Assessment and Testing for Zika Virus Infection in Pregnant Women and their Newborns: Information for California Birthing Hospitals (February 7, 2018)

California continues to identify new cases of Zika virus infection in pregnant women with potential serious risks to their babies, though the incidence of new Zika infections in California travelers declined through 2017. Maternity hospitals play a critical role in Zika virus exposure screening, specimen collection, Zika virus testing and evaluation of pregnant women and their newborns. The information below outlines the steps to take and key resources necessary for California birthing hospitals to ensure all pregnant women are screened for Zika virus exposure, appropriate maternal and infant Zika virus testing is conducted, and recommended infant management and follow-up are arranged. This document takes into account the latest recommendations from the Centers for Disease Control and Prevention (CDC).

Zika Basics:
Zika virus infection during pregnancy has been linked to problems such as miscarriage, stillbirth, birth defects (affecting about 10% of pregnant women with laboratory confirmed Zika) and potential long-term impacts for their affected infants. Most people with Zika virus infection don't know they have it. Only an estimated 20% have symptoms. For more information on Zika, please see the CDC or CDPH Zika websites.

Congenital Zika syndrome is unique to fetuses and infants infected with Zika virus before birth and is described by a spectrum of features, including:

- Severe microcephaly in which the skull has partially collapsed
- Decreased brain tissue with a specific pattern of brain damage, including subcortical calcifications
- Damage to the back of the eye, including macular scarring and focal pigmentary retinal mottling
- Congenital contractures, such as clubfoot or arthrogryposis
- Hypertonia restricting body movement soon after birth.

Standard precautions are recommended to prevent the spread of Zika in healthcare settings, including labor and delivery. CDC recommendations are available for healthcare providers to help prevent exposure to Zika virus in healthcare settings.

Geographic Areas with Risk of Zika Virus Transmission:
Areas with Zika risk are identified by the CDC and the World Health Organization (WHO). CDPH recommends the following references for determining Zika risk.

- For symptomatic pregnant women/persons, refer to the CDC Areas with Risk of Zika (https://wwwnc.cdc.gov/travel/page/zika-information).
- For asymptomatic pregnant women, use the WHO Zika Virus Classification Tables (http://www.who.int/emergencies/zika-virus/classification-tables/en/) using risk classification "Category 1" and "Catgory 2" countries to help limit the risk of false positive test results. The only documented transmission of Zika virus in the U.S. has been in Texas and Forida, but active transmission is **not ongoing at this time**.

Definition of Possible Zika Virus Exposure during Pregnancy:

- Travel to or living in an area with Zika risk (see above) during their pregnancy or up to 8 weeks before conception (six weeks prior to last menstrual period).
- Sex without barrier protections (male or female condoms and dental dams) with a male partner who had possible exposure to Zika within 6 months prior to sexual contact, or a female partner who had possible exposure to Zika within 8 weeks of sexual contact. Sexual activity includes vaginal, anal, and oral sex, as well as sharing of sex toys.

EXPOSURE ASSESSMENT & ZIKA VIRUS TESTING

1) Assess All Pregnant Women for Possible Zika Virus Exposure[1, 2]

All pregnant women should be assessed for possible Zika virus exposure (see above) at each prenatal care visit and at hospital admission. This evaluation should include a travel history to an area with risk of Zika virus transmission, an assessment of signs and symptoms of Zika virus disease (acute onset of fever, rash, arthralgia, or conjunctivitis) and a woman's sexual partner's potential exposure.

In-hospital assessment for possible Zika virus exposure should be incorporated as part of the medical/nursing intake process for all pregnant women for both antepartum and delivery admissions. CDC's *Screening Pregnant Women for Zika Testing* tool (https://www.cdc.gov/zika/pdfs/ZikaPreg_ScreeningTool.pdf) includes screening questions for Zika exposure and additional questions to help assess Zika risk.

Prenatal Zika virus test results should be shared with the birthing hospital prior to delivery. For pregnant women with a possible Zika virus exposure history or laboratory evidence of Zika virus infection, **birthing hospitals should work with their local health department to follow-up on pending maternal test results and plan for Zika virus testing of the infant (as indicated)**. For infants with prenatal abnormalities, providers may consider planning for delivery at a birthing hospital that includes the range of pediatric subspecialty care, if possible. *Maternal exposure history and testing results should be shared with providers caring for the newborn after delivery, including outpatient providers.*

2) Conduct Maternal Zika Virus Testing at Antenatal Hospital Visits and Delivery as Indicated

Pregnant women with an ***exposure history*** and ***no prior laboratory evidence*** of possible Zika virus infection should be tested for Zika virus as outlined below.

a. Symptomatic Pregnant Women with possible Zika virus exposure and symptoms (acute onset of fever, rash, arthralgia, or conjunctivitis) of Zika virus disease should be tested:

1. Concurrent Zika virus nucleic acid test (NAT) in serum and urine and IgM antibody testing if 12 weeks or less since symptom onset. If non-negative IgM

and Zika NAT negative, confirm with plaque reduction neutralization test (PRNT). See CDPH Comprehensive Zika Virus Information for Healthcare Providers for additional information on confirmatory PRNT testing to evaluate for cross-reactivity with dengue and other flaviviruses.

2. If previous NAT and IgM were obtained prior to two weeks of symptom onset and both NAT and IgM are negative, a repeat IgM test within 12 weeks of symptom onset should be considered.

b. Asymptomatic Pregnant Women *with ongoing*† possible Zika virus exposure should have been tested during the prenatal period. For women ***without*** prior evidence of laboratory-confirmed Zika virus infection, pending/unavailable test results, or possible Zika virus exposure since last negative test result, conduct:

1. NAT testing on serum and urine
2. IgM antibody testing may be considered but is not routinely recommended. Prolonged IgM persistence may make it challenging to determine whether the infection occurred during the current pregnancy or prior to the current pregnancy so timing of exposure needs to be considered. If done, IgM testing may be performed concurrently with NAT testing.

c. Asymptomatic Pregnant Women with recent *but without ongoing* exposure to Zika virus are not routinely tested **but instead should be assessed carefully** for factors that increase the likelihood of Zika infection.

1. If not yet tested after recent Zika virus exposure, risk factors that may prompt testing include:
    - Locally-transmitted Zika infections reported in the region of travel at the time of the possible exposure
    - Sexual partner with travel to Zika-risk areas or unprotected (e.g., without use of male or female condom or dental dam) sexual exposure
    - Longer duration of travel (e.g., over four weeks) or multiple sexual exposures
    - Engagement in higher risk activities (e.g., outdoor recreation as opposed to indoor activities) while in an area with risk of Zika transmission
    - Known mosquito bites in areas with risk of Zika transmission
    - Lack of use of protective clothing and insect repellent on a regular basis in an area with risk of Zika transmission
    - Compromised integrity of housing in an area with risk of Zika transmission (e.g., lack of window screens or air conditioning)
    - Other household members diagnosed with Zika virus infection
    - High risk patient occupation, e.g., potential laboratory or needle stick exposure

† Currently living in or frequently (daily or weekly) traveling to areas with Zika virus transmission or having ongoing unprotected exposures to a potentially infected sexual partner.

- Patient is recipient of recent transfusions or transplants, especially in an area with risk of Zika transmission, and there is not reliable testing of blood supply for Zika virus (the U.S. routinely tests blood donations for Zika virus)
- Patient underwent fertility treatment and was a recipient of a recent semen or egg donor in an area with a risk for Zika transmission, and there was no screening done at the time of donation.
- Patient preferences and decision-making

2. When testing is indicated, conduct:

   Concurrent Zika virus NAT (urine and serum) and IgM antibody testing if 12 weeks or less since exposure. If non-negative IgM and Zika NAT negative, confirm with PRNT. Prolonged IgM persistence may make it challenging to determine whether the infection occurred during the current pregnancy or prior to the current pregnancy.

d. Pregnant women with recent possible Zika virus exposure and a fetus with prenatal ultrasound findings consistent with congenital Zika syndrome should have received Zika virus NAT and IgM testing during pregnancy. Birth hospitals should obtain the Zika test results.

e. Placental specimen collection[1]:

Pathology testing of placental tissues for Zika virus infection may be considered to aid in maternal diagnosis for women with an exposure history/epidemiologic link to an area with risk of Zika transmission, as appropriate.

Placental Zika virus testing may be considered on a case-by-case basis in consultation with public health and is prioritized for: 1) symptomatic mothers with probable (unspecified flavivirus) Zika virus infection; and 2) exposed mothers with an infant or fetus with possible Zika virus-associated birth defects but no definitive diagnosis of Zika virus infection during pregnancy.

If Zika virus test results are pending or placental testing is under consideration, providers may consider fixing and storing placental tissues until the results are available and a final decision on placental Zika virus testing has been made.

Birthing hospitals should work with their local health department regarding placental specimen collection and information needed for pre-approval and submission.

See CDC Interim Guidance for Zika Virus Testing of Formalin-Fixed, Paraffin-Embedded Placental, Fetal, or Infant Autopsy Tissues for additional guidance and CDC Collecting and Submitting Placental and Fetal Tissue Specimens for Zika Virus Testing for tissue collection details.

3) Conduct Newborn Zika Virus Testing as Indicated[3]

a. Indications for Zika Virus Testing at Birth

1. Infants with clinical findings suggestive of congenital Zika syndrome and possible maternal Zika virus exposure during pregnancy, regardless of maternal testing results.
2. Infants born to mothers with laboratory evidence of possible Zika virus infection during pregnancy.

   Note: Birthing hospitals may consider collecting infant specimens for concurrent Zika virus testing if maternal testing is being done at delivery. If infant testing is being conducted but maternal infection is not yet confirmed, consider concurrent maternal testing to inform infant Zika test result interpretation.

b. Laboratory Testing of Infants for Congenital Zika Virus Infection

1. Zika virus NAT testing should be performed on both infant serum and urine and Zika virus IgM antibody testing should concurrently be performed on infant serum. If non-negative IgM and negative Zika NAT, confirm with PRNT.
2. For infants with clinical findings consistent with congenital Zika syndrome, testing CSF for Zika virus NAT and IgM antibodies should be considered, especially if serum and urine testing are negative and another etiology has not been identified.
3. If CSF is collected for other purposes, NAT and IgM antibody testing should be performed on CSF.

c. Newborn Specimen Collection

1. Newborn specimens should be collected within 2 days of delivery, if possible. If testing is performed later, distinguishing between congenital, perinatal, and postnatal infection is difficult. If timing of infection cannot be determined, infants should be managed as if they have congenital Zika virus infection.
2. Testing cord blood is not recommended because of issues with precision and accuracy.

See CDC Evaluation and Testing for Congenital Zika Virus Infection for additional information.

Fetal loss[1]**:** If a pregnant woman with laboratory evidence of Zika virus infection experiences a fetal loss, CDC recommends consideration of fetal and placental pathology testing for Zika virus infection on a case-by-case basis to aid in fetal or maternal Zika diagnosis. Hospitals should work with their local health department regarding specimen collection details.

See CDC Interim Guidance for Zika Virus Testing of Formalin-Fixed, Paraffin-

Embedded Placental, Fetal, or Infant Autopsy Tissues for additional guidance and CDC Collecting and Submitting Placental and Fetal Tissue Specimens for Zika Virus Testing for tissue collection details.

4) **Sharing Information with Pediatric Outpatient Provider**
Maternal exposure history and maternal and infant Zika test results should be shared with pediatric providers caring for the infant as an outpatient.

INFANT EVALUATION & FOLLOW-UP

See the CDC algorithm for evaluation for infants with possible congenital Zika virus infection.

1) **Conduct Recommended Clinical Evaluation of All Newborn Infants Born to Mothers with Possible Zika Virus Exposure**

Infants with abnormalities consistent with congenital Zika syndrome, regardless of maternal Zika virus test results

- Routine newborn care with comprehensive physical exam, including standardized measurement of head circumference
- Zika virus testing
- Head ultrasound by 1 month of age
- Comprehensive ophthalmologic exam by 1 month of age
- Newborn hearing screen, preferably automated auditory brainstem response (ABR)
    - If not ABR for newborn screen then ABR by 1 month of age
- Evaluate for other causes of congenital anomalies
- Refer to developmental specialist and Early Start through their local Regional Centers for early intervention services
- Provide family support services
- Consider additional consultation with infectious disease specialist, clinical geneticist, neurologist, and others based on clinical findings

Further neuroimaging (MRI, CT) in consultation with a neurologist may be considered. Transfer to a hospital with subspecialty care typically is not necessary unless there is an urgent clinical need.

Infants with normal exams born to mothers with laboratory evidence of possible Zika virus infection during pregnancy

- Routine newborn care with comprehensive physical exam, including standardized measurement of head circumference
- Zika virus testing
- Head ultrasound by 1 month of age to detect subclinical brain findings

- Comprehensive ophthalmologic exam by 1 month of age to detect subclinical eye findings
- Newborn hearing screen, preferably automated ABR by 1 month of age
- If findings suggestive of congenital Zika syndrome are identified at any time, evaluation should follow recommendations for infants with clinical findings of congenital Zika syndrome with referral to appropriate specialists and further evaluation

Infants with normal exams born to mothers with NO laboratory evidence of Zika virus infection

- Routine newborn care with comprehensive physical exam, including standardized measurement of head circumference
- Newborn hearing screening
- Further clinical evaluation for congenital Zika virus infection is not routinely indicated but health care providers can consider additional evaluation in consultation with families, taking into account infant's complete physical exam with emphasis on neurologic findings, risk of screening (e.g., identification of incidental findings), and maternal risk factors for Zika infection (e.g., presence and timing of symptoms, and type, location and length of possible Zika virus exposure)
- If findings suggestive of congenital Zika syndrome are identified at any time, evaluation should follow recommendations for infants with clinical findings of congenital Zika syndrome with referral to appropriate specialists and further evaulation

In-hospital level of care for newborn: Unless otherwise medically necessary, newborns with findings consistent with congenital Zika syndrome are not required to be transferred to the neonatal intensive care unit (NICU) for infant examinations, evaluations, or specimen collection. 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. Rooming-in with mother is recommended when possible. Transfer to a facility with access to pediatric subspecialty care typically is not necessary unless there is an urgent clinical need.

In addition, free and confidential counselors speaking English and Spanish are available at MotherToBaby to talk to families about Zika virus infection during pregnancy.

2) Arrange Follow-up Evaluation and Management Prior to Hospital Discharge for ALL Infants

All infants, *including those without findings of congenital Zika syndrome*, should have an established medical home to receive routine pediatric preventive care, including comprehensive physical exams, growth parameters (e.g., head circumference, weight, and length), immunizations, developmental monitoring and screening using validated

screening tools recommended by the American Academy of Pediatrics, and vision screening as recommended by the American Academy of Pediatrics.

For normal-appearing infants born to mothers with laboratory evidence of Zika infection, a head ultrasound, comprehensive ophthalmologic exam and ABR should be done by 1 month of age if not done at the birthing hospital.

3) Additional Follow-up Care of Infants with Findings Consistent with Congenital Zika Syndrome

Infants with clinical findings consistent with congenital Zika syndrome require a multidisciplinary team and an established medical home for coordination of care to ensure abnormal findings are addressed. Follow-up appointments with specialists and services recommended during hospital evaluation should be made prior to discharge. Decisions on further evaluation should be guided by clinical findings and made in consultation with the family. Follow-up visits with specialists will be based on the specialist(s) recommendations. Birthing hospitals and primary care providers may consider using Zika Care Connect, which provides a searchable network of healthcare specialists who care for patients affected by Zika.

Pediatric providers should maintain vigilance for additional clinical findings:

- Neurologic status and delays in development
- Post-natal onset microcephaly
- Signs of increasing intracranial pressure (e.g., vomiting, mental status changes) should prompt brain imaging to assess for hydrocephalus after birth
- Visual impairment
- Signs of dysphagia or problems with swallowing
- Consider diaphragmatic paralysis among infants with respiratory distress

All infants with congenital Zika syndrome should be referred to a developmental specialist and Early Start early intervention services through their local Regional Center.

For referral to the California Children's Services (CCS) program, contact your local county CCS office. California Children's Services (CCS) is a state program for children with certain diseases or health problems. Eligible children will be referred to providers knowledgeable in the care of children with special health care needs.

Family Support: Families should be connected with family supportive services in the community prior to hospital discharge.

4) Follow-up on Maternal Zika Virus Testing at Delivery

Pediatric providers should inquire about maternal exposure history and maternal Zika virus testing conducted at delivery. If maternal Zika virus testing is done at delivery and test results indicate laboratory evidence of possible Zika virus infection during pregnancy, infant Zika virus testing should be ordered.

5) Neonatal Evaluation for Acute Perinatal Zika Virus Infection

Maternal-infant transmission of Zika virus is possible during delivery. Acute Zika virus disease should be suspected in a symptomatic infant within the first 2 weeks of life whose mother was potentially exposed to Zika virus within approximately 2 weeks of delivery. Infant symptoms in acute infection include one or more of the following: fever, rash, conjunctivitis, or arthralgia. (See under *Postnatal Zika Virus Infection* on CDC's Evaluation & Testing webpage, https://www.cdc.gov/pregnancy/zika/testing-follow-up/evaluation-testing.html.)

6) Encourage and Support Breastfeeding

Breastfeeding should be encouraged for nutrition and bonding. Although Zika virus has been detected in breast milk, no cases of Zika virus infection associated with breastfeeding have been reported, and current evidence suggests that the benefits of breastfeeding outweigh the theoretical risk of Zika virus transmission.[2]

REPORTING

1) Report Zika Virus Infection of Mother and Infant to Public Health and the Zika Pregnancy and Infant Registry

Please contact your local health department to report:

- all pregnant women with laboratory evidence of possible Zika virus infection and their infants (regardless of infant Zika test results)
- infants with laboratory evidence of possible congenital Zika virus infection and their mothers.

Zika virus infection is a reportable condition in California (Title 17, CCR § 2500).

The US Zika Pregnancy and Infant Registry (USZPIR) includes both asymptomatic and symptomatic **pregnant women** with laboratory evidence of possible Zika virus infection with pregnancy completion date up to and including March 31, 2018, and follow-up on their **infants** at 2, 6, 12, 18 and 24 months (regardless of infant test results). Infants with laboratory evidence of congenital Zika virus infection are also included in the Registry. California providers reporting to the USZPIR should do so by contacting CDPH. For more information and assistance on reporting to CDPH for the USZPIR, contact ZikaOutcomes@cdph.ca.gov or call (510) 620-3151.

NOTE: In January 2018, CDC began referring to the existing US Zika Pregnancy Registry as the US Zika Pregnancy *and Infant* Registry.

RESOURCES

US Zika Pregnancy and Infant Registry:

- Please contact CDPH for reporting to the US Zika Pregnancy and Infant Registry
- For more information, contact ZikaOutcomes@cdph.ca.gov or call (510) 620-3151
- Website: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/USZikaPregnancyRegistry.aspx

MotherToBaby:

- Free and confidential counselors speaking English and Spanish and knowledgeable about Zika infection in pregnancy are available to families Phone: 1-866-626-6847
- Text: 1-855-999-3525
- Website: http://mothertobaby.org/contact-expert/

California Children's Services (CCS)

- California Children's Services (CCS) is a state program for children with certain diseases or health problems. Through this program, eligible children up to 21 years old can get the health care and services they need.
- Website: http://www.dhcs.ca.gov/services/ccs/Pages/default.aspx
- Local CCS Program Contacts: http://www.dhcs.ca.gov/services/ccs/Pages/CountyOffices.aspx

Zika Care Connect:

- Toll-free helpline for providers and patients: 1-844-677-0447 Monday-Friday (9 a.m. – 5 p.m. Eastern Time), English and Spanish
- Email: helpline@zikacareconnect.org
- Website: https://www.zikacareconnect.org/

CDPH, CDC, and WHO Tools:

- CDPH Outpatient Screening Algorithm-Child/Adult
- CDPH Patient Self-Assessment Tool
- CDC Areas with Risk of Zika
- WHO Zika Risk Classification
- CDC Zika Screening Tool for Pregnant Women
- CDC Evaluation for Infants with Possible Congenital Zika Virus Infection

CDPH and CDC Resources:

- CDPH Comprenensive Zika Virus Information for Healthcare Providers
- CDPH Zika Education Toolkits (posters, talking points, social media messages on Zika and Pregnancy, Sex, Travel and Family Planning)

Provider Organization Resources:

- American Academy of Pediatrics Zika Resources
- American Congress of Obstetricians and Gynecologists Zika Resources
- Practice Advisory Interim Guidance for Care of Obstetric Patients During a Zika Virus Outbreak (ACOG and Society for Maternal-Fetal Medicine)

REFERENCES

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2. The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM). Practice Advisory Interim Guidance for Care of Obstetric Patients During a Zika Virus Outbreak. Washington, DC: ACOG and SMFM; September 15, 2017. Available at: https://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak
3. Adebanjo T, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection – United States, October 2017. MMWR 2017; 66(41); 1089-1099.