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

December 19, 2016

Updated December 19, 2016; updated information is in purple.

Overview

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. This California Department of Public Health (CDPH) document outlines the information needed and the role of the local public health department in facilitating advance preparation. In addition, information is provided for health care providers who may be involved in the initial clinical evaluation and ongoing monitoring of affected infants. Testing procedures address both live births and fetal losses with evidence of maternal or fetal Zika virus infection.

Indications for Infant Testing

Newborn Infants

The US Centers for Disease Control and Prevention (CDC) recommends infants born to women with possible Zika virus infection while pregnant be evaluated for congenital Zika virus infection and sequelae in two situations:

> (1) infants born to *mothers with laboratory evidence of Zika virus infection* during pregnancy (or with *tests that were inconclusive*), 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, intracranial calcifications or other brain anomalies, or eye anomalies, among others.

In addition, CDPH recommends evaluation for congenital Zika virus infection in the following situation:

> (3) in the case of normal appearing infants born to *mothers with risk factors for maternal Zika virus infection* and for whom *maternal testing was not performed or test results are not available before delivery*. Infant specimens should be collected within 2 days of delivery and tested for Zika virus in parallel with maternal testing.

Fetal Loss

CDC also recommends Zika virus testing in the case of a **fetal loss** in a woman with *risk factors for maternal Zika virus infection* such as travel to or residence in an area with

Zika virus transmission or unprotected sex with a male or female partner who traveled to or resided in an area with active Zika virus transmission.

Details of these indications and recommended tests can be found at the following link and in subsequent sections below: Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016 | MMWR http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm

Local Health Jurisdiction - Advance Planning in Response to Possible Maternal Zika Virus Infection

The following procedural components outline appropriate evaluation, testing, and reporting of suspected congenital Zika virus infection among newborns and in cases of fetal demise. In order for providers and local health jurisdictions to perform the following procedures in a timely manner, it is recommended that local health jurisdictions (LHJ) **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

***Laboratory evidence of maternal Zika virus infection includes:**

- ✓ Zika virus RNA detected in any maternal clinical specimen by real-time reverse transcription-polymerase chain reaction (rRT-PCR); **or**
- ✓ Positive Zika virus immunoglobulin M (IgM) with confirmatory neutralizing antibody titers for Zika virus or flavivirus. (Because of the decline in IgM antibody and viral RNA levels over time, negative maternal testing > 12 weeks after exposure does not rule out maternal infection.)

See **Appendix A**: LHJ Checklist for Infant Evaluation of Congenital Zika Virus Infection

Mother not tested/ test results not available before delivery/tested outside of appropriate window

Infants born to mothers with *risk factors for maternal Zika virus infection* (travel to or residence in an area of Zika virus transmission or sex with a partner who traveled to or resided in such an area) and for whom *maternal testing was **not** performed or Zika test results not available before delivery*, should have:

- A comprehensive physical examination, including standardized measurement of head circumference.
- Maternal and infant diagnostic testing for Zika virus, in parallel. (CDC recommends infant testing should be performed if maternal testing is consistent with laboratory evidence of Zika virus infection. However, due to the logistical challenges of waiting for maternal test results and the limitations with maternal testing beyond 12 weeks following exposure/symptom onset, CDPH recommends maternal and infant Zika virus testing in parallel.)
- Information for Collection and Submission of Specimens at Time of Birth http://www.cdc.gov/zika/hc-providers/test-specimens-at-time-of-birth.html

- Infant specimens (serum and urine) should be collected within 2 days of delivery.

If an infant appears clinically well, further evaluation, including head ultrasound and ophthalmologic assessment, can be deferred until maternal and infant test results are available, unless there are concerns about infant follow-up.

Specimen Collection and Laboratory Testing for Congenital Zika Virus Infection

Specimen collection for a newborn:

Serum and/or urine specimens (cerebrospinal fluid is an optional secondary test specimen) should be obtained ***within the first 2 days of life***. 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. 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 rRT-PCR testing should be performed on both infant serum and urine
- Zika virus IgM enzyme-linked immunosorbent assay (ELISA) should concurrently be performed on infant serum
- If cerebrospinal fluid is obtained for other studies, rRT-PCR testing for Zika virus RNA and Zika virus IgM should be performed on CSF

Specimen collection in the case of fetal demise:

Zika virus testing is recommended in the case of a fetal loss in a woman with possible Zika virus exposure while pregnant. Specimens should be collected for Zika virus testing, histopathology, and immunohistochemical staining on fetal tissue, umbilical cord, placenta and fetal membranes, as available. Fixed tissue specimens are optimal. For more information see the updated guidance for Health Care Providers caring for pregnant women with possible Zika Exposure. https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm

For additional information visit the CDC website for collecting placental and fetal or infant tissues (http://www.cdc.gov/zika/hc-providers/tissue-collection-submission.html)

For *each* tissue specimen submitted, the following forms must be completed:

[ ] CDC human specimen submittal form (Form 50-34; the 2016 CDC DASH form)
http://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf

[ ] CDPH VRDL specimen submittal form (VRDL Form Lab 300)
http://www.cdph.ca.gov/programs/vrdl/Documents/VRDL_General_Human_Specimen_Submittal_Form_Lab300.pdf

Table 1: Specimen Collection and Storage of specimens for Zika virus testing in infants (updated 11/16/16)

Specimen	When to Collect	Preferred Amount	Container	Storage and Shipment Conditions	Tested at CDC	Tested at VRDL
Serum (infant)†	<2 days post onset	≥2 ml (one tube preferred)	Red or tiger top tube	Cold	N/A	Serology, PCR
Serum (mother)	At time of collection of infant serum	≥2 ml (one tube preferred)	Red or tiger top tube	Cold	N/A	Serology, PCR
Urine (infant)	<2 days post onset	≥2 ml (one tube preferred)	Sterile screw-cap tube with parafilm in separate bag	Cold	N/A	PCR
Urine (mother)	At time of collection of infant serum	≥2 ml (one tube preferred)	Sterile screw-cap tube with parafilm in separate bag	Cold	N/A	PCR
CSF	If collected for other studies	≥1 ml	Sterile cryovial	N/A	Serology, PCR	PCR
Amniotic Fluid	When available	≥1 ml	Sterile cryovial	Frozen	PCR	N/A
Placental/ Fetal Tissue§	When available	0.5-1.0 cm	Sterile container	Both a.) cold formalin fixed and b.) frozen tissues	HP, IHC, PCR	N/A

† Infant serum is recommended over cord blood for serological and PCR testing.

§ For additional information on collecting placental and fetal or infant tissues visit the CDC's website for Collecting and Submitting Placental and Fetal Tissue Specimens for Zika Testing. http://www.cdc.gov/zika/hc-providers/tissue-collection-submission.html

Additional details regarding specimen collection can be found on the Zika Laboratory Testing Guidance. https://www.cdph.ca.gov/programs/vrdl/Documents/Zika_Testing_VRDL_Quicksheet.pdf

Abbreviations: HP = Histopathology; IHC = Immunohistochemical staining; PCR = Reverse transcription-polymerase chain reaction

CDC has interim guidance on the evaluation and testing of infants with possible Congenital Zika virus infection. http://www.cdc.gov/zika/pdfs/zika_peds.pdf

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

Health Care Provider - Clinical Evaluation

Before Hospital Discharge

In addition to Zika virus laboratory testing, all newborn infants with maternal risk factors for Zika virus infection should undergo a comprehensive physical exam including standardized measurement of head circumference, newborn hearing screening, and head ultrasound. Additional clinical evaluation is recommended at birth and periodically during the first year of life for infants with abnormalities consistent with congenital Zika virus syndrome.

CDC has a decision tree and checklist for evaluation and outpatient management for infants with possible congenital Zika virus infection. http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf

Outpatient Management

If abnormalities are noted during prenatal evaluations, counseling specific to congenital Zika infections should occur during pregnancy, preferably with involvement from the obstetric and pediatric providers.

The care of infants with abnormalities consistent with congenital Zika infections requires a multidisciplinary team and an established medical home to facilitate the coordination of care. Consideration should be given to using preexisting coordinated multidisciplinary care clinics. Families of infants with congenital Zika virus disease should receive information that includes discussion of concerns for development, function, feeding and growth, and prognosis.

Breastfeeding should be encouraged and supported for nutrition and enhanced bonding. 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 evidence from the Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection indicates the benefits of breastfeeding outweigh any theoretical risks associated with Zika virus infection transmission through breast milk. (http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm) Primary care providers should assess the infant for evidence of feeding difficulties and refer for consultations as needed.

Overall, families and caregivers of infants with congenital Zika infections will require ongoing psychosocial assessment and support. Health care providers should work closely with parents to ensure that the care plan that is developed is consistent with the infant's needs and the family's wishes. Families might also face financial stressors, social stigma, and other forms of discrimination.

Infants with laboratory evidence of Zika virus infection but without apparent abnormalities at birth are

recommended to have additional monitoring until further information is available regarding outcomes because some neurological sequelae are subtle or have delayed onset.

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 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 website https://www.cdph.ca.gov/pubsforms/forms/CtrldForms/cdph8680.pdf

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

Appendix A: LHJ Checklist for Infant Evaluation of Congenital Zika Virus Infection

[ ] Review CDC 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
[ ] Consider alerting local public health lab of incoming specimen for transport to CDPH VRDL and/or CDC
[ ] 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

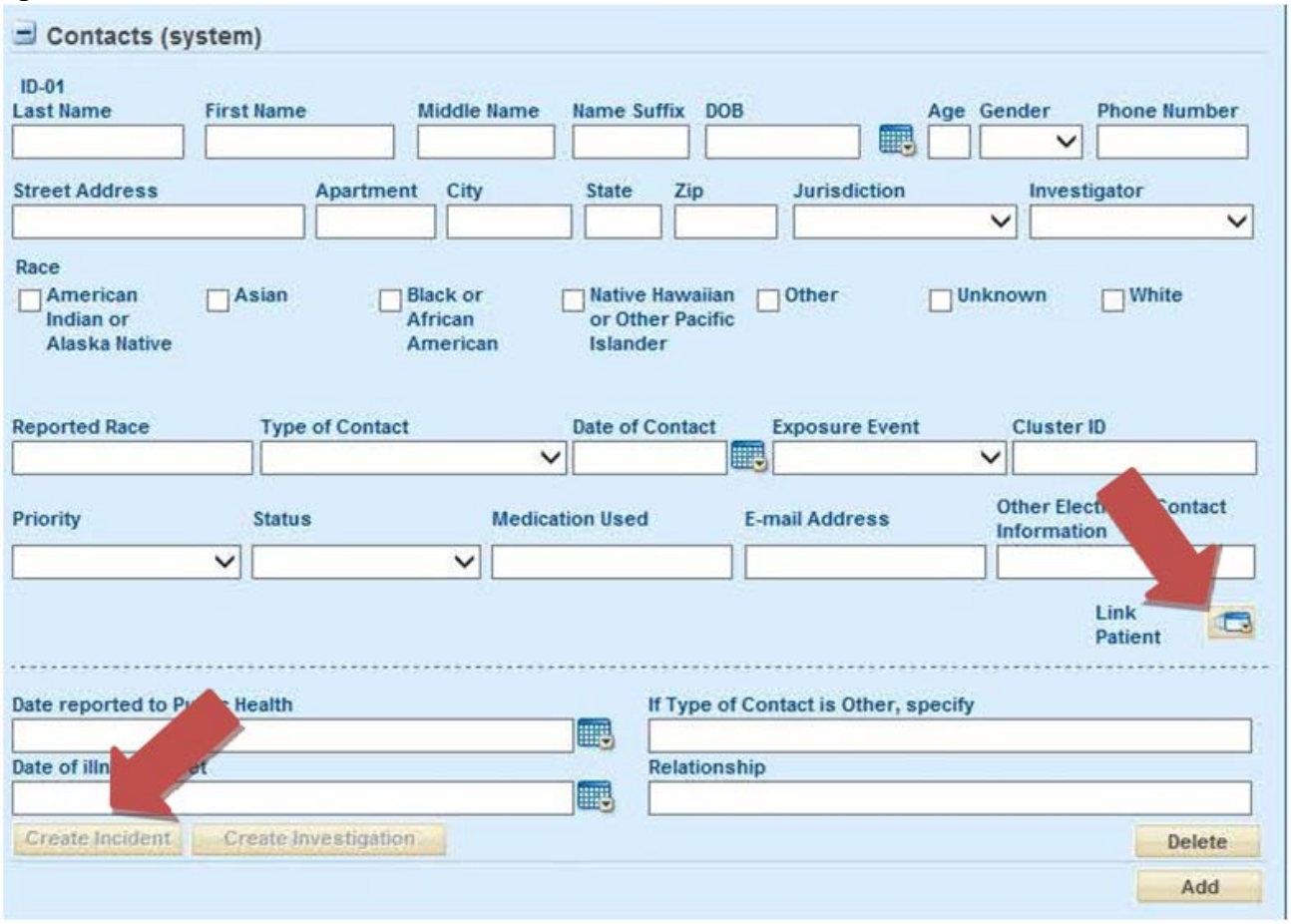
To initiate a neonate investigation:

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:

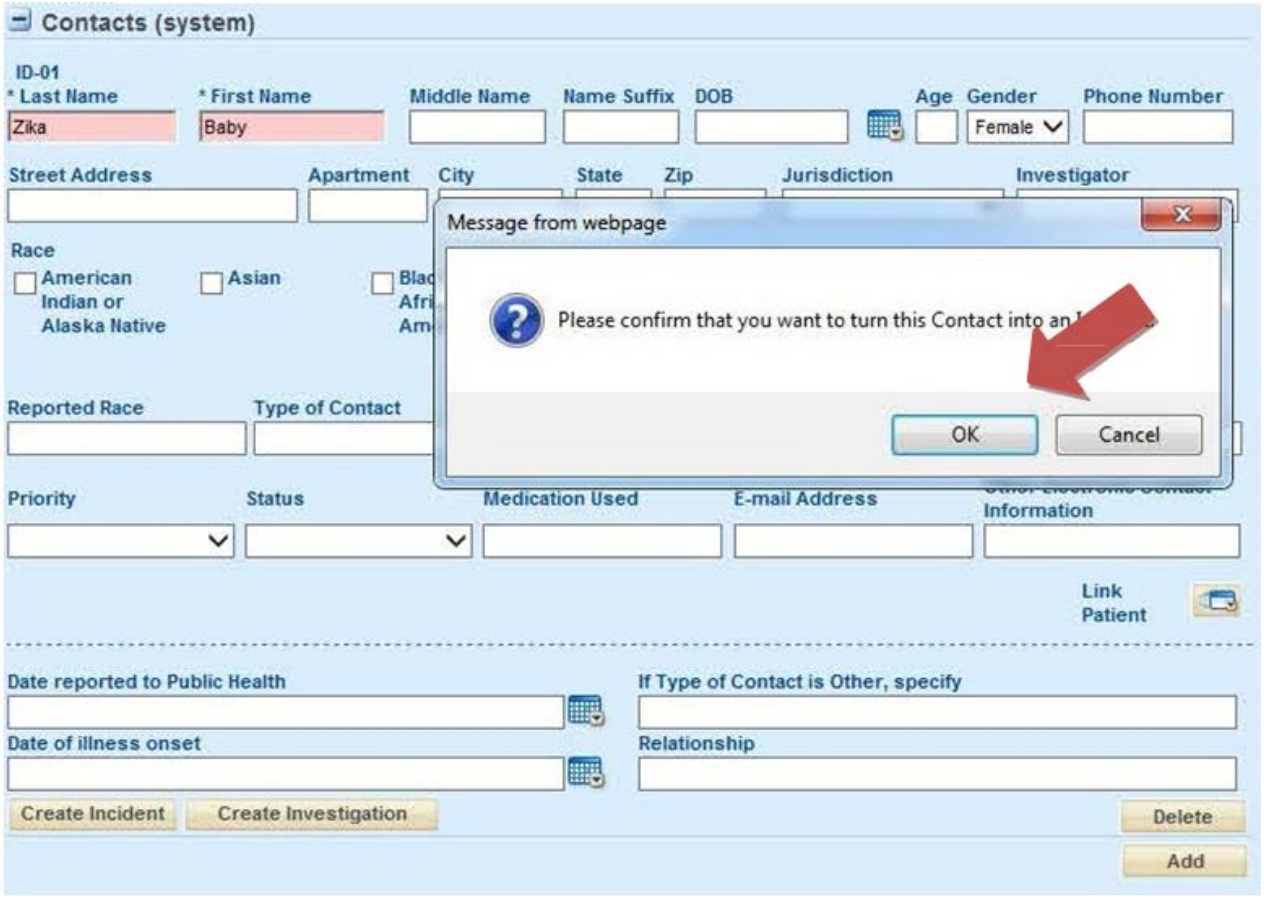


3. Click **Save** to save changes on the Epidemiologic Info tab.

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.

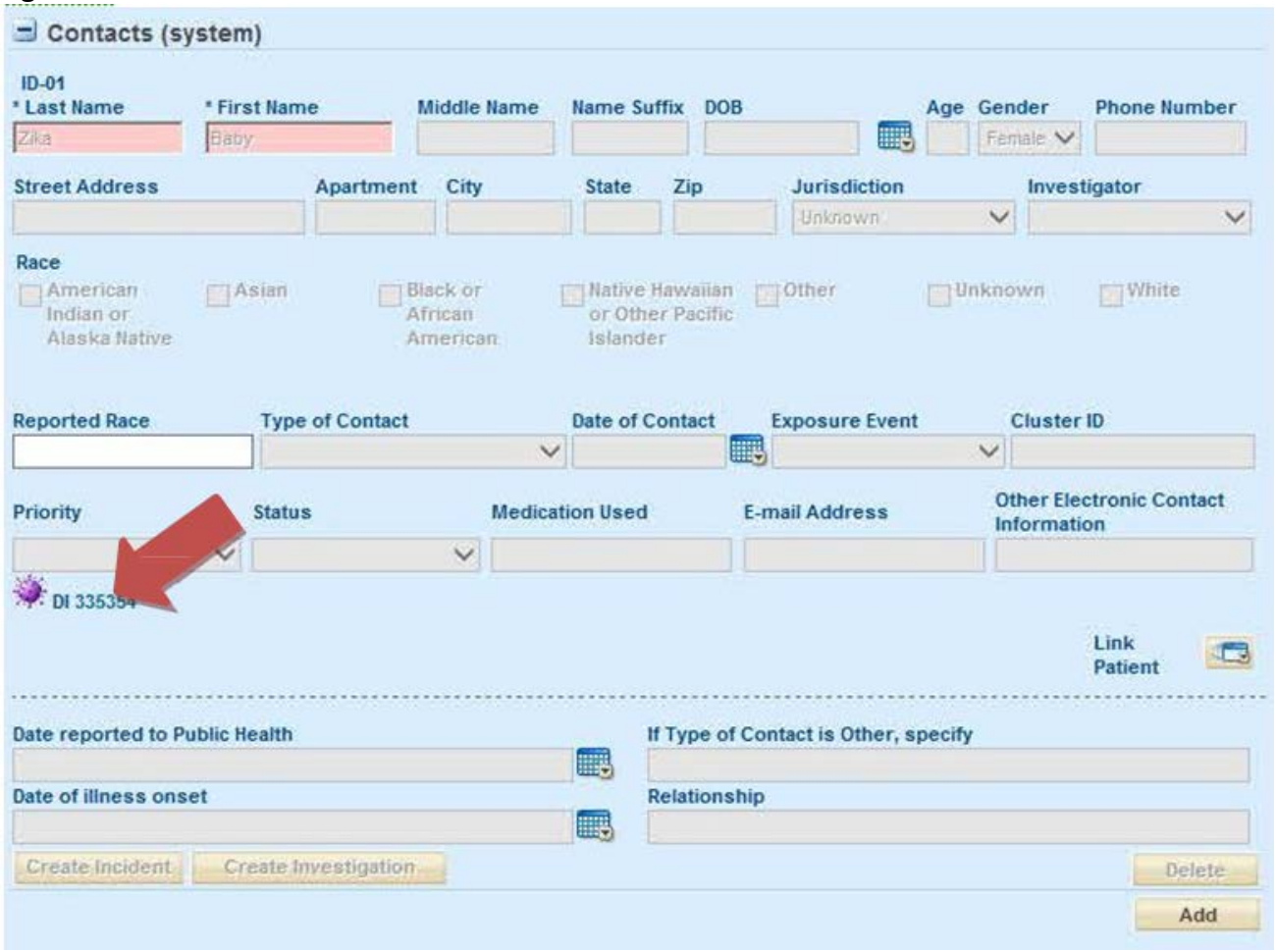
5. Click **"OK"** in pop-up box to confirm that you want to turn the infant into a new Incident. A pop-up box will subsequently notify you that "The contact has been successfully turned to a new incident." (Figure 2)

Figure 2.



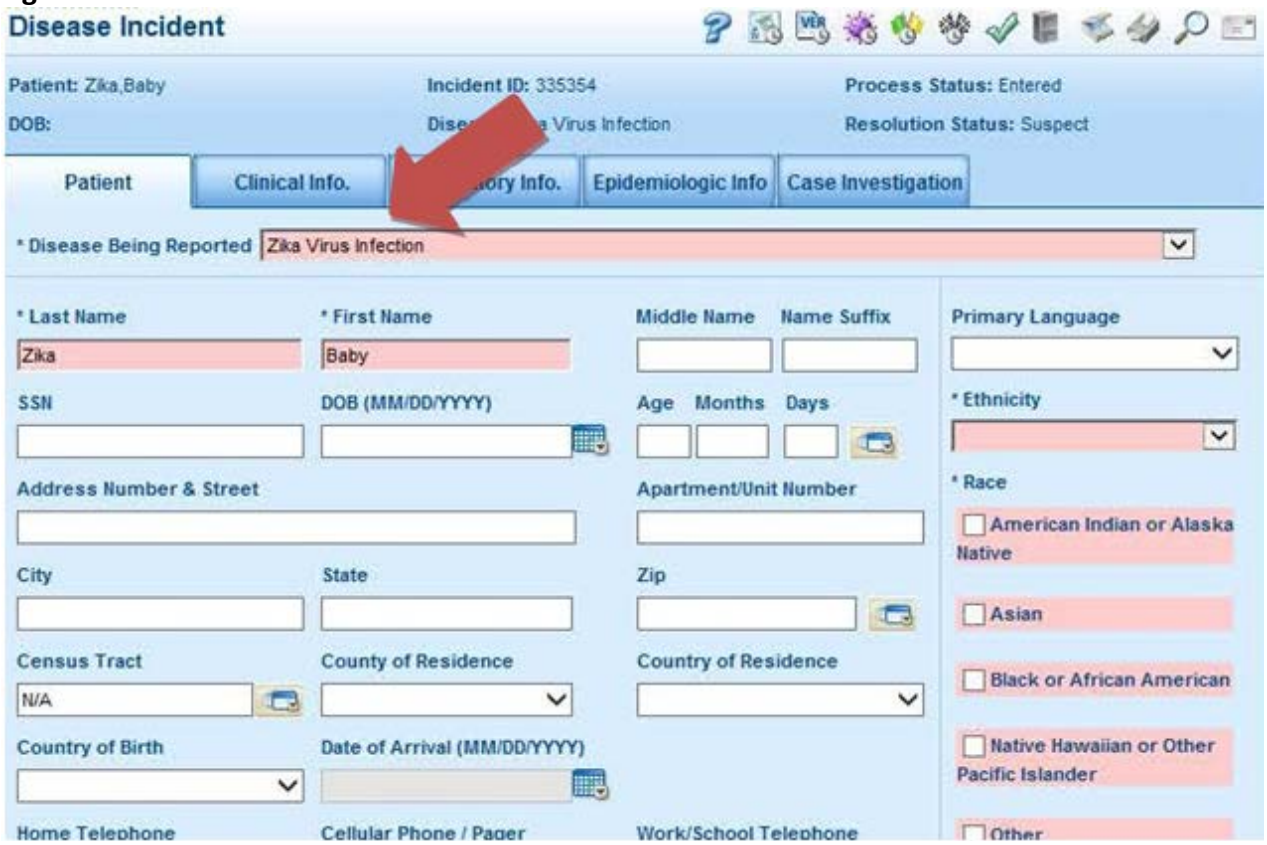
6. Click on new DI Incident link to go to the infant's new Incident (Figure 3).

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 a n d mother in CalREDIE! The same steps can be used to link sexually transmitted cases in CalREDIE.