Evaluation Procedures for Suspected Congenital Zika Virus Infection – Fetus, Newborn and Infant

September 28, 2017

Overview

Identification of congenital Zika virus infection through appropriate maternal and infant Zika virus testing is a priority due to the important implications for infant monitoring and management and access to appropriate diagnostic and treatment services, which may rely on documented infection. We are still learning about the performance of Zika virus testing to diagnose congenital exposure. Therefore, the intention of the information outlined below is to maximize the opportunity to identify congenital Zika virus exposure and infection among live births, fetal losses or infant deaths following a live birth to a mother with possible Zika virus exposure in pregnancy.

Evaluation for congenital Zika virus infection involves specimen collection around the time of delivery, and therefore requires advance planning, coordination and communication between public health officials and health care providers. The purpose of this document is to provide information for local public health departments to use in these efforts, including:

- Local Health Department considerations
- Indications for Zika virus testing at delivery
- Specimen collection and lab testing for congenital Zika virus infection
- Zika virus case reporting and instructions for linking maternal and infant Zika cases in CalREDIE
- Resources for health care providers on the clinical evaluation of infants

Local Health Department Considerations – Advance Planning in Response to Possible Maternal Zika Virus Infection

In order for providers and local health jurisdictions to evaluate suspected congenital Zika virus infection in an effective and timely manner, it is recommended that local health jurisdictions/departments (LHD) be aware in advance of the following information for all pregnant women with laboratory evidence of Zika virus infection during pregnancy or with Zika tests still pending at time of delivery:

- Estimated date of confinement (EDC) or due date
- Obstetric/Maternal-Fetal Medicine providers and contact information
- Birthing hospital where delivery is planned
  - For infants with prenatal abnormalities, plan for delivery at a birth 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.

See Appendix A: LHJ Checklist for Infant Evaluation of Congenital Zika Virus Infection
LHD should assist providers with requests for placental, fetal and infant autopsy tissue testing and specimen collection, including information needed for pre-approval and submission. LHD should contact CDPH at 916-552-9725 or send in a secure email to charsey.porse@cdph.ca.gov for approval of placental testing and submission.

**Indications for Zika Virus Testing at Delivery**

**Newborn Infants**

*Both the Centers for Disease Control and Prevention (CDC) and the California Department of Public Health (CDPH) recommend Zika virus testing for:*

1. Infants born to mothers with laboratory evidence* of Zika virus infection during pregnancy, and
2. Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and possible maternal exposure to Zika virus through travel or sexual contact regardless of maternal Zika virus test results. Congenital Zika syndrome includes a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes microcephaly, structural brain anomalies, posterior eye anomalies, contracture of one or more joints, and functional neurologic abnormalities.

*CDC also recommends newborn Zika virus testing be considered and CDPH recommends testing be conducted for:*

1. Infants born to mothers with an epidemiologic link† to an area with risk of Zika and who were not yet tested (even if all or part of exposure was outside the 12 week window).
2. Infants born to mothers with negative testing‡ but with ongoing possible maternal Zika virus exposure.
3. Infants born to mothers whose negative testing was performed more than 12 weeks after the mother’s possible exposure.

In all scenarios, infant specimens should be collected within 2 days of delivery, if possible.

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* Laboratory evidence of maternal Zika virus infection includes:
  - Zika virus RNA detected in any maternal clinical specimen by Nucleic Acid Test (NAT) real-time reverse transcription-polymerase chain reaction (rRT-PCR or RT-PCR); or
  - Positive Zika virus immunoglobulin M (IgM) with confirmatory neutralizing antibody titers (plaque reduction neutralization test or PRNT) for Zika virus or flavivirus. (Because of the decline in IgM antibody and viral RNA levels over time, no detection of Zika virus on maternal testing > 12 weeks after exposure does not rule out maternal infection.)

† An epidemiologic link (exposure history) during pregnancy or the periconception period (8 weeks before conception, 6 weeks before LMP) includes travel to or residence in an area with risk of Zika, or sex without a condom with a partner who traveled to or lived in such as area.

‡ “Negative testing” refers to Zika virus testing results that indicate no evidence of recent Zika virus infection.
Maternal Zika Virus Testing at Delivery

CDPH recommends *maternal Zika virus testing in parallel with infant testing* whenever infant testing is indicated (as outlined above) and maternal Zika virus infection has *not* been confirmed. Parallel testing of maternal and infant specimens may help with test result interpretation considering the logistical challenges of waiting for maternal test results, limitations with maternal testing beyond 12 weeks following exposure/symptom onset, and potential loss to follow-up for subsequent testing.

*Both CDC and CDPH recommend Zika virus testing for:*

(1) Mothers with a history of Zika virus exposure within the prior 12 weeks (start and end dates of exposure within the 12-week window) and not yet tested.

*CDC also recommends maternal Zika virus testing be considered and CDPH recommends testing be conducted for:*

(1) Mothers with a history of Zika virus exposure more than 12 weeks (all or part of exposure outside the 12-week window) prior to specimen collection and not yet tested.

*CDPH also recommends maternal Zika virus testing whenever infant testing is indicated (as outlined above) and maternal Zika virus infection has not been confirmed such as:*

(1) Mother previously tested negative outside of the 12-week window.

(2) Maternal laboratory tests results not available

Placental Zika Virus Testing to Aid in Maternal Zika Diagnosis

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, as appropriate.

Placental testing for Zika virus is prioritized for symptomatic pregnant women with probable (unspecified flavivirus) Zika virus infection and for women with a fetus or infant with Zika virus-associated birth defects and without a definitive diagnosis of Zika virus infection during pregnancy. In the context of Zika virus-associated birth defects, placental testing may be considered on a case-by-case basis if there has been no previous maternal Zika virus testing; inconclusive Zika test results; or confirmed infection but timing of infection with respect to the pregnancy is unclear.

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

**Placental Zika Virus Testing Guidance:**

*Interim Guidance for Zika Virus Testing of Formalin-Fixed, Paraffin-Embedded Placental, Fetal, or Infant Autopsy Tissues* (CDC)
Fetal Demise or Infant Death Following a Live Birth

CDC recommends consideration of Zika virus testing of placental, fetal and infant autopsy tissues on a case-by-case basis to aid in fetal, infant or maternal Zika diagnosis in the case of a fetal loss or infant death (following a live birth) to a mother with possible Zika virus exposure during pregnancy.

In the case of a fetal loss or infant death (following live birth) to a woman with laboratory evidence of Zika virus infection, Zika virus testing of placental, fetus or infant autopsy tissues should be considered to aid in fetal and infant diagnosis.

In addition, Zika virus testing of placental, fetus or infant autopsy tissues should be considered to aid in fetal, infant and maternal diagnosis in the case of a fetal loss or infant death (following live birth) to a woman with any of the following:

1. inconclusive Zika test results;
2. no maternal testing; or,
3. presumptive Zika/flavivirus infection but timing of infection cannot be determined (e.g., living in area with active Zika virus transmission, repeated travel or sexual exposure).

Tissues may be collected and stored until pending maternal Zika test results are available and a final decision on testing has been made.

Infants with Congenital Anomalies and No Evidence of Infection on Newborn Zika Virus Testing

For infants born with anomalies consistent with Zika virus syndrome and initial serum and urine results do not indicate Zika virus infection, Zika virus testing of CSF should be considered. There are limited reports of infants with congenital Zika virus infection in which CSF was the only sample with evidence of Zika infection.

Resources on Indications for Testing for Congenital Zika Virus Infection:

- [Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016](#)
- [Implementing CDC Guidance for Infant Neuroimaging and Infant and Placental Testing June 30, 2017](#)
- [Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017](#). See Table 2.

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§ Inconclusive Zika test results: Non-negative IgM with symptom onset or exposure > 12 weeks before specimen collection.
Specimen Collection and Laboratory Testing for Congenital Zika Virus Infection

Hospitals should contact their local health department regarding collection and submission of placental, fetal and infant autopsy samples. All testing of placental, fetal and infant autopsy samples for Zika virus infection is conducted at the CDC and specimen approval and handling is facilitated by CDPH/Viral and Rickettsial Disease Laboratory.

Newborn Specimen Collection and Zika Virus Testing

Serum and/or urine specimens (cerebrospinal fluid is an optional secondary test specimen) should be obtained within the first 2 days of life, if possible. Testing infant specimens collected within the first few weeks to months after birth may still be useful in the evaluation for possible Zika virus infection, especially among infants born in areas without risk of Zika. For infants born in areas with Zika risk, if testing is performed beyond 2 days of life, 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. Testing cord blood is not recommended because of issues with precision and accuracy. Although Zika virus infection in infants is not a clinical emergency, urgent communication with the pregnant patient’s obstetric and neonatal providers might be necessary.

Recommended infant laboratory evaluation includes:
- Zika virus ribonucleic acid (RNA) nucleic acid testing (NAT, e.g. RT-PCR testing) on both infant serum and urine.
- Zika virus IgM testing concurrently on infant serum.
- Testing of cerebrospinal fluid may also be considered if serum and urine results are negative; NAT (rRT-PCR) testing and Zika virus IgM should be performed on CSF.

In the case of presumptive maternal infection (non-negative Zika IgM with PRNT pending) on testing conducted prior to delivery, newborn specimens may be submitted OR may be collected and stored pending maternal test results, though the logistics of specimen holding may be infeasible.

Maternal Specimen Collection for in Parallel Maternal-Infant Zika Virus Testing

Maternal specimens should be collected in parallel with infant testing if maternal Zika virus infection has not been confirmed (e.g. not yet tested, previously tested negative outside of 12-week window, or lab tests not available).

Recommended maternal laboratory evaluation includes:
- Zika virus NAT testing (rRT-PCR) on maternal serum and urine if less than 2 weeks since exposure.
- Zika virus IgM testing concurrently on maternal serum and, for serum collected >
2 weeks since exposure, reflex to PCR following non-negative IgM.

**Fetal and Infant Autopsy Specimen Collection for Fetal Demise or Infant Death Following a Live Birth**

Specimens should be collected for Zika virus testing, histopathology, and immunohistochemical staining on fetal or infant autopsy tissue, umbilical cord, placental disk, and fetal membranes, as available. Fixed tissue specimens are optimal. Tissues may be collected and stored until pending maternal Zika test results are available and a final decision on testing has been made. Staff who collect and handle specimens should refer to [Zika biosafety guidelines for laboratory and pathology procedures](#).

Providers should contact their [local health department](#) for additional information and assistance with specimen submission.

**Placental Specimen Collection**

If there are pending Zika test results or placental testing is under consideration, providers should fix and store placental tissues until the results are available and a final decision on placental Zika virus testing has been made.

Testing will be considered in consultation with public health. Providers should contact their [local health department](#) regarding placental specimen collection and information needed for pre-approval and submission.

**Resources and Forms for Specimen Collection and Submission for Zika Virus Testing:**

- [Zika Laboratory Testing Guidance (CDPH)](#)
- [Collecting & Submitting Placental and Fetal Tissue Specimens for Zika Virus Testing](#) (includes information on placental, fetal and infant autopsy tissues) (CDC)
- [Information for Collection and Submission of Specimens at Time of Birth](#) (CDC)
- For each tissue specimen submitted, the following forms must be completed:
  - [CDC human specimen submittal form](#) (Form 50-34; 2016 CDC DASH form)
  - [CDPH VRDL specimen submittal form](#) (VRDL Form Lab 300)
Zika Virus Case Reporting

Any infant under evaluation for congenital Zika virus infection requires his or her own case report form for suspected Zika virus infection, separate from the form created for the mother.

Providers should contact their local health department for reporting information.

**Jurisdictions participating in CalREDIE:** Create a separate incident in CalREDIE for the infant and complete information in all tabs as appropriate. Information on how to link the maternal and infant information in CalREDIE can be found at the end of this document in Appendix B.

**Jurisdictions not participating in CalREDIE:** Complete the Zika Case Report form and fax to Dr. Charsey Porse at 916-552-9725 or send in a secure email to charsey.porse@cdph.ca.gov The CDPH Zika Case Report form can be found on the CDPH Controlled Forms webpage (https://www.cdph.ca.gov/CDPH%20Document%20Library/ControlledForms/cdph8680.pdf).

See Appendix B: Linking Maternal and Infant Incident Reports in CalREDIE

**Resources for Health Care Providers on the Clinical Evaluation of Infants**

The CDC has an updated algorithm for the initial evaluation and outpatient management for infants with possible Congenital Zika virus infection (https://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf).

More information on the evaluation, management and follow up of infants with possible congenital Zika virus infection can be located on the CDC Zika virus webpage for infants and children (https://www.cdc.gov/zika/hc-providers/infants-children.html).

**Resource Weblinks**

**CDC Interim Guidance for Zika Management**

- **Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016**
  https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6533e2.pdf

- **Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017**
  https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6533e2.pdf

**CDC Guidance Tools/Websites for Zika Virus Testing and Specimen Collection**

- **Implementing CDC Guidance for Infant Neuroimaging and Infant and Placental**
Interim Guidance for Zika Virus Testing of Formalin-Fixed, Paraffin-Embedded Placental, Fetal, or Infant Autopsy Tissues

Collecting & Submitting Placental and Fetal Tissue Specimens for Zika Virus Testing (includes information on placental, fetal and infant autopsy tissues)

Information for Collection and Submission of Specimens at Time of Birth

CDPH Zika Laboratory Testing and Submission Guidance and Instructions
CDPH Zika Laboratory Testing Guidance
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaLaboratoryTestingGuidance_VRDL.pdf

CDPH and CDC Lab Submittal Forms
CDPH VRDL specimen submittal form (VRDL Form Lab 300):
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/VRDL_General_Human_Specimen_Submittal_Form.pdf

CDC human specimen submittal form (Form 50-34; 2016 CDC DASH form):

CDPH Case Report Forms

California Local Health Department Contact Information, Communicable Diseases
https://www.cdph.ca.gov/Programs/CCLHO/CDPH%20Document%20Library/LHD_CD_Contact_Info_ADA.pdf
Appendix A: LHJ Checklist for Infant Evaluation of Congenital Zika Virus Infection

[ ] Review CDC and CDPH guidelines to assure infant meets criteria for evaluation
[ ] Contact obstetrics provider to review recommended evaluation and confirm EDC and hospital where delivery will take place
[ ] Communicate with provider and/or hospital laboratory regarding appropriate specimen collection timing, storage, and transportation
[ ] Alert local public health lab of incoming specimen for transport to CDPH VRDL and/or CDC, as appropriate.
[ ] As appropriate, review CDC guidelines for infant evaluation with obstetrics provider and/or pediatric provider at hospital where delivery will take place
[ ] Complete CDPH Zika Case Report Form for infant (PDF or CalREDIE)
[ ] Ensure CDPH Zika Case Report Form completed for maternal case (PDF or CalREDIE)
[ ] Complete any additional forms required by individual local health jurisdiction
[ ] Complete any additional forms requested by CDC (forwarded by CDPH, if applicable)
[ ] Complete CDC laboratory DASH form for each tissue specimen
[ ] Complete CDPH VRDL specimen submittal form for each specimen
Appendix B: Linking Maternal and Infant Incident Reports in CalREDIE

Congenital Zika Virus Infection:
Linking Maternal and Neonatal Investigations in CalREDIE to Initiate a Neonate Investigation:

(1) Enter the mother’s case information into her own Disease Incident, per standard procedure.

(2) With the mother’s case open, on the “Epidemiologic Info” tab, scroll down to “Contacts (system)” click ‘Link Patient’ to see if the infant already exists in CalREDIE (Figure 1).
   a. Search on any combination of Name, DOB, Address, and/or Phone. If a match is found, click (highlight) your match then click OK.
   b. If not found, click Cancel and enter First and Last Name of the infant as well as any available demographics. **Minimum fields required: Last Name, First Name.**

Note: If the infant’s last name is not yet known, enter the mother’s last name for the infant. If the infant’s first name is not yet known, enter Baby, Baby Girl, or Baby Boy, as gender-appropriate for the infant.

Figure 1:
(3) Click Save to save changes on the Epidemiologic Info tab.
(4) Click “Create Incident” to turn infant into a new Disease Incident. You must Save (step #3) to enable the “Create Incident” button. Do not use the Create Investigation button.
(5) Click “OK” in pop-up box to confirm that you want to turn the infant into a new Incident. A pop-up box will subsequently notify you that “The contact has been successfully turned to a new incident.” (Figure 2)

Figure 2.
(6) Click on new DI Incident link to go to the infant’s new Incident (Figure 3).

Figure 3.
(7) On the infant’s Patient tab, the Disease Condition will default to “Zika Virus Infection”. Name, address, race, and gender will carry over from the Contacts (systems) entry in the mother’s incident (Figure 4).

Figure 4.

(8) Enter required information on the infant’s Patient, Clinical, Laboratory, Epidemiology, and Case Investigation Tabs.

(9) Click “Submit” to save Incident in CalREDIE.

You have now successfully accomplished:
Creating a new Incident for a Congenital Zika investigation, and generating a link between the infant and mother in CalREDIE! The same steps can be used to link sexually transmitted cases in CalREDIE.