Zika Virus Information for Healthcare Providers

September 25, 2017

Contents

A. Zika Fundamentals for Health Care Providers

I. Identifying Patients at Risk

- All pregnant women, women planning pregnancy and patients who have symptoms consistent with Zika virus disease should be assessed for potential Zika virus exposures.
- Criteria for possible exposure to Zika virus include:
  - Recent travel to an area with risk of Zika, or
  - Recent unprotected sexual contact with a male who has traveled within the prior 6 months to an area with risk of Zika or with a female who has traveled within the prior 8 weeks to an area with risk of Zika.
- California Department of Public Health (CDPH) recommendations for identifying persons at risk of Zika infection are based on Centers for Disease Control and prevention (CDC) guidance, regional epidemiology of Zika cases and travel patterns of Californians.
- A CDPH Zika Screening Algorithm is available online (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaAlgorithmPoster.pdf).

II. Clinical Features:

- Primary symptoms compatible with Zika virus disease include
  - maculopapular rash,
  - fever over 100.4F/38C,
  - arthralgia
  - conjunctivitis.
- Other potential symptoms include myalgia and headache, but these symptoms alone are not considered sufficient to qualify as a suspect case due to non-specificity
- Symptom onset should be within 2 weeks of travel or last known exposure.

III. Assessing Patient Risk and Shared Decision Making

- Multiple clinical variables are likely to influence the level of risk of disease in any given clinical setting, and therefore will influence the positive and negative predictive value of laboratory testing. Both the CDC and CDPH emphasize the importance of shared decision-making between providers and patients in deciding whether or not to test in a given clinical situation, based upon individualized risk factors. Remaining questions in such situations may be directed to local health departments. Some of these factors include:
  - Presence or absence of primary or secondary clinical symptoms
  - Incidence of Zika related infection in the travel-related region at the time of the possible exposure
  - Duration of the exposure/travel
  - Type of travel
  - Presence of known mosquito bites
  - Use of protective clothing and insect repellent
  - Integrity of housing in the location of exposure (e.g., window screens, air conditioning, etc.)

- Other household members with diagnosed Zika virus disease
- Patient occupation: laboratory or needle stick exposure
- Patient recipient of transfusions or transplants, even though testing of blood supply is currently being conducted
- Patient preferences and values
- Classic presentation of Zika virus disease in a region with known Aedes vector mosquitoes

IV. Testing Guidance for Zika Infection

- Laboratory testing for Zika should be considered for the following patients with travel or sexual exposure to Zika:
  - Patients who have at least one of the four primary symptoms of Zika (see above), or
  - Asymptomatic pregnant patients with an episode of possible Zika exposure during or up to 8 weeks prior to pregnancy, or
  - Asymptomatic pregnant patients with ongoing exposures to Zika due to residence, repeated travel or sexual exposure.
  - Pregnant women who are found to have a fetus with prenatal ultrasound findings consistent with Congenital Zika Syndrome.
- For details regarding specimen collection and test selection, see C. Laboratory Testing.
- Zika testing should also be considered for symptomatic patients with travel, employment or residence in California counties where *Aedes* vector mosquitoes are endemic but without a history of travel or sexual exposure to Zika risk areas. Consult with the local public health jurisdiction to rule out a possible incident of local transmission. See Evaluation for Possible Local Transmission.

V. Reported Zika Cases and *Aedes* Mosquitoes in California

- The CDPH Zika website is updated weekly with the number of confirmed and probable Zika cases by California county (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TravelAssociatedCasesofZikaVirusinCA.pdf).
- To date, there has been no local mosquito-borne transmission of Zika virus in California. Thus far, Zika virus infections have been documented only in persons exposed through travel to a Zika affected area or sexual contact with a traveler.
- View an updated map of California counties where *Aedes* vector mosquitoes are present (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/AedesDistributionMap.pdf).
- View an interactive map with more detailed information about the distribution of *Aedes* vector mosquitoes in California (http://cdphdata.maps.arcgis.com/apps/webappviewer/index.html?id=57367199287a4d18a2cecf107854255b).

VI. General Patient Education and Prevention Messaging

- Pregnant women in any trimester of pregnancy should be advised not travel to any area with risk of Zika.
- View the CDPH list of countries and locations with risk of Zika.
- If patients are planning travel to areas with risk of Zika, they should be advised to

protect themselves from mosquito bites and sexual transmission.
  - Apply EPA-registered mosquito repellents; wear long-sleeved shirts and long pants; and use air conditioning or window/door screens to keep mosquitoes outside or use a mosquito bed net.
  - Use condoms/barriers correctly every time they have sex or abstain from sex.
- After returning from an area with risk of Zika, use mosquito repellent for 3 weeks to prevent spreading Zika to California mosquitoes and the community.
- People who have Zika infection or have been potentially exposed to Zika virus (through travel or sexual contact) should abstain from sex or use condoms (male or female) and dental dams to prevent transmitting the virus to their sexual partner, as follows:
  - Pregnant couples in which either partner is exposed or infected should abstain from sexual contact or use barrier protection for the duration of the pregnancy.
  - Non-pregnant women should abstain from sexual contact or use barrier protection for 8 weeks after last exposure or symptom onset.
  - Males should abstain from sexual contact or use barrier protection for 6 months after last exposure or symptom onset.
- Zika Outreach & Education Materials Toolkits for Healthcare Professionals are available. Toolkits address Zika and -Pregnancy, -Travel, -Family Planning and -Sex and contain posters (in English and Spanish), discussion points, and social media posts. They are available on the CDPH Zika website (http://cdph.ca.gov/Zika).

B. Guidance by Patient Population

I. General Population

- Zika virus testing is indicated for **symptomatic individuals (regardless of pregnancy status) who have been exposed to Zika** within 2 weeks of symptom onset.
  - Symptomatic individuals should undergo testing for Zika virus according to **C. Laboratory Testing**, below, or in the CDPH Zika Screening Algorithm.
- Zika testing of the **non-pregnant** population for Zika virus infection could be considered for two primary reasons:
  - To determine if an exposed and symptomatic patient is actively infected and/or capable of transmitting disease to others
  - To determine if an unexposed potentially infected patient represents a first (index) case for a local transmission event
- **Evaluation for Possible Local Transmission**: The risk of local Zika virus transmission in California is low. However, mosquitoes that can transmit Zika virus are present in some parts of California. To rule out a possible case of locally transmitted Zika infection in a California region with a local *Aedes* vector mosquito population, lab testing for Zika may be considered in consultation with the local public health department and CDPH if Zika virus infection is suspected in someone **without recent travel or sexual exposure history,** including newborns with findings consistent with congenital Zika syndrome and no maternal exposure history.

II. Pregnant Patients and Their Sexual Partners

Pregnant women in California who have been exposed to Zika through travel or sexual contact should be tested for Zika, regardless of the presence or absence of symptoms.

a. Pregnancy Outcomes

- Zika virus infection during pregnancy has been linked to problems such as miscarriage, stillbirth, and birth defects.
- Zika causes microcephaly and other serious brain anomalies in infants. *Zika-associated birth defects* include microcephaly, calcium deposits in the brain indicating possible brain damage, excess fluid in the brain cavities and surrounding the brain, absent or poorly formed brain structures, abnormal eye development, or other problems resulting from damage to brain that affects nerves, muscles and bones, such as clubfoot or inflexible joints, and confirmed hearing loss.
- *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.
- In 2016, about 5% of fetuses and infants born to women with laboratory evidence of recent possible Zika virus infection in the U.S. territories had possible Zika-associated birth defects, comparable to the percentage reported in the 50 U.S. states during 2016. Among women with confirmed recent Zika virus infection in the *first trimester*, between 8% (U.S. territories) and 15% (50 U.S. states and DC) had a fetus or infant with Zika-associated birth defects. The discrepancy between populations may be attributed in part to the laboratory definition of "confirmed" infection, with U.S territories using NAT (e.g. RT-PCR) only whereas the 50 U.S. states/DC confirmed infection using either NAT or IgM.
- Many unknowns related to Zika virus infection in pregnancy remain. The full spectrum of defects caused by Zika virus infection in pregnancy continues to evolve, and factors that contribute to a woman's risk of adverse pregnancy or birth outcomes continue to be a subject of research.
- Among infants with prenatal exposure to Zika virus, absence of microcephaly at birth does not exclude congenital Zika virus infection or the presence of Zika-related brain and other abnormalities.

b. Prevention

- Pregnant women in any trimester or within 8 weeks of anticipated pregnancy should not travel to areas with risk of Zika.
- If pregnant women or their sexual partners who have lived in or traveled to an area with Zika are unable to abstain from sex, they should use condoms (male or female) and dental dams from start to finish every time they have sex (oral, vaginal, or anal) during the pregnancy. This includes same sex couples, and applies even if the pregnant woman's partner does not have symptoms of Zika or feel sick. Pregnant women should not share sex toys throughout the entire

pregnancy.
- Women should avoid exposure to Zika virus within 8 weeks prior to conception (6 weeks prior to last menstrual period). If exposure occurs, follow the testing recommendations for women exposed during pregnancy.

c. Screening for Exposure History

- Health care providers should ask all pregnant women at *every* prenatal visit about their residence in and travel history to areas with risk of Zika and the residence/travel history of their sex partners.
- Providers should ask about exposure *before* and *during* the current pregnancy including place, duration and type of travel in order to understand the potential intensity of exposure.
- Tools to assist providers in gathering patient histories related to Zika are available on the CDPH Zika Information for Health Professionals webpage.
  - Zika Virus Exposure Patient Self-Assessment Form – in English (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaVirusExposureSelfAssesmentForm.pdf)
  - Zika Virus Exposure Patient Self-Assessment Form – in Spanish (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaVirusExposureSelfAsssementFormSpanish)

- Pediatricians and primary care providers should ask about possible maternal Zika exposure, Zika virus test results, special testing or evaluation, examinations or diagnoses by pediatric subspecialists, signs of congenital Zika syndrome, any additional concerns about the baby during newborn care.

d. Lab Testing of Pregnant Patients

On July 24, 2017, CDC released updated Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure – United States and U.S. Territories. Both the CDC and CDPH emphasize a shared decision making model with testing decisions considered in accordance with patient preferences, risk tolerance, and clinical judgment and in line with state or local jurisdictional recommendations. CDC extends discretion to states where regional epidemiology and travel patterns may deviate from patterns seen in other parts of the country. In light of this discretion and due to epidemiologic and travel pattern issues specific to California, as of July 24, 2017, CDPH's recommendation regarding exposed asymptomatic pregnant women differs from the CDC recommendations for the U.S. as noted in the guidance below.

See CDPH August 2, 2017 Updated Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure which describes CDPH rationale and deviations from CDC guidance (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UpdatedZikaGuidanceforHCPsCaringforPregnantWomen.pdf).

- Testing in California is recommended for all pregnant women with possible exposure to Zika virus, regardless of symptoms, in accordance with the time of exposure or symptom onset according to **C. Laboratory Testing**, below.

e. Reporting to Public Health

- Pregnant patients with laboratory evidence of Zika virus infection or suspect cases with Zika-associated birth defects should be **reported immediately to the local Health Department**.
- Providers who are using the CalREDIE Provider Portal may enter the information directly into CalREDIE. Otherwise, providers should check with their local health department on how to report cases.
- Reporting of these patients will enable patient tracking and expedite testing and reporting of results.
- See contact information for local health department communicable disease reporting (https://www.cdph.ca.gov/Programs/CCLHO/CDPH%20Document%20Library/LHD_CD_Contact_Info_ADA.pdf)

f. Management and Monitoring Recommendations for Zika-infected Pregnant Patients

- Ultrasound: Pregnant women with laboratory evidence of Zika virus infection should be monitored frequently during pregnancy.
  - Pregnant women with confirmed or probable Zika virus infection should be counseled and monitored with serial fetal ultrasounds every 3–4 weeks to assess fetal anatomy, particularly neuroanatomy, and to monitor growth.
  - Pregnant women with preliminary/presumptive positive Zika virus infection should be counseled and monitored with serial ultrasounds pending final Zika test results.
  - For exposed mothers without lab confirmation, timing and frequency of ultrasound monitoring should be individualized according to risk, considering factors such as the timing of Zika lab testing (e.g. beyond 12 weeks from Zika exposure) and circumstances of exposure.
  - For pregnant women with an exposure more than 12 weeks prior to seeking prenatal care or with ongoing exposure, decisions for serial ultrasound monitoring beyond standard prenatal care should be made on a case by case basis, taking into consideration the individual circumstances of the exposure and patient preferences. Any abnormalities identified by prenatal ultrasound should be followed with repeat imaging.
  - Major ultrasound findings that have been associated with congenital Zika virus syndrome include microcephaly, intracranial calcifications, ventriculomegaly, arthrogryposis, and abnormalities of the corpus callosum, cerebrum, cerebellum, and eyes.
- Amniocentesis:
  - Amniocentesis should be individualized for each clinical circumstance in accordance with the recommendations of clinical specialists.
  - It is unknown how sensitive or specific NAT (e.g. RT-PCR) testing of amniotic fluid is for congenital Zika virus infection or whether a positive test is predictive of subsequent fetal abnormalities.

- The CDC provides counseling guidance and a variety of clinical tools online (https://www.cdc.gov/zika/hc-providers/pregnant-woman.html). However, it should be noted, in keeping with the discretion extended to states to apply regional epidemiology as described above, that CDPH guidance may continue to deviate from recommendations applied to the U.S. population in general.

g. The U.S. Zika Pregnancy Registry (USZPR)

The purpose of the USZPR is to provide data to further elucidate the full range of potential outcomes for fetuses and infants of mothers with Zika virus infection during pregnancy; to anticipate and plan to meet the needs of pregnant women and their families for clinical and public health services; and to inform updates to clinical guidance for managing pregnant women and their affected infants.

The USZPR includes both asymptomatic and symptomatic pregnant women with laboratory evidence of possible Zika virus infection and their infants up to 1 year of age. The USZPR also includes infants with laboratory evidence of congenital Zika virus infection and their mothers.

- CDPH is the point of contact for USZPR data submission for California to CDC. Providers and local health departments should submit data forms to CDPH for compilation and submission to CDC. Instructions for data submission are available on the CDPH US Zika Pregnancy Registry website (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/USZikaPregnancyRegistry.aspx).
- Local health departments or CDPH may be in contact with health care providers to assist with data collection.
- Potential data points included in the USZPR include: the time of maternal diagnosis; second trimester; third trimester; at delivery; and infant follow-up at 2, 6, and 12 months.
- Data collection for the Zika Pregnancy Registry is intended to capture existing information in the medical record at the above milestones.
- For questions about enrolling affected pregnant patients and their infants with the USZPR, contact us at ZikaOutcomes@cdph.ca.gov or call (510) 620-3151.

h. Counseling Recommendations

- Free and confidential counselors speaking English and Spanish are available at **MotherToBaby** to talk to families about Zika virus infection or diagnosis during pregnancy. Contact information: Phone 1-866-626-6847, Text 1-855-999-3525, or contact information webpage (http://mothertobaby.org/contact-expert/).
- Visit the CDC's Zika patient counseling webpage for more information and specific counseling suggestions (https://www.cdc.gov/zika/hc-providers/pregnant-women/patient-counseling.html).

III. Patients who traveled to Areas with Risk of Zika Prior to Conception

- For women or men *with or without symptoms of Zika virus disease who meet criteria for Zika exposure or have been diagnosed with Zika virus disease*, CDC recommends that healthcare providers:

  - Advise women to wait **at least 8 weeks** after return from travel or symptom onset before trying to get pregnant.
  - Advise men to wait **at least 6 months** after return from travel or symptom onset before trying to get pregnant with their partner.
  - People with possible Zika exposure should not have sex during this time period or should use condoms (male or female) and dental dams to avoid infecting their partners. To be effective, condoms must be used every time, from start to finish during vaginal, anal and oral sex and there should be no sharing of sex toys.
- The relationship between the time of conception and maternal Zika virus viremia and the ultimate effects of disease on the fetus remains under study, but Zika infection earlier in pregnancy (e.g. during first trimester) appears to increase the likelihood of more severe neurodevelopmental sequelae in the infant.
- Zika virus testing for the purpose of assessing the risk of sexual transmission is of uncertain value, because the current understanding of the duration and pattern of shedding in the male and female genitourinary tract is limited. Therefore, testing of specimens to assess risk for sexual transmission is currently *not* recommended.

IV. Patients who are Not Pregnant but Planning Pregnancy

- CDC recommends that women trying to get pregnant and their male partners talk to their healthcare provider before traveling to areas where there is Zika virus transmission.
- Healthcare providers should discuss pregnancy intention and reproductive options with women of reproductive age. For women traveling to areas with Zika risk, preconception care should include a discussion (ideally before travel) about mosquito bite prevention, signs and symptoms of Zika virus infection, and the potential risks associated with travel and Zika virus infection.
- Health care providers should assist patients to access highly effective contraceptive methods (e.g. Long Acting Reversible Contraception) if they would like to delay pregnancy.
- Patients should consider several factors regarding risk:
  - Risk of acquiring vector-borne Zika depends on the duration and extent of exposure to infected mosquitoes and the steps taken to prevent mosquito bites.
  - Most Zika virus infections are asymptomatic when they occur.
- If patients do travel, because sexual transmission is possible, both men and women should strictly follow steps to prevent mosquito bites during the trip.
- The CDC Interim Zika Guidance released on May 5, 2017, (which has been since updated) describes the option for providers to consider obtaining a baseline Zika IgM serology for patients who are imminently planning a pregnancy but who are unable to avoid ongoing exposures to Zika. Preconception Zika virus testing may help providers identify the timing of a potential asymptomatic Zika infection relative to the timing of a pregnancy should the IgM serology convert to positive during the pregnancy.

V. Patients Undergoing Fertility Treatment

- Zika virus transmission through assisted reproductive technology has not been reported; however, transmission through gametes or embryos is theoretically possible.

- Fertility treatment for sexually active couples using their own gametes and embryos should follow the timing recommendations for persons attempting conception; although recommendations may need to be adjusted depending on individual circumstances (see above recommended waiting periods).
- The Food and Drug Administration has developed guidance for donated tissues in the context of a Zika virus outbreak, including donated sperm, oocytes, and embryos. The guidance states that living donors will be deemed ineligible for anonymous donation if they have any of the following risk factors:
  - Medical diagnosis of Zika virus infection in the past 6 months
  - Residence in or travel to an area with risk of Zika within the past 6 months
  - Within the past 6 months, had sex with a male partner who, during the 6 months before sexual contact, either 1) received a diagnosis of or experienced an illness consistent with Zika virus disease or 2) had traveled to an area with risk of Zika

FDA Tissue Donor Screening Recommendations
(https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf)

VI. Infants

See CDPH guidance for the evaluation of suspected cases of Congenital Zika Syndrome (CZS)
(https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/GuidanceforCongenitalZikaInfectionEvaluation.pdf).

a. Indications for Zika Virus Testing at Birth

In all scenarios outlined below, 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. Testing cord blood is not recommended because of issues with precision and accuracy.

- **Newborn Infant Testing**
  - ***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[1] of Zika virus infection* during pregnancy, and
    (2) *Infants who have abnormal clinical or neuroimaging findings suggestive*

[1] 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.)

*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[2] 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[3] 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.

- **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 test results not available

- **Placental Testing**

[2] 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.
[3] "Negative testing" refers to Zika virus testing results that indicate no evidence of recent Zika virus infection.

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.

- **Fetal Loss and Testing**

  If a pregnant woman with laboratory evidence of Zika virus infection experiences a fetal loss, pathology testing for Zika virus infection should be offered. Hospitals should work with their local health department regarding specimen collection details. See CDC Collecting and Submitting Placental and Fetal Tissue Specimens for Zika Virus Testing.

b. Newborn Evaluation and Management for Possible Congenital Zika Virus Infection

See the CDC algorithm for initial evaluation and outpatient management of infants for possible congenital Zika virus infection (http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf).

Pediatricians and primary care providers should ask about possible maternal Zika virus exposure or possible congenital Zika syndrome during newborn care. In addition to Zika virus testing as outlined above and in **C. Laboratory Testing**, below, see recommendations below for care of infants born to mothers with possible Zika virus exposure.

- ***Infants with abnormalities consistent with congenital Zika syndrome*** born to mothers with either laboratory evidence of Zika virus infection; not yet tested; or tested negative more than 12 weeks after exposure or symptom onset, newborn evaluation before hospital discharge should include:
  - Routine newborn care, including standardized measure of head circumference, neurologic exam
  - Head ultrasound
  - Consultation with multiple specialists
  - Ophthalmology exam
  - Auditory evaluation with auditory brainstem response (ABR)
  - Additional laboratory testing (CBC, metabolic panel, LFTs)
  - Further neuroimaging (MRI, CT) and transfer to a hospital with subspecialty care may also be considered
- **Infants with *normal exams* born to *mothers with laboratory evidence of Zika virus infection* should have**:
  - Routine newborn care, including standardized measurement of head circumference and neurologic exam, head ultrasound, and standard newborn hearing screening.

- **Infants with *normal exams* born to mothers *with no laboratory evidence of Zika virus infection* and testing within 12 weeks of possible exposure should receive**:
  - Routine care, including standard newborn hearing screen, neurologic exam and head circumference.
- **Infants with *normal exams* born to *exposed mothers* who have not undergone Zika virus testing or tested negative more than 12 weeks after exposure or symptom onset should receive**:
  - A comprehensive physical exam including standardized measurement of head circumference, neurologic exam, and newborn hearing screening.
  - A head ultrasound and ophthalmological exam should also be considered before discharge based upon level of risk or concerns about reliability of infant follow-up.

c. 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 an infant symptomatic within the first 2 weeks of life whose mother traveled to or resided in a Zika affected area within 2 weeks of delivery. Infant symptoms in acute infection include ≥2 of the following: fever, rash, conjunctivitis, or arthralgia. (See CDC MMWR, February 26, 2016, http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm)

- If an infant shows signs and symptoms of acute Zika virus disease within the first 2 weeks of life, CDC recommends that both the mother and infant be tested for Zika virus infection.

VII. Postpartum Patients and Breastfeeding

- Although Zika virus RNA has been detected in breast milk, transmission of Zika infection through breastfeeding has not been documented.
- Mothers are encouraged to breastfeed infants even in areas where Zika virus is found, as available evidence indicates the benefits of breastfeeding outweigh any theoretical risks associated with Zika virus infection transmission through breast milk. (See CDC MMWR, February 26, 2016)
- There are no current recommendations to test breast milk.
- There is no current evidence that Zika virus infection in one pregnancy poses a risk of infection or birth defects in future pregnancies.

VIII. Patients with Guillain-Barré Syndrome

- Patients who have **both** a diagnosis of Guillain-Barré Syndrome and meet criteria for exposure to Zika virus should undergo testing for Zika virus according to **C. Laboratory Testing**, below.

C. Laboratory Testing

I. Testing Recommendations by Patient Population

- Testing for Non-Pregnant Symptomatic Individuals:
  - Test serum and urine by Zika virus ribonucleic acid (RNA) nucleic acid testing

(NAT, e.g. RT-PCR testing). NAT testing should be performed on serum collected <2 weeks after onset of symptoms (urine collected <3 weeks after onset).
    - Zika virus and/or dengue virus IgM testing of serum. If IgM is negative on serum collected <2 weeks after onset, repeat IgM testing on a second serum collected 2 to 12 weeks after onset.
- Testing for Symptomatic Pregnant women:
    - Concurrent testing of serum and urine by NAT and Zika virus IgM testing of serum as soon as possible and up to 12 weeks after symptom onset.
    - Testing of placental tissue specimens at time of birth can be considered for diagnostic purposes when there is no definitive diagnosis of laboratory confirmed Zika virus infection
- Testing for Asymptomatic pregnant women with recent but *not ongoing* exposure to Zika virus:
    - Test serum and urine by Zika virus NAT. NAT testing should be performed on serum collected <2 weeks after last known exposure (urine collected <3 weeks after onset). If NAT testing is negative, collect a second serum >2 weeks after last known exposure for IgM testing.
    - Zika virus and/or dengue virus IgM testing of serum collected >2 weeks after last known exposure. If IgM result is detected or equivocal, reflex to NAT testing (e.g. RT-PCR testing) and PRNT,
- Testing for Asymptomatic pregnant women with *ongoing* possible Zika virus exposure:
    - NAT testing on serum and urine at least once per trimester
    - IgM antibody testing during the first and second trimester
    - Testing should be performed unless a previous test has been positive.
- Testing for pregnant women with prenatal findings consistent with congenital Zika virus disease:
    - Follow the testing algorithm suggested for Symptomatic pregnant women
    - If amniocentesis is being performed as part of clinical care, NAT testing of amniocentesis specimens should also be performed.
    - Testing of placental tissue specimens at time of birth can be considered for diagnostic purposes when there is no definitive diagnosis of laboratory confirmed Zika virus infection. Placental or fetal tissue testing may be considered in other scenarios on a case by case basis after CDPH has been consulted and received pre-approval from CDC.
- Testing for infants with possible congenital exposure to Zika virus:
    - Test serum and urine by Zika virus NAT (whole blood is also an acceptable specimen for NAT testing, however, a whole blood specimen must be accompanied by a tube of serum for IgM serology.
    - Zika virus IgM serology should concurrently be performed on infant serum
    - If cerebrospinal fluid is obtained for other studies, NAT testing for Zika virus RNA and Zika virus IgM should be performed on CSF.

For additional details regarding testing for pregnant patients, see CDPH's Updated Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure:

(https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UpdatedZikaGuidanceforHCPsCaringforPregnantWomen.pdf)

II. Test Performance by Specimen Type

- Zika NAT testing
  - NAT testing can most reliably detect Zika virus in serum during the first two weeks following onset of symptoms or infection and in urine or whole blood for the first three weeks following onset of infection.
  - Recent evidence suggests that Zika virus RNA can be detected for a long period of time in serum (Oduyebo T et al, July 2017) and perhaps longer in whole blood versus the serum of infected persons. There are documented cases in which Zika virus RNA has been detected in various samples for longer periods of time than originally determined. Zika virus RNA has been shown to be detectable in whole blood and urine for longer periods of time than in serum.
- Zika IgM testing
  - Zika antibody may be detected as early as a few days following onset of infection but a negative IgM test result on a specimen collected <2 weeks after onset does not rule out a recent Zika virus infection (i.e., IgM may be falsely negative). IgM testing should be performed on specimens collected between 2 weeks and 12 weeks following onset of infection.
  - IgM tests may remain positive for significantly longer than 12 weeks. Because of this, the interpretation of timing of infection for a positive result during pregnancy is unreliable unless the timing of seroconversion is documented (see May 5, 2017, CDC Health Advisory, https://emergency.cdc.gov/han/han00402.asp).
  - Positive or equivocal Zika IgM results require confirmatory testing because IgM tests for Zika virus may give false positive results**.** The main reason for false positive results is that there is serologic cross reactivity among related flaviviruses including dengue, West Nile, yellow fever, and Japanese encephalitis viruses. Previous exposure to or vaccination against a flavivirus could result in a false positive Zika virus IgM. Some false positives may be due to other non-specific reactions without prior virus exposure.
  - Information that may help to interpret a potentially false positive IgM result by influencing pretest probability include:
    - History of other virus infection or vaccination
    - Symptoms of acute infection and timing related to exposure
    - Confirmed Zika infection in a sexual partner or household member
    - Other evidence of congenital Zika infection or complication, such as fetal microcephaly or intracranial calcifications
    - Duration and quality of travel exposure
- Confirmatory PRNT testing
  - Confirmatory PRNT testing results could come back as:
    - Evidence of a recent infection with Zika virus
    - Evidence of a recent infection with another virus (such as dengue)
    - Evidence of infection with a flavivirus of undetermined type (positive for more than one virus)
    - No evidence of infection (preliminary IgM test is false positive)

- For symptomatic and asymptomatic pregnant women with possible Zika virus exposure who seek care >12 weeks after symptom onset or possible exposure, IgM antibody testing might still be considered and if fetal abnormalities are present, NAT testing (e.g. RT-PCR testing) should also be performed on maternal serum and whole blood and urine, if submitted.
- Because IgM antibody and viral RNA levels decline over time, negative testing conducted greater than 12 weeks after symptom onset or possible exposure may be a false negative result and does not rule out recent Zika virus infection. Therefore, when testing beyond 12 weeks after symptom onset or possible exposure, serial fetal ultrasounds should be considered during prenatal care.

III. Specimen Collection, Storage and Submission

VRDL Zika Testing Guidance (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaLaboratoryTestingGuidance_VRDL.pdf)

- Amniotic fluid, if collected, should be collected in a CSF collection tube. The sample should be frozen (-70C) and shipped on dry ice.
- Specimen preparation for the evaluation of suspected Congenital Zika Syndrome in a newborn is described in the CDPH Guidance for Congenital Zika Infection Evaluation.
- If whole blood is submitted, it will require an EDTA whole blood specimen in addition to serum for a potential subsequent IgM test and, if elected, a urine specimen.

IV. Test Turn Around Time

- The time required for results of testing to be reported varies depending upon specimen transport, sample type submitted, timing of sample collection from symptom onset, the lab performing testing, and the type of test being performed. Some tests are rapid while others take up to 7 days to complete
- In California, Zika virus testing is conducted by:
  - Local public health labs (Contact your local public health department to see if testing is available locally)
  - CDPH Viral and Rickettsial Disease Laboratory (VRDL)
  - Commercial labs

- NOTE: In California, Zika IgM confirmation with PRNT is conducted only at VRDL

D. Prevention of Transmission

I. Protection against mosquito vector transmission

- The best way to prevent the spread of Zika through mosquito bites is by:
  - Wearing long sleeve shirts and long pants
  - Covering the crib, stroller, and baby carrier with mosquito netting
  - Treating your clothing and gear with permethrin or buying pre-treated items
  - Using Environmental Protection Agency (EPA)-registered insect repellents as directed on the product label
  - Staying in places with air conditioning and window and door screens to keep mosquitoes outside

  - Sleeping under a mosquito bed net if air conditioned or screened rooms are not available or if sleeping outdoors
  - See CDPH mosquito control information (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/MosquitoControlFAQs.pdf)
- Special precautions for infants and children younger than 3 years old:
  - Do not use insect repellent on babies younger than 2 months old
  - Caregivers/adults should spray insect repellent onto their own hands and then apply to a child's face
  - Do not apply insect repellent onto a child's hands, eyes, mouth or cut or irritated skin
  - Do not use products containing oil of lemon eucalyptus or para-menthane-diol on children younger than 3 years old
- California residents exposed to Zika Virus through travel to an area at risk for Zika or through sexual contact with a person with exposure should apply mosquito repellent and avoid mosquito exposure for three weeks after return to California to prevent potentially transmitting the virus to local mosquitoes. This is especially important for residents of California counties known to be habitat for the vector mosquitoes, *Aedes aegypti* and *Aedes albopictus*. See a map of counties where these mosquitoes are present (https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/AedesDistributionMap.pdf).
- View an interactive map with more detailed information about the distribution of *Aedes* vector mosquitoes in California (http://cdphdata.maps.arcgis.com/apps/webappviewer/index.html?id=57367199287a4d18a2cecf107854255b).

II. Protection against sexual transmission

- If patients are planning travel to areas where Zika is present, they should be advised to abstain from sex or use condoms (male or female) and dental dams correctly every time they have sex during travel.
- People who have Zika infection or have been potentially exposed to Zika infection (through travel or sexual contact) should abstain from sex or use condoms (male or female) and dental dams to prevent transmitting the virus to their sexual partner, as follows:
  - Pregnant women should abstain from sexual contact or use barrier protection for the duration of the pregnancy
  - Non-pregnant females should abstain from sexual contact or use barrier protection for **8 weeks** after last exposure or symptom onset.
  - Males should abstain from sexual contact or use barrier protection for **6 months** after last exposure or symptom onset.

III. Protection against transmission in healthcare settings

- Standard precautions are recommended to prevent the spread of Zika virus in healthcare settings.
- The U.S. Food and Drug Administration posted new guidance for the screening of donated blood for Zika virus on August 26, 2016 under Title 21 of the Code of Federal Regulations (CFR) 630.3(h)(2).

- The potential for transmission of Zika virus to the recipient of transplanted tissue is possible, but the magnitude of the risk of Zika transmission by solid organ transplantation is unknown at this time. It is recommended by organ procurement organizations that donor deferral should be considered for recipients who are women of childbearing age or pregnant if there is history of donor travel to Zika-endemic areas in the 28 days prior to donation. In the case of potential living donors with Zika infection, donation should be deferred where possible. See Organ Procurement and Transplantation Network's guidance on Zika virus (https://optn.transplant.hrsa.gov/news/guidance-on-zika-virus/).

E. Useful Resources

I. Patient Education Toolkits

- CDPH has created various educational materials that you can use for patient outreach. These materials are organized into four toolkits for Zika and Pregnancy, Zika and Travel, Zika and Family Planning and Zika and Sex
- Each toolkit contains educational posters in English and Spanish, talking points for healthcare providers and educators, and social media posts that you can use on your social media sites.
- All of these materials are available for free download on the CDPH Zika webpage and printed posters are available for order.

II. CDPH Zika Website

- http://www.cdph.ca.gov/Zika

III. Public Q & A

- See the CDPH Zika Questions and Answers resource for the public.

F. Quick References and Tools

CDPH Zika Screening Algorithm:
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaAlgorithmPoster.pdf

CDC Updated Interim Pregnancy Guidance Algorithm:
http://www.cdc.gov/zika/pdfs/testing_algorithm.pdf

CDC Interim guidance: Evaluation and testing of infants with possible congenital Zika virus infection: http://www.cdc.gov/zika/pdfs/zika_peds.pdf

CDC Initial Evaluation and Outpatient Management During the First 12 Months of Life for Infants with Possible Congenital Zika Virus Infection:
http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf

CDPH Evaluation and Follow-Up Procedures for Suspected Congenital Zika Virus Infection – Fetus, Newborn and Infant:

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/GuidanceforCongenitalZikaInfectionEvaluation.pdf

CDPH Patient Self-Assessment Form - A self-administered screening tool for clinics to use to screen patients for potential exposure, in English:
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/GuidanceforCongenitalZikaInfectionEvaluation.pdf,

CDPH Patient Self-Assessment Form, in Spanish:
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaVirusExposureSelfAsssementFormSpanish.pdf

For further information regarding lab management, see CDPH Zika Virus Testing FAQs for Healthcare Providers:
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaVirusTestingFAQsforHCPs.pdf

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

CDC Interactive Program to Assess Your Pregnant Patient for Zika Testing:
https://www.cdc.gov/zika/hc-providers/index.html

G. Literature References

CDC Health Advisory. Update: Interim Guidelines for Prevention of Sexual Transmission of Zika Virus — United States, 2016. (February 23, 2016) http://emergency.cdc.gov/han/han00388.asp

Cuevas, E. et al Preliminary Report of Microcephaly Potentially Associated with Zika Virus Infection During Pregnancy – Colombia, January-November 2016 MMWR Morb Mortal Wkly Rep: ePub December 9, 2016 DOI: http://dx.doi.org/10.15585/mmwr.mm6549e1

Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:182–187. (Feb 26, 2016) DOI: http://dx.doi.org/10.15585/mmwr.mm6507e1.

Honein, M et al Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy *JAMA* online December 13, 2016. doi:10.1001/jama.2016.19006 http://jamanetwork.com/journals/jama/fullarticle/2593702

Johansson M, Mier-y-Teran-Romero L, Reefhuis J, et al. Zika and the Risk of Microcephaly. NEJM N Engl J Med 2016; 375:1-4. DOI: http://www.nejm.org/doi/full/10.1056/NEJMp1605367

Lustig Y, Mendelson E, Paran N, Melamed S, Schwartz E. Detection of Zika virus RNA in

whole blood of imported Zika virus disease cases up to 2 months after symptom onset, Israel, December 2015 to April 2016. Euro Surveill. 2016;21(26):pii=30269. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.26.30269

Oduyebo T, Igbinosa I, Petersen E, et al. Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure – United States, July 2016. MMWR Morb Mortal Wkly Rep 2016;65:739-744. (July 29, 2016) DOI: http://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm

Oduyebo T, Petersen EE, Rasmussen SA, et al. Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:122–127. (Feb 12, 2016) DOI: http://dx.doi.org/10.15585/mmwr.mm6505e2.

Oduyebo T, Petersen EE, Rasmussen SA, et al. Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure — United States, July 2017. MMWR Morb Mortal Wkly Rep 2017;66:781-793 https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6629e1.pdf

Olson, C, et al Preventing Transmission of Zika Virus in Labor and Delivery Settings Through Implementation of Standard Precautions — United States, 2016 MMWR Morb Mortal Wkly Rep. March 25, 2016 / Vol. 65 / No. 11 https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6511.pdf

Oster AM, Brooks JT, Stryker JE, et al. Interim Guidelines for Prevention of Sexual Transmission of Zika Virus — United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:120–121. (Feb 12, 2016) DOI: http://dx.doi.org/10.15585/mmwr.mm6505e1.

Oster AM, Russell K, Stryker JO, et al. Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus — United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:1–3. (March 25, 2016) DOI: http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e3er.htm

Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure – United States, September, 2016. MMWR Morb Mortal Wkly Rep 2016:65:1077-1081. DOI: http://dx.doi.org/10.15585/mmwr.mm6539e1

Petersen EE, Polen KND, Meaney-Delman D, et al. Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:1–8. (March 25, 2016) DOI: http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e2er.htm

Petersen EE, Polen KND, Meaney-Delman D, et al. Update: Interim Guidance for Health

Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:315-321. (April 1, 2016) DOI: http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e2.htm?s_cid=mm6512e2_w

Rasmussen SA, Jamieson DJ, Honein MA, Petersen, LR. Zika virus and birth defects--reviewing the evidence for causality. N Engl J Med 2016;374:1981-1987. DOI: http://www.nejm.org/doi/full/10.1056/NEJMsr1604338

Russell K, Oliver, SE, Lewis L, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection – Unites States, August 2016. MMWR Morb Mortal Wkly Rep 2016:65:870-878. DOI: http://dx.doi.org/10.15585/mmwr.mm6533e2

Van der Linden V, Pessoa A, Dobyns W, et al. Description of 13 Infants Born During October 2015- January 2016 with Congenital Zika Virus Infection Without Microcephaly at Birth – Brazil. MMWR Morb Mortal Wkly Rep. ePub: 22 November 2016. http://dx.doi.org/10.15585/mmwr.mm6547e2

Velho Barreto de Araújo, T et al *Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study* Lancet, September 15, 2016 http://dx.doi.org/10.1016/S1473-3099(16)30318-8