another exam (including retinal assessment) is recommended at age 3 months. ABR testing is the preferred test to detect hearing loss resulting from neurologic damage. If the initial newborn hearing screen was performed using only otoacoustic emission testing, the infant should be referred for ABR screening before 1 month of age. If the newborn hearing screen was normal, an ABR should be performed at age 4–6 months. If vision or hearing results are abnormal, referrals to appropriate specialists should occur as soon as possible.

Infants with abnormal brain development can be at risk for hypothalamic dysfunction leading to pituitary insufficiency, and early manifestations of endocrine dysfunction might not be detected by routine newborn screening.[28] Thyroid screening, including measurement of thyroid stimulation hormone (TSH) and thyroxine (either free T4 or both

total T4 and estimated free T4) should be performed at age 2 weeks and again at age 3 months. If either of these results is abnormal, further evaluation of pituitary function should be performed by an endocrinologist.

Developmental monitoring should occur at each routine visit, and standardized, validated screening tools should be used to assess the presence of developmental delay.[24] Referral to a developmental specialist and early intervention services should occur as soon as possible. It is important that primary care providers continue to monitor the child's development and progress with standardized, validated developmental screening tools to ensure that the child's developmental needs are addressed.

Overall, families and caregivers of infants with congenital Zika syndrome will require ongoing psychosocial assessment and support. Health care providers should work closely with parents to ensure that the care plan that is developed is consistent with the infant's needs and the family's wishes. Monitoring for depression among caregivers should occur during primary care visits, because depression or family stress might be associated with the infant's complex medical needs. Families might also face financial stressors, social stigma, and other forms of discrimination. Existing national and local resources for families of children with complex care needs should be made available to families.[29]

Referrals for abnormal findings should occur as clinically indicated, either to a pediatric specialist or a specialist with expertise in the care of children. In areas with limited access to pediatric subspecialty care, the numerous services recommended for infants with congenital Zika syndrome might not be readily available; in these situations, telehealth might be explored as a potential means of providing subspecialty care and support to families in areas with limited access.[30]

Infants with laboratory evidence of Zika virus infection but without apparent abnormalities at birth are recommended to have additional monitoring (Box 4), until further information is available regarding outcomes, because some neurologic sequelae of congenital Zika virus infection (e.g., seizures, cognitive impairment, and vision and hearing abnormalities) might be subtle or have delayed onset. During routine infant follow-up with primary care providers, a standardized, validated developmental screening tool should be used at age 9 months, as currently recommended by the American Academy of Pediatrics,[24] or sooner, if there are any developmental concerns. Referral to a developmental specialist and early intervention programs should be considered as soon as caregiver or provider concerns are noted, and additional referrals to specialists should be made as clinically indicated.

A vision screening, including assessment of visual regard, should be performed at each well child visit, and referral to an ophthalmologist should be made for any caregiver or provider concerns. Infants with abnormalities on initial hearing screen should be referred to an audiologist for a complete evaluation. Later development of hearing loss in infants without other clinical findings has been observed in other congenital infections;[15] however, the likelihood that an infant with congenital Zika virus infection without clinical findings consistent with congenital Zika syndrome and with an initial normal hearing screen will develop hearing loss is unknown. ABR testing of infants at age 4–6 months can be considered, although the risk from sedation needs to be taken into account. Infants who

passed an initial ABR and without an ABR at age 4–6 months should be referred for behavioral audiologic diagnostic testing at age 9 months, or sooner for any hearing concerns. Behavioral audiologic testing is recommended because of the potential need for sedation with ABR testing in infants.

As a critical component of patient care and to facilitate early identification of developmental delays, families should be empowered to be active participants in their child's monitoring and care. Anticipatory guidance provided to caregivers should emphasize developmental milestones, feeding and growth, sleep, irritability, and seizure recognition.

A disproportionate burden of congenital Zika virus infection might affect families with already limited access to health care. Families might face language and cultural barriers, financial barriers, and inadequate access. Rural populations might have difficulty accessing specialists. Barriers to care for all affected infants and their families should be addressed through linkage to national, state, and local health programs.