



# TRENDS-in-MEDICINE

## BULLETIN: ZIKA VIRUS UPDATE

February 28, 2016  
by Lynne Peterson

Zika is getting worse in the U.S., not just through travel but also through sexual transmission, and pregnancies are being affected. In a teleconference with reporters, Thomas Frieden, MD, MPH, director of the Centers for Disease Control and Prevention (CDC), Denise Jamieson, MD, MPH, a captain in the U.S. Public Health Service (USPHS) and co-lead of the CDC's Pregnancy and Birth Defects Team, CDC Zika Virus Response Team, and other government officials provided an update on the Zika virus situation.

Dr. Frieden's bottom line was that the message hasn't changed: Pregnant women should avoid travel to places where Zika is spreading, people in affected areas should avoid mosquitoes and sexual transmission, and the biggest risk of Zika is to pregnant women and fetuses.

He said there have been two anticipated developments and one unanticipated development in the past three weeks. The continued spread of Zika in places where the *Aedes aegypti* mosquitoes that transmit Zika live, including Puerto Rico, was expected and occurred. The CDC also expected (and saw) hundreds and thousands of American travelers returning from Zika-affected areas. What he said wasn't anticipated was the extent of sexual transmission. U.S. residents now have also had pregnancies affected by Zika, but all of these have been from travel to affected areas, not through sexual transmission.

As of the time of this call, the CDC has 147 reports of U.S. Zika infection, with 107 in the U.S. (in 24 states and the District of Columbia) and 40 in U.S. territories. The hot spot in the U.S. and its territories is Puerto Rico, which has 117 known cases of Zika infection. Dr. Frieden said, "There is a potential for hundreds and thousands of Zika cases in Puerto Rico, and, potentially, tragically, affected pregnancies as well. There are no known cases of anyone getting infected with the Zika virus from *mosquitoes* in the U.S., except for the territories of Puerto Rico, American Samoa, and the U.S. Virgin Islands.

CDC said 14 new reports of possible sexual transmission of Zika are being investigated, with 2 already confirmed. In all cases for which CDC has information, travelers were men whose reported symptom onset was within 2 weeks before the non-traveling female partner's symptoms began. The CDC said, "At this time, there is no evidence that women can transmit Zika virus to their sex partners; however, more research is needed to understand this issue."

The CDC is no longer identifying what states have confirmed cases of Zika, which Dr. Frieden said is at the request of the states. *Are they worried about the effect on tourism?*

**Pregnancy.** The key focus remains on pregnant women. As of February 17, CDC said 9 pregnant women, all residents of the U.S., have had laboratory-confirmed Zika virus infection, and 10 additional reports of Zika virus disease among pregnant women are currently under investigation. Of these 9 confirmed pregnancy cases:

- None of the women died or had Zika virus-related hospitalizations.
- 2 of the 9 women had abortions. Both had Zika symptoms in the first trimester. One fetus had brain abnormalities on ultrasound and MRI, but no information is available on the other fetus.

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- 1 infant was born with microcephaly. The woman had symptoms of Zika in the first trimester. It is not clear, but this is likely the previously reported case of an anencephalic infant (the worst form of microcephaly) born to a woman in Hawaii who had traveled to Brazil.
- 2 babies were born apparently healthy. One of these was a woman who developed Zika symptoms in the third trimester.
- 2 women had miscarriages. Both of these had Zika symptoms in the first trimester. Zika was found in placental tissue, which Dr. Frieden said “suggests Zika may have caused the miscarriage, but 10%-20% of all pregnancies may end in miscarriage, so the presence of Zika does not mean it caused it, but it is suggestive it may have.”
- 2 pregnancies are ongoing (one at 18 weeks and the other at 14 weeks) without known complications, but it is too early to be certain these babies will be normal. One of these had Zika symptoms in the first trimester, and the other had symptoms in the second trimester.

Zika infection appears to be more dangerous in the first trimester of a pregnancy, but experts can't rule out risk later. CDC has established a registry.

*Asked how soon fetal abnormalities can be detected,* Dr. Jamieson said, “Microcephaly can be difficult to detect on ultrasound early on. The later on in the pregnancy, the easier it is to see the abnormalities of the skull and brain...However, it is not clear if these abnormalities develop later on.”

The CDC's advice:

- Pregnant women should postpone travel to Zika-affected areas.
- If a male partner has traveled to or lives in a Zika-affected area, women are “strongly encouraged” to use condoms if they have sex.
- Pregnant women themselves who have traveled to a Zika active area can be tested 2-12 weeks after they return to the U.S.

### Other developments

Dr. Frieden said the mosquitoes that spread Zika are very hard to get rid of, so the focus is on protecting pregnant women, reducing travel, and reducing sexual transmission. He called the *Aedes aegypti* mosquito the “cockroach” of mosquitoes, saying it lives indoors in dark places, is hard to eradicate, and eradication efforts are “frustrated by sheer numbers” of the bugs.

Dr. Frieden said the key things *not* known right now about Zika are:

- **Whether Zika definitely causes microcephaly.** The link between Zika and microcephaly in newborns is getting stronger but is still not certain. Dr. Frieden said, “There is no definitive proof that Zika infection alone is the cause of microcephaly, but the evidence is growing.”

*Asked if the Brazilian rate of microcephaly really exceeds the expected rate, given that Brazil apparently markedly undercounted microcephaly before 2015,* Dr. Jamieson said, “The numbers here in the U.S. are small...We do have good baseline data here...and it does occur for lots of reasons...but we did not expect to see these brain abnormalities in this small case series...So, it is unexpected and more than we would have expected.”

- Whether any **phase of pregnancy** has a higher or lower risk from Zika. Dr. Frieden said, “From rubella, we might expect the first trimester to be higher risk,” but it isn't known if that is true for Zika.
- If infants without microcephaly who are born to mothers who got Zika at some point in the pregnancy will have **other health problems**. He said this may not be known for many years.

**Guillain-Barré.** Dr. Frieden said studies on Zika and Guillain-Barré are underway, including one with Brazil, “We see Guillain-Barré after many different infections, including West Nile, so it would not be the least surprising if Guillain-Barré is definitely associated with Zika, and given the time course of Guillain-Barré after peaks of Zika, I think most epidemiologists would say it is almost certainly related.” However, he offered no information on the number of cases of Guillain-Barré thought to be associated with Zika.

**Prevention.** Besides warning people about avoiding travel to infected areas or getting bit by mosquitoes and encouraging mosquito eradication efforts, the CDC is making Zika Prevention Kits available free to women in Puerto Rico, American Samoa, and the U.S. Virgin Islands. The kits contain educational material, insect repellent, condoms, a thermometer, and tablets to put into standing water to prevent mosquitoes from hatching there.

**Sexual transmission.** In the past 3 weeks, the CDC received 14 reports of suspected sexual transmission of Zika from multiple states:

- 2 were confirmed transmissions.
- 4 are probable cases of Zika transmission.
- 2 were ruled out.
- 6 are still under investigation.
- All occurred in women who had sexual contact with a man who had traveled to a Zika-infected area, who was symptomatic at the time of transmission, and who did not use a condom. A CDC official said, “Men [exposed to Zika] should use a condom the right way every time or consider not having sex.”
- All men confirmed and likely to have transmitted Zika so far “have done so when ill or shortly after their illness resolved. This doesn’t mean transmission later on is impossible. It may be that we haven’t seen this yet...Studies on how long Zika remains in semen may take months to determine.”

**Testing.** There are two types of tests that CDC has developed and is rolling out to its Laboratory Response Network (LRN). For now at least, the diagnostic tests will be available only through the LRN, though Dr. Frieden said, “We are in conversations with several commercial entities on a non-exclusive license agreement for the test, and we are open to...the technology to other parts of the private sector.”

1. **A test for active infection.** This can already be performed at >20 labs around the U.S., but the test takes about a week to run.
2. **A test for infection days to months after infection,** the CDC’s Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA). Zika is not detectable in an infected person until at least 4 days after the start of the illness, and the person can then test positive for several weeks. This test is being made available to the LRN through an Emergency Use Authorization (EUA) from the FDA. Dr. Frieden said, “It will take time before this is widely available.” The FDA said the test will not be available in U.S. hospitals or other primary care settings.

*Asked if asymptomatic people can transmit Zika and if they will be tested as well,* Dr. Frieden said that would require testing too many people, and the testing might not be done at the right moment for detection. In a chikungunya study in Puerto Rico, blood donor blood was tested, and that showed an extremely rapid spread, with ~25% of adults testing positive within just 8-9 months. He added that dengue fever and chikungunya can also affect pregnant women in Zika-affected areas, “There is a lot of cross reactivity, even with the best tests, that make it difficult to differentiate one infection from another.”

Shortly after the call, the FDA released information on its Emergency Use Authorization for the CDC laboratory tests for Zika. FDA said the test identifies antibodies to immunoglobulin M, or IgM that appear in the blood of a person infected with Zika virus, beginning 4-5 days after the start of illness and that last for ~12 weeks. The test is intended for use on *symptomatic* people and/or people who have recently traveled to an area during a time of active Zika transmission.

The FDA said the test was approved because there are no commercially available diagnostic tests cleared or approved by the FDA for the detection of Zika virus infection. Yet, the FDA also cautioned that interpreting the results of this test “require careful interpretation.” There can be both false positives and false negatives.

- A positive test result indicates that a person was likely infected recently with the Zika virus. However, the test can give an incorrect positive. These false-positive results can occur when someone has been infected with another closely related virus (such as dengue virus). When positive or inconclusive results occur, additional testing (plaque reduction neutralization test) to confirm the presence of antibodies to Zika virus will be performed by CDC or a CDC-authorized laboratory.
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- A negative test result does not necessarily mean that a person has not been infected with Zika virus. If a sample is collected just after a person becomes ill, there may not be enough antibodies for the test to measure, resulting in a false negative. Or, if the sample was collected >12 weeks after illness (infection), it is possible that the body has successfully fought the virus, and antibody levels have dropped below the detectable limit.

**Travel.** Shortly after the call, the CDC issued a travel advisory about the 2016 Summer Olympics in Brazil, advising:

- Pregnant women to consider not going. If they must go, they should talk to their doctor first, strictly avoid mosquito bites, use condoms during sex if a male partner goes along.
- Women trying to become pregnant should discuss the travel risks with their doctor before going. She and her partner should also strictly follow mosquito bite prevention recommendations.

### In other Zika news:

- **Birth defects.** A Brazilian case study, published in *PLOS Neglected Tropical Diseases*, reported on a potential link between Zika and stillbirth, describing a pregnant woman whose fetal ultrasound showed not only microcephaly and intracranial calcifications, but hydrops fetalis (a heart condition). The infant was stillborn at 32 weeks gestation, and an autopsy found evidence of Zika virus in the brain and spinal fluids but not the heart, lung, liver, or placenta.
- **Genomics.** Chinese researchers reported that they have decoded the genomic sequence of the Zika virus.
- **The spread.**
  - **China** reported its first two cases. One was a person who caught it in Venezuela before returning home to China. No other details are available on the other case.
  - **France** reported its first sexually-transmitted case of Zika in a woman whose partner had traveled to Brazil.
  - **Florida** reported 32 confirmed cases, all acquired outside the U.S.
  - **Oregon** reported a pregnant woman who was infected. It is not clear if this was included in the CDC's count.
- **Testing.**
  - **Bioneer's AccuPower ZIKV**, a multiplex real-time RT-PCR Zika virus detection kit, was granted a CE-IVD Mark. The rapid assay can test for Zika, dengue fever, and chikungunya simultaneously.
  - Texas Children's Hospital and Houston Methodist Hospital have developed a tool they said can identify the genetic material of the Zika virus and potentially speed up diagnosis and treatment. So far, the tool is only available at those hospitals, but the hospitals want to expand access.
- **Treatment and prevention.**
  - A partnership has been formed among researchers from the FDA, National Institutes of Health, CDC, and HHS in the U.S. and their counterparts in Brazil for the development of a vaccine and diagnostics against the Zika virus.
  - **Inovio** said its Zika vaccine looks promising in mice and hopes to start a Phase I trial later this year.

