



Guidance for Reviews of Zika-Related Fatalities

National Center for Fatality
Review and Prevention

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GUIDANCE FOR REVIEWS OF ZIKA-RELATED FATALITIES

Purpose:

This document is intended to inform Child Death Review (CDR) and Fetal and Infant Mortality Review (FIMR) teams' reviews of fetal, infant, and child deaths known to be related, or potentially related, to Zika virus infection. It is not intended to be all inclusive of the latest Zika information and guidance available, particularly as that information changes quickly. Not all mother-to-child transmissions of Zika will result in death, so teams may want to consider also using this guidance for "sentinel event" reviews and not limiting themselves to review of cases where fetal, infant, or child death is the final outcome.

Target Audience:

CDR and FIMR coordinators, Review Team members, and Community Action Team members may find this document helpful as a reference before and/or during review meetings.

Overview:

Zika virus disease is caused by the Zika virus, which is spread to people primarily through the bite of an infected *Aedes* species mosquito (*Aedes aegypti* and *Aedes albopictus*). The illness is usually mild with symptoms lasting up to a week, and many people do not have symptoms or will have only mild symptoms. However, Zika virus infection during pregnancy can cause serious birth defects such as microcephaly and other brain abnormalities. ¹ http://www.cdc.gov/zika/healtheffects/birth_defects.html

¹ Melo, A.S., Aguiar, R.S., Amorim, M.M.R., et al. (2016). Congenital Zika Virus Infection: Beyond Neonatal Microcephaly. *JAMA Neurology*, published online October 3, 2016. doi:10.1001/jamaneurol.2016.3720

Congenital Zika syndrome is a pattern of birth defects found among fetuses and babies infected with Zika virus during pregnancy. Congenital Zika syndrome is described by the following five features:

- Severe microcephaly where the skull has partially collapsed
- Decreased brain tissue with a specific pattern of brain damage
- Damage to the back of the eye
- Joints with limited range of motion, such as clubfoot
- Too much muscle tone restricting body movement soon after birth

Microcephaly is the condition that has been most widely reported in relation to Zika. It is a condition where a baby's head is smaller than expected when compared to babies of the same sex and age. During pregnancy, a baby's head grows because the baby's brain grows. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth, which results in a smaller head size.

Babies with microcephaly can have a range of other problems, depending on how severe their microcephaly is. Microcephaly has been linked with the following problems:

- Seizures
- Developmental delays (problems with speech, sitting, standing, and walking)
- Intellectual disability (decreased ability to learn and function in daily life)
- Problems with movement and balance
- Feeding problems, such as difficulty swallowing
- Hearing loss
- Vision problems

These problems can range from mild to severe and are often lifelong. Severe microcephaly also can be life-threatening.

Microcephaly is not a common condition. Before the current Zika outbreak, state birth defects tracking systems estimated that microcephaly ranges from 2 babies per 10,000 live births to about 12 babies per 10,000 live births in the US. <http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html>.

As of November 23, 2016, there have been 35 confirmed cases of congenital syndrome associated with Zika virus infection in the US, with no reported deaths. Puerto Rico has reported 4 cases of confirmed cases of congenital syndrome associated with Zika, with 5 deaths among those cases (one case was a twin birth/death). http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=37069&lang=en

Not all babies born with congenital Zika infection will have all of these problems, but there is emerging literature on additional abnormalities being found in infants exposed to Zika during the mother's pregnancy. Some infants with congenital Zika virus infection who do not have microcephaly at birth may later experience slowed head growth and develop postnatal microcephaly. A range of neurologic, ocular, joint and craniofacial abnormalities have been observed among infants with presumed or confirmed congenital Zika virus infection.

Other problems linked to Zika infection during pregnancy include miscarriage, stillbirth, hearing deficits, and impaired growth. Scientists continue to study how Zika virus affects mothers and their children to better understand the full range of potential health problems that Zika virus infection during pregnancy may cause. http://www.cdc.gov/zika/healtheffects/birth_defects.html

Several countries that have experienced Zika outbreaks recently have reported increases in people who have Guillain-Barré syndrome (GBS). GBS is a rare sickness of the nervous system in which a person's own immune system damages the nerve cells, causing muscle weakness, and sometimes, paralysis. GBS can be triggered by a variety of infections, including other mosquito-borne viruses like dengue (<http://www.cdc.gov/dengue/>) and chikungunya (<http://www.cdc.gov/chikungunya/index.html>). <http://www.cdc.gov/zika/healtheffects/gbs-qa.html>

Transmission: There are five known methods of transmission for Zika.

1. Through mosquito bites: Most common is transmission through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*). These are the same mosquitoes that spread two other viruses, dengue and chikungunya. Mosquitos can become infected when they feed on a person already infected with the virus, and they can spread the virus to other people through bites.
2. From mother to child: A pregnant woman already infected with Zika virus can pass the virus to her fetus during the pregnancy or around the time of birth.
3. Through sex: Zika can be passed through sex, from a person who has Zika to his or her partners. Zika can be passed through sex, even if the infected person does not have symptoms at the time.
4. Through blood transfusions: As of October 24, 2016, there have not been any confirmed blood transfusion transmission cases in the United States. However, there are investigations of multiple reports of blood transfusion transmission cases in Brazil.
5. Through laboratory and health care settings: As of October 24, 2016, no cases of confirmed Zika virus transmission in healthcare settings have been reported in the United States, and as of June 2016, there has been one reported case of laboratory-acquired Zika virus disease in the United States. <http://www.cdc.gov/zika/transmission/index.html>

Prevalence:

Zika virus was first discovered in a monkey in the Zika Forest of Uganda in 1947. Before 2015, Zika outbreaks occurred in Africa, Southeast Asia, and the Pacific Islands.

There are currently 59 countries and territories worldwide reporting active Zika virus transmission. Countries with endemic Zika include some countries in Africa, the Pacific Islands, and Asia. <https://wwwnc.cdc.gov/travel/page/zika-travel-information>. For an up-to-date map of All Countries & Territories with Active Zika Virus Transmission, visit: <https://www.cdc.gov/zika/geo/active-countries.html>

As of November 16, 2016, there were 4,116 reported cases of Zika in the US (not including the territories) that were associated with travel, and the numbers continue to rise. One hundred thirty-nine locally acquired mosquito-borne cases have been reported, all in the Miami-Dade area of Florida. For updated information on the numbers of travel associated and locally acquired cases of Zika, visit: <https://www.cdc.gov/zika/intheus/maps-zika-us.html>.

Zika virus disease and Zika virus congenital infection are nationally notifiable conditions. Current information from the Centers for Disease Control on prevalence can be accessed at: <https://www.cdc.gov/zika/geo/united-states.html>

Symptoms:

Many people with Zika, as many as 85%, will have no symptoms or will only have mild symptoms. Symptoms may last several days to a week. People usually do not get sick enough to go to the hospital, and deaths related to Zika are extremely rare.

Most common symptoms:

- Fever
- Rash
- Joint pain
- Conjunctivitis (red eyes)

Other symptoms:

- Muscle pain
- Headache

Risk Factors for Zika (for Pregnant Women):

- Pregnant women who live in or have recently traveled to an area with Zika
- Pregnant women who have had sex without a condom with a partner who lives in or traveled to an area with Zika

Preparing for Review of Cases:

- Educate CDR/FIMR team members on Zika basic information; provide basic fact sheet during the review.
- Get the right people to the table. If the team does not already have the following expertise in place, it may be helpful to consider adding to the team:
 - o Obstetrician
 - o Maternal fetal medicine specialist (perinatologist)
 - o Pediatrician
 - o Neonatologist
 - o Advanced practice nurses or nurse practitioners in the above specialties
 - o Expand local public health officials to include Family Planning, STI clinic staff
 - o Epidemiologist
 - o Clinical geneticist
 - o Endocrinologist
 - o Infectious disease specialist
 - o Neurologist/pediatric neurologist
 - o Lactation specialist

The most effective review team would include practitioners who have had experience treating pregnant women and infants with Zika virus.

Questions for Teams to Consider:

- Are there additional records the team needs to gather, discuss, and review?
- Did this mother get adequate prenatal care?
- Were the prenatal care provider and mother aware of the Zika exposure? If not, why not?
- Did the prenatal care provider conduct appropriate Zika screening?
- Did the prenatal care provider give relevant Zika advice?
- Was the mother tested for Zika? Did the mother receive the test results?
- If tested, *when* was the mother tested for Zika?
- If the mother tested positive for Zika, did the provider conduct (or refer the mother for) Zika specific assessments of the fetus? Were there any abnormalities identified?
- What was the mode of Zika exposure, if known (i.e., mosquito bite/sexual intercourse/blood transfusion)?
- At what point in the pregnancy did exposure to Zika occur?
 - If exposure occurred pre-pregnancy, was the mother aware of the exposure? Was the pregnancy planned?
 - If the mother was aware of the exposure to Zika, what resources did she and her family utilize to better understand their situation and possible options?
- Were there any gaps in the surveillance in the area where Zika was acquired? If so, what could be done to alleviate that?

Recommendations to health providers and systems for preventing or mitigating Zika virus infection

Note: In general, as with any death review, teams should explicitly identify who would be responsible for each area within their community or system. Clear roles, responsibilities, and a point of contact for who would be responsible/accountable for taking action should be established. For example, healthcare providers would not be in the position to perform all of the following community-level activities, but the local health department's environmental health team or community health workers might.

1. Provide preconception care (care before women get pregnant) and counseling for women and their partners.
 - Health care providers should counsel those attempting to conceive to avoid known areas with active Zika transmission; they should consider postponing travel.
 - Health care providers should assess history of potential exposure. This includes:
 - Living in or travel to an area with active Zika transmission
 - Sex without a condom with someone who lives in or has traveled to an area with active Zika transmission.
 - Preconception counseling to women with possible Zika virus exposure should include information about the signs and symptoms of Zika virus disease and the potential adverse outcomes associated with Zika virus infection in pregnancy.
<https://www.cdc.gov/zika/pregnancy/women-and-their-partners.html>
 - Women with potential exposure should be advised to wait to conceive at least 8 weeks after symptom onset (if symptomatic) or last possible exposure (if asymptomatic).

- o Men with potential exposure should be advised to wait at least 6 months after symptom onset (if symptomatic) or last possible exposure (if asymptomatic) for unprotected sex.
 - o Information should be provided on available strategies to prevent unintended pregnancy, including not having sex or using the most effective contraceptive methods that can be used correctly and consistently (correct and consistent use of condoms reduces the risk for sexually transmitted infections, including Zika). <https://www.cdc.gov/zika/pregnancy/preventing-pregnancy.html>
2. Testing of serum for evidence of Zika virus infection should be performed in persons with possible exposure to Zika virus who have one or more of the following signs or symptoms within 2 weeks of possible exposure: acute onset of fever, rash, arthralgia, or conjunctivitis. For non-pregnant symptomatic persons: <https://www.cdc.gov/zika/hc-providers/types-of-tests.html>. The latest guidance can be found on the CDC web site: <https://www.cdc.gov/zika/laboratories/lab-guidance.html>
3. Zika exposure in pregnant women:
- a. Health care providers should assess their patients' travel histories and follow the CDC's interim guidance for pregnant women traveling to or residing in areas with active Zika virus transmission. https://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm?s_cid=mm6529e1_e
For information about pregnant women with potential exposure: <https://www.cdc.gov/zika/hc-providers/pregnant-woman.html>
 - b. Providers should also consider serial ultrasound examinations every 3 – 4 weeks to assess fetal anatomy and growth. Follow the CDC algorithm* (Figure 1) for a pregnant woman with possible Zika virus exposure. <http://www.cdc.gov/zika/hc-providers/pregnant-woman.html>

4. Counseling should be provided to people in Zika areas on environmental actions to take to avoid mosquito bites: <https://www.cdc.gov/zika/prevention/prevent-mosquito-bites.html>
 - Use window screens in homes, air conditioning where possible
 - Assess work environment and residence in area with high mosquito density
 - Be knowledgeable of levels of Zika virus transmission in the local area
 - Take personal measures to prevent mosquito bites
 - Protective clothing
 - Use of EPA-registered insect repellent
 - Emptying/removing standing water in containers
5. Reporting: Healthcare providers should report suspected Zika virus disease cases to their state, tribal, local, and territorial health departments to facilitate diagnosis and to mitigate the risk of local transmission. State, tribal, local and territorial health departments are requested to report laboratory-confirmed cases to CDC, via the following methods:
 - a. Report of laboratory confirmed cases through ArboNET (<http://www.cdc.gov/westnile/resourcepages/survsources.html>)
 - b. Pregnancy registries, including pregnant women with laboratory evidence of Zika virus infection, regardless of whether they had symptoms (US Zika Pregnancy Registry: <http://www.cdc.gov/zika/hc-providers/registry.html> and Zika Active Pregnancy Surveillance System in Puerto Rico: <http://www.cdc.gov/zika/public-health-partners/zapss.html>)

6. Birth defects surveillance: Birth defects among infants born to women with Zika virus infection during pregnancy should be reported to state-based birth defects surveillance systems.
7. Testing and management of infants with possible congenital Zika virus infection: an Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection is available from CDC: http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
 - a. Testing should be guided by:
 - i. Whether the infant has abnormalities consistent with congenital Zika syndrome (e.g., microcephaly, intracranial calcifications, or other brain or eye abnormalities).
 - ii. The mother's Zika virus testing results.
 - b. Congenital Zika virus infection can be diagnosed by RNA NAT (nucleic acid testing). <http://www.cdc.gov/zika/hc-providers/infants-children.html>
8. Provide linkages to psychosocial support
<http://www.who.int/csr/resources/publications/zika/psychosocial-support/en/>

FIGURE 1

Clinical management of a pregnant woman with suspected Zika virus infection		
Interpretation of Laboratory Results*	Prenatal Management	Postnatal Management
<u>Recent Zika virus infection</u>	<ul style="list-style-type: none"> Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth[†] Decisions regarding amniocentesis should be individualized for each clinical circumstance[‡] 	<p>LIVE BIRTHS:</p> <ul style="list-style-type: none"> Cord blood and infant serum should be tested for Zika virus rRT-PCR, Zika IgM, and dengue virus IgM antibodies. If CSF is obtained for other reasons, it can also be tested. Zika virus rRT-PCR and IHC staining of umbilical cord and placenta is recommended.[§] <p>FETAL LOSSES:</p> <ul style="list-style-type: none"> Zika virus rRT-PCR and IHC staining of fetal tissues is recommended.[§]
<u>Recent flavivirus infection; specific virus cannot be identified</u>		
<u>Presumptive recent Zika virus infection**</u>	<ul style="list-style-type: none"> Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth[†] Amniocentesis might be considered; decision should be individualized for each clinical circumstance[‡] 	<p>LIVE BIRTHS:</p> <ul style="list-style-type: none"> Cord blood and infant serum should be tested for Zika virus rRT-PCR, Zika IgM, and dengue virus IgM antibodies. If CSF is obtained for other reasons, it can also be tested. Zika virus rRT-PCR and IHC staining of umbilical cord and placenta should be considered.[§] <p>FETAL LOSSES:</p> <ul style="list-style-type: none"> Zika virus rRT-PCR and IHC staining of fetal tissues should be considered.[§]
<u>Presumptive recent flavivirus infection**</u>		
<u>Recent dengue virus infection</u>	<ul style="list-style-type: none"> Clinical management in accordance with existing guidelines (http://apps.who.int/iris/bitstream/10665/44188/1/9789241547871_eng.pdf). 	
<u>No evidence of Zika virus or dengue virus infection</u>	<ul style="list-style-type: none"> Prenatal ultrasound to evaluate for fetal abnormalities consistent with congenital Zika virus syndrome.[†] Fetal abnormalities present: repeat Zika virus rRT-PCR and IgM test; base clinical management on corresponding laboratory results. Fetal abnormalities absent: base obstetric care on the ongoing risk of Zika virus exposure to the pregnant woman. 	

Abbreviations: CSF = cerebrospinal fluid; IgM = immunoglobulin M; IHC = immunohistochemical; PRNT = plaque reduction neutralization test; rRT-PCR = real-time reverse transcription-polymerase chain reaction.

* Refer to the previously published guidance for testing interpretation (<http://www.cdc.gov/mmwr/volumes/65/wr/mm6521e1.htm>).

[†] Fetal abnormalities consistent with congenital Zika virus syndrome include microcephaly, intracranial calcifications, ventriculomegaly, arthrogryposis, and abnormalities of the corpus callosum, cerebrum, cerebellum, and eyes.

[‡] Health care providers should discuss risks and benefits of amniocentesis with their patients. It is not known how sensitive or specific rRT-PCR testing of amniotic fluid is for congenital Zika virus infection, whether a positive result is predictive of a subsequent fetal abnormality, and if it is predictive, what proportion of infants born after infection will have abnormalities.

[§] Refer to pathology guidance for collection and submission of fetal tissues for Zika virus testing for detailed information on recommended specimen types (<http://www.cdc.gov/zika/laboratories/test-specimens-tissues.html>).

** rRT-PCR or PRNT should be performed for positive or equivocal IgM results as indicated. PRNT results that indicate recent flavivirus infection should be interpreted in the context of the currently circulating flaviviruses. Refer to the laboratory guidance for updated testing recommendations (<http://www.cdc.gov/zika/laboratories/lab-guidance.html>). Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.



CS267383A July 28, 2016

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2. **National Birth Defects Prevention Network**. Major birth defects data from population-based birth defects surveillance programs in the United States, 2006–2010. Birth Defects Research (Part A): Clinical and Molecular Teratology. 2013;97:S1–S172.
3. **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>
4. **World Health Organization**, <http://www.who.int/sysmedia/images/topics/zika.jpg>
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