Zika Virus: Anatomy of a Global Health Crisis

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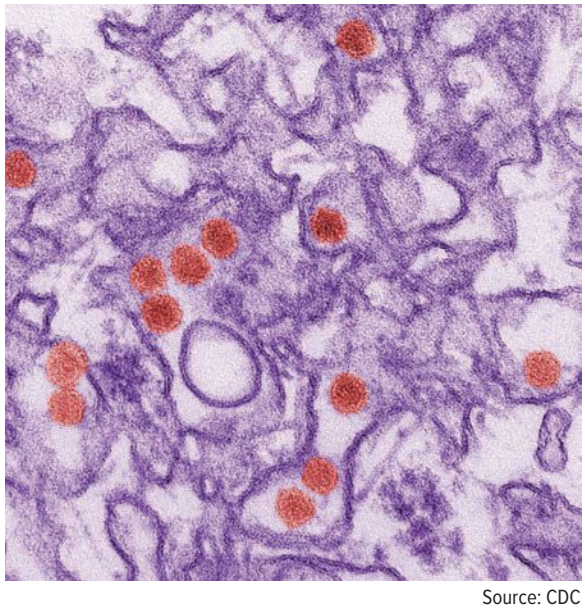
INTRODUCTION

Zika virus infection (ZVI) has been making headlines as the newest health threat on the world stage. In this article, we address the rapid global spread of this insidious disease, and the prospects for successful prevention and treatment.

Zika virus (Figure 1) is a mosquito-borne flavivirus (a member of the family *Flaviviridae*)[1] related to yellow fever virus, dengue virus, and West Nile virus.[2] It is a single-stranded positive RNA virus (10,794-nt genome) that is transmitted by mosquitoes of the *Aedes* species—including *Ae. africanus*, *Ae. luteocephalus*, *Ae. hensilli*, *Ae. aegypti,* and *Ae. albopictus*—in geographic areas with warm climates, particularly Africa and South America.[2,3] In the U.S., *Ae. albopictus* (Figure 2) has been found as far north as the Great Lakes.[4]

The virus was discovered in rhesus monkeys during routine surveillance for yellow fever in the Zika forest near Entebbe, Uganda, in 1947.[5] The first cases of ZVI in humans were reported in Uganda and in the United Republic of Tanzania in 1952.[6] From the late 1960s to the 1980s, the geographic distribution of the Zika virus expanded to equatorial Asia, including India, Pakistan, Malaysia, and Indonesia.[7–10] From Southeast Asia, the infection crossed the Pacific to Yap Island in the Federated States of Micronesia, where the first large outbreak occurred in 2007.[11,12] The Zika virus also caused a major epidemic in French Polynesia in 2013–2014, generating thousands of suspected infections.[13,14] Neighboring New Caledonia reported imported cases from French Polynesia in 2013 and an outbreak in 2014.[15,16]

Figure 1 Transmission Electron Micrograph of Zika Virus



Source: CDC

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Figure 2 Asian Tiger Mosquito, *Aedes albopictus*

Source: CDC

In May 2015, Brazil reported the first cases of locally transmitted ZVI in the Americas.[17] Phylogenetic studies found that the closest strain to the one that emerged in Brazil had been isolated during the epidemic in French Polynesia and the Pacific Islands.[2] According to one expert, the introduction of Zika virus into Brazil may have been a consequence of the Va'a World Sprint Championship canoe race, held in Rio de Janeiro in August 2014.[18] Four Pacific nations (French Polynesia, New Caledonia, Cook Islands, and Easter Island) in which Zika virus was circulating had teams participating in that contest.

In July 2015, Brazil reported an apparent association between ZVI and Guillain–Barré syndrome in adults.[19] In October, Brazil also pointed to a possible link between ZVI and microcephaly (Figure 3) in the infants of infected mothers.[20]

In February 2016, as ZVI spread through the range of *Aedes* mosquitoes in the Americas, the World Health Organization (WHO) declared that the disease constituted a Public Health Emergency of International Concern.[21] By mid-February 2016, Zika virus transmission had been documented in 48 countries and territories (Table 1).[22]

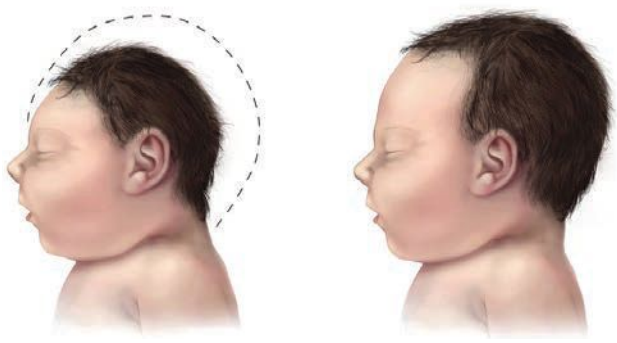
Importantly, 80% of Zika-infected individuals do not become symptomatic.[23] Those with symptoms generally experience fever, rash, joint pain, and conjunctivitis lasting for up to one week, and the clinical features tend to be mild.[24] The virus is expected to be carried worldwide by international travel, far beyond the range of its mosquito vectors.[3] In addition, a handful of cases have suggested sexual transmission of the disease by infected men.[25–29] Perhaps most troubling, the Zika virus appears to be able to cross the placental barrier in pregnant women, with disastrous consequences for the fetus.[30,31] The convergence of these factors makes ZVI a truly global concern.

A timeline summarizing key events in the developing Zika crisis appears as Table 2.[32–134]

DIAGNOSIS

Symptomatic adults with ZVI typically present with rash and an elevated body temperature (greater than 98.96° F), along

Figure 3 An Infant With Microcephaly (Left) Compared With an Infant With a Typical Head Size



Source: CDC

with at least one of the following: arthralgia, myalgia, nonpurulent conjunctivitis, conjunctival hyperemia, headache, or malaise.[135] It is difficult to diagnose ZVI, however, because the symptoms are similar to those of dengue and chikungunya viral infections, which are spread via the same mosquitoes that transmit Zika.[23,136,137] In addition to dengue and chikungunya, other diagnostic considerations include leptospirosis, malaria, rickettsia, group A *Streptococcus*, rubella, measles, and parvovirus, enterovirus, adenovirus, and alphavirus infections (e.g., Mayaro, Ross River, Barmah Forest, O'nyong-nyong, and Sindbis viruses).[138]

ZVI may be suspected based on symptoms and the patient's recent history (e.g., residence or travel to an area where Zika virus is known to be present), but the clinical diagnosis can be confirmed only by laboratory testing for the presence of Zika virus RNA in the blood or other body fluids, such as urine or saliva.[139] Reverse transcriptase polymerase chain reaction (RT-PCR) testing should be performed on serum collected within one to three days after symptom onset or on saliva or urine samples collected during the first three to five days after symptom onset.[140,141] An RT-PCR for dengue as the main differential diagnosis should be negative.[135]

Serological tests, including immunofluorescence assays and enzyme-linked immunosorbent assays, may indicate the presence of anti-Zika virus immunoglobulin M (IgM) and IgG antibodies, which typically develop toward the end of the first week of illness.[140,141] These tests must demonstrate an increased antibody titer in paired samples, with an interval of approximately two weeks.[135] Test results are usually available four to 14 days after receipt of the specimen.[140] Cross-reaction with related flaviviruses, such as dengue, is common in serological assays; therefore, clinicians must view the results with caution.[140]

Serological assays for Zika antibodies include Anti-Zika Virus ELISA (IgG/IgM) and IIFT Arboviral Fever Mosaic 2 (IgG/IgM) from Germany,[142] and Zika Virus Rapid Test from Canada.[143] However, no commercially available diagnostic tests have been cleared by the Food and Drug Administration (FDA) for the detection of Zika virus.[144] In February 2016, Houston Methodist Hospital and Texas Children's Hospital announced the joint development of the first U.S. rapid Zika test.[116] The Texas test is capable of identifying viral DNA in blood, amniotic fluid, urine, or spinal fluid, and can distinguish ZVI from dengue, West Nile, or chikungunya virus infections. Results are obtained within several hours. In addition, a new laboratory test from the Centers for Disease Control and Prevention (CDC) has been authorized for emergency use by the FDA. The Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) is designed to detect antibodies against the Zika virus.[121]

The CDC has issued guidance for the evaluation of infants or children (up to 18 years of age) with possible ZVI. The agency advises that the testing of infants with possible congenital ZVI who were born to mothers who traveled to or resided in areas affected by Zika virus during pregnancy should be guided by two considerations: 1) whether microcephaly or intracranial calcifications were detected in the infant prenatally or at birth, and 2) the mother's Zika virus testing results. Acute ZVI should be suspected in an infant or child less than 18 years of age who: 1) has traveled to or resided in an affected area within the past two weeks, and 2) has at least two of the following manifestations: fever, rash, red eyes (conjunctivitis), or arthralgia. Acute ZVI should also be suspected in an infant in the first two weeks

Table 1 Countries and Territories With Local (Autochthonous) Zika Virus Circulation (2007–2016)[22]

2007–2009
- Yap Island, Micronesia
- Gabon

2012–2014
- French Polynesia
- Isla de Pascua, Chile
- Cook Islands
- New Caledonia
- Malaysia
- Philippines
- Cambodia
- Indonesia
- Thailand

January 2015
- New Caledonia

February 2015
- Brazil
- Solomon Islands

April 2015
- Vanuatu

July 2015
- Samoa
- Fiji

October 2015
- Colombia
- Cabo Verde

November 2015
- Samoa
- El Salvador
- Guatamala
- Mexico
- Paraguay
- Suriname
- Venezuela

December 2015
- French Guiana
- Honduras
- Martinique
- Panama
- Puerto Rico

January 2016
- Bolivia
- U.S. Virgin Islands
- Dominican Republic
- Costa Rica
- Guadeloupe
- Saint Martin
- Nicaragua
- Barbados
- Maldives
- Ecuador
- Guyana
- Jamaica
- Curaçao
- Samoa
- American Samoa
- Haiti
- Thailand
- Tonga

February 2016*
- Aruba
- Bonaire, Netherlands

*As of February 17, 2016

Table 2 A Timeline of Key Events in the Developing Zika Crisis

1947
- Scientists conducting routine surveillance for yellow fever in the Zika forest near Entebbe, Uganda, isolate Zika virus in a rhesus monkey.[5]

1948
- Zika virus is found in *Aedes africanus* mosquitoes in the Zika forest.[5]

1952
- The first cases of Zika virus infection (ZVI) in humans are detected in Uganda and in the United Republic of Tanzania.[6]

1954
- Zika virus is isolated from a young girl in Nigeria.[32]

1958
- Two additional Zika virus strains are isolated in *Ae. africanus* mosquitoes from the Zika forest area.[33]

1964
- A researcher in Uganda who became ill while working with Zika strains isolated from mosquitoes provides the first proof that the virus causes human disease.[34]

1960s–1980s
- Zika virus is detected in mosquitoes and rhesus monkeys in countries across equatorial Africa.[35–42] The known geographical distribution of the virus expands to equatorial Asia, including India, Pakistan, Indonesia, and Malaysia.[7–10]

2007
- Zika virus spreads from Southeast Asia to cause the first large outbreak in humans on the Pacific island of Yap in the Federated States of Micronesia. Before this event, only 14 cases of human ZVI had been documented worldwide.[11,12]

2008
- A U.S. scientist conducting field work in Senegal becomes ill with ZVI upon his return home to Colorado and infects his wife in the first documented case of sexual transmission of the virus.[25]

2012
- Researchers publish findings on the characterization of Zika virus strains collected in Cambodia, Thailand, Malaysia, Nigeria, Senegal, and Uganda.[35,43] An analysis of Zika virus from Yap Island supports previous epidemiological evidence that the Yap outbreak originated in Southeast Asia.[11,12]

2013–2014
- Zika virus causes outbreaks in four groups of Pacific islands: French Polynesia, Easter Island, Cook Islands, and New Caledonia.[15,44]
- **December 2013:** A patient recovering from ZVI on Tahiti Island in French Polynesia seeks treatment for bloody sperm. Zika virus is isolated from his semen, adding to the evidence that Zika virus can be sexually transmitted.[26]
- **March 20, 2014:** During the 2013–2014 outbreak of Zika virus in French Polynesia, two mothers and their newborns are found to have ZVI. The infants' infections appear to have been acquired by transplacental transmission or during delivery.[30]
- **March 31, 2014:** During the outbreak in French Polynesia, 1,505 asymptomatic blood donors are found to be positive for Zika virus by reverse transcriptase polymerase chain reaction (RT-PCR) tests. These findings alert authorities to the risk of post-transfusion Zika fever.[45]

2015
- **May 7:** The Pan American Health Organization (PAHO) and the World Health Organization (WHO) issue a joint epidemiological alert on ZVI.[46]
- **July 15:** Brazil confirms Zika virus circulation in that country. This is the first report of locally acquired ZVI in the Americas.[17]
- **July 17:** Brazil reports the detection of neurological disorders associated with a history of ZVI. Forty-nine cases are confirmed as Guillain–Barré syndrome.[3,47]
- **October 31:** Brazil reports an unusual increase in the number of cases of microcephaly among newborns since August, totaling 54 by October 30.[3,48]
- **November 3:** Colombia reports 239 cases of locally acquired ZVI.[49]
- **November 11:** Brazil reports 141 suspected cases of microcephaly. Officials declare a national public health emergency as cases of suspected microcephaly continue to increase.[3,50]
- **November 17:** PAHO and WHO issue an epidemiological alert asking PAHO member states to report observed increases of congenital microcephaly and other central nervous system (CNS) malformations.[51] Brazil's Ministry of Health reports the detection of Zika virus in amniotic fluid samples from two pregnant women whose fetuses were confirmed by ultrasound examinations to have microcephaly.[52]
- **November 21:** Brazil reports that 739 cases of microcephaly, including one fatal case, are being investigated in nine states.[53]
- **November 24:** Authorities in French Polynesia hypothesize that ZVI may be linked to CNS malformations if mothers are infected during the first or second trimester of pregnancy.[54] El Salvador reports its first RT-PCR–confirmed cases of locally acquired ZVI.[55]
- **November 26:** Mexico reports three RT-PCR–confirmed cases of ZVI; two were locally acquired, and the third had traveled to Colombia.[56]
- **November 27:** Venezuela[57] and Paraguay[58] report RT-PCR–confirmed cases of locally acquired ZVI.
- **November 28:** Brazil detects the Zika virus genome in blood and tissue samples from an infant with microcephaly. Brazil also reports the Zika-associated deaths of two adults and one newborn.[59]
- **December 1:** PAHO and WHO issue an alert on ZVI's association with neurological syndromes and congenital malformations in the Americas. The alert includes guidelines for laboratory detection of the virus.[60]
- **December 6:** Cabo Verde, a group of islands off the coast of western Africa, reports that it has 4,744 suspected cases of locally acquired ZVI. No neurological complications are observed.[61]
- **December 16:** Honduras reports two RT-PCR–confirmed cases of locally acquired ZVI.[62]
- **December 17:** Four ZVI cases are confirmed by RT-PCR in Panama.[63]
- **December 21:** French Guiana and Martinique report their first RT-PCR–confirmed cases of locally acquired ZVI.[64]
- **December 22:** Brazilian researchers publish evidence that the characterization of Zika virus as a "mild cousin of dengue" may not be accurate because of the possibility of more-serious disease symptoms, especially in immunocompromised patients.[65]
- **December 29:** Brazil updates the number of suspected microcephaly cases to 2,975.[66]
- **December 31:** The Centers for Disease Control and Prevention (CDC) reports the first RT-PCR–confirmed case of locally acquired ZVI in the Commonwealth of Puerto Rico.[67]

2016
- **January 4:** Brazil reports 3,174 suspected cases of microcephaly, including 38 deaths.[68]

Table 2 A Timeline of Key Events in the Developing Zika Crisis (continued)

- **January 5:** Researchers report the first diagnoses of intrauterine transmission of Zika virus in two pregnant women in Brazil whose fetuses were diagnosed with microcephaly. Although blood tests in both women are negative, Zika virus is detected in amniotic fluid.[69]
- **January 7:** The Maldives report that a Finnish national who worked in the country became ill upon his return to Finland, where he tested positive for ZVI on RT-PCR.[70] Scientists find that Zika virus strains in four patients in Suriname belong to the Asian genotype and are almost identical to the strain that circulated in French Polynesia in 2013.[71] Ophthalmologists in Brazil report severe ocular malformations in three infants born with microcephaly.[72]
- **January 12:** In collaboration with health officials in Brazil, the CDC releases laboratory findings from four microcephaly cases in Brazil. The findings indicate the presence of Zika virus in brain tissue from two newborns. In addition, the placenta of two fetuses miscarried during the first 12 weeks of pregnancy test positive by RT-PCR. The findings are considered the strongest evidence to date of an association between ZVI and microcephaly.[73]
- **January 14:** Guyana reports its first RT-PCR–confirmed case of locally acquired ZVI.[74]
- **January 15:** The CDC issues interim travel guidance for pregnant women, advising those in any trimester to consider postponing travel to areas with ongoing local transmission of Zika virus or to take precautions against mosquito bites if they must travel.[75] Barbados reports its first RT-PCR–confirmed case of locally acquired ZVI.[74] A case of microcephaly is reported in Hawaii in the infant of a woman who had resided in Brazil early in her pregnancy.[76]
- **January 16:** The Plurinational State of Bolivia reports its first RT-PCR–confirmed case of locally acquired ZVI. Panama confirms six cases of ZVI; two were locally acquired, three were imported from Columbia, and one was from the Bolivarian Republic of Venezuela.[3,77]
- **January 18:** Haiti reports its first RT-PCR–confirmed cases of locally acquired ZVI.[77]
- **January 19:** El Salvador reports an unusual increase in cases of Guillain–Barré syndrome.[78]
- **January 21:** Brazil reports 3,893 suspected cases of microcephaly, including 49 deaths.[77]
- **January 22:** Brazil reports that 1,708 cases of Guillain–Barré syndrome have been registered by hospitals.[79]
- **January 23:** The Dominican Republic reports its first RT-PCR–confirmed cases of ZVI; eight were locally acquired and two were imported from El Salvador.[77]
- **January 25:** The CDC reports the first RT-PCR–confirmed case of locally acquired ZVI on the island of St. Croix in the U.S. Virgin Islands.[80] France reports two confirmed cases of Guillain–Barré syndrome in Martinique; one of the patients tests positive for ZVI.[77]
- **January 26:** The CDC issues treatment guidelines for infants exposed to Zika virus.[81] A Virginia resident who had traveled abroad tests positive for ZVI.[82]
- **January 27:** The White House announces that most of its efforts to fight the Zika virus will focus on sharing information about the risks with the public.[83]
- **January 29:** Officials in Brazil report that infants with microcephaly also have serious eye damage.[84] Suriname reports 1,107 suspected cases of ZVI; 308 are confirmed by RT-PCR.[77]
- **January 30:** Jamaica reports its first RT-PCR–confirmed case of locally acquired ZVI.[85]
- **February 1:** Brazil's top health official tells Reuters that the Zika virus outbreak is worse than believed because most cases show no symptoms.[86] WHO announces that the recent association of ZVI with microcephaly and other neurological disorders constitutes a Public Health Emergency of International Concern.[87] New York City offers free Zika tests for people with symptoms of ZVI.[88]
- **February 2:** Texas reports a case of sexual transmission of ZVI. The patient had not recently travelled outside the U.S., but developed symptoms after sexual contact with a traveler. This is the first U.S. Zika case in someone who had not traveled abroad, and the third indication that the virus can be sexually transmitted.[27,89] A Brazilian official says pregnant women should not travel to that country for the Olympic Games in August.[90] Chile announces its first RT-PCR–confirmed cases of ZVI on the mainland in travelers returning from Colombia, the Bolivarian Republic of Venezuela, and Brazil.[87] Two ZVI cases are reported in Australia; both individuals had visited Haiti.[91]
- **February 3:** The CDC puts its emergency operations center on the highest level of activation to respond to the Zika outbreak.[92] The WHO calls for further investigation into the sexual spread of ZVI.[93]
- **February 4:** Brazilian health officials confirm a case of ZVI transmitted by transfused blood from an infected donor.[87] The United Kingdom announces plans to spray insecticide inside planes from Zika-affected countries.[94]
- **February 5:** Brazilian health officials say they have found live Zika virus in the urine and saliva of infected people.[95] The CDC recommends that men who have recently returned from areas with Zika virus use condoms during sexual intercourse, especially with a pregnant partner, to prevent virus transmission.[96] Puerto Rico's governor declares a public health emergency because of the Zika virus.[97]
- **February 7:** Suriname reports an increase in cases of Guillain–Barré syndrome; 10 cases are confirmed to be positive for Zika virus by RT-PCR urine tests.[87] France announces that travelers returning from any outbreak zones of the Zika virus will have to wait at least four weeks before giving blood to avoid the risk of transmission.[98]
- **February 8:** The Obama administration asks Congress for $1.8 billion to fight the Zika outbreak.[99] The U.S. Olympic Committee tells sports federations that athletes and staff concerned for their health should consider not going to the Olympics in Rio de Janeiro in August.[100]
- **February 10:** Colombia reports that nearly 100 people with Guillain–Barré syndrome also have Zika symptoms.[87] China confirms its first case of ZVI in a man in Jiangxi province.[101] Finland reports two cases of ZVI; one subject had returned from a vacation in the Maldives.[102]
- **February 12:** The National Institute of Allergy and Infectious Diseases announces that the Zika virus may "hide" in parts of the body that are shielded from the immune system, making it harder to fight.[103] In England, Zika virus is found in the semen of a man two months after he was first infected, suggesting that the virus may linger in semen long after symptoms of the infection fade.[104]
- **February 13:** The WHO announces that Guillain–Barré syndrome is on the rise in five Latin American countries (Brazil, Colombia, El Salvador, Suriname, and Venezuela), but with no proven link to ZVI.[105] Colombia reports that more than 5,000 pregnant women have ZVI.[106]
- **February 15:** Russia reports its first case of ZVI after a tourist contracted the disease in the Dominican Republic.[107]
- **February 16:** The FDA recommends the deferral of individuals from donating blood if they have been to areas with active Zika virus transmission, potentially have been exposed to the virus, or have

table continues

Table 2 A Timeline of Key Events in the Developing Zika Crisis (continued)

had confirmed ZVI.[23] Mexico confirms that six pregnant women are infected with Zika virus, bringing the total number of cases to 80.[108]

- **February 17:** Researchers in Rio de Janeiro report that Zika virus can cross the placental barrier.[109] Brazilian government officials say "most" of the country's confirmed microcephaly cases are linked to ZVI.[110]
- **February 18:** The World Bank makes $150 million in financing available to help fight Zika in affected Latin American and Caribbean countries.[111]
- **February 19:** The CDC issues updated guidelines for health care providers caring for infants or children with possible ZVI.[112]
- **February 20:** South Africa reports its first case of confirmed ZVI in a Colombian man.[113]
- **February 22:** Cuba deploys 9,000 troops in an effort to avoid the Zika virus by eradicating mosquitoes.[114]
- **February 23:** The CDC reports that it is investigating 14 new reports of possible sexual transmission of Zika virus, including several involving pregnant women. The agency says sexual transmission may be a "more likely" means of transmission for the virus than previously thought.[115] In Texas, two hospitals announce that they have developed a rapid RNA test for Zika virus.[116]
- **February 24:** The Czech Republic reports its first cases of ZVI.[117] Colombia announces a "probable" case of microcephaly in an aborted fetus. Zika virus was identified in the mother's amniotic fluid.[118]
- **February 25:** A Yale School of Public Health researcher reports that, in addition to microcephaly, ZVI may cause hydrops fetalis (the abnormal accumulation of fluid in fetal compartments), hydranencephaly (the almost complete loss of brain tissue), and fetal demise (stillbirth).[119,120]
- **February 26:** The FDA authorizes a new CDC laboratory test for ZVI for emergency use. The Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) is intended for use in detecting antibodies in blood samples from people with a history of symptoms associated with ZVI and/or people who have recently traveled to an area during a time of active Zika virus transmission.[121]
- **February 27:** France reports Europe's first sexually transmitted ZVI case. A woman was infected after her partner returned from Brazil.[122]
- **February 28:** French scientists confirm a link between ZVI and Guillain–Barré syndrome in the 2013–2014 Polynesian outbreak. The risk of developing Guillain–Barré is calculated at 24 people for every 100,000 infected by the virus.[123]
- **March 1:** The FDA issues new guidelines aimed at preventing Zika virus transmission via human cell and tissue products.[124] Cuba reports its first case of ZVI; the patient is a female doctor from Venezuela whose husband had contracted the virus in their home country.[125]
- **March 2:** New Zealand's health ministry announces that it is investigating whether the Zika virus was sexually transmitted from a man to his female partner. The man had tested positive for Zika after he visited an unnamed country.[126]
- **March 3:** Google reports that its engineers are working with the United Nations Children's Emergency Fund (UNICEF) to analyze data in an effort to map and anticipate the global spread of Zika virus.[127] French researchers link ZVI to the paralyzing disorder myelitis in a 15-year-old girl in Guadeloupe. The presence of Zika virus in the girl's cerebrospinal fluid suggests that the virus might be neurotropic.[128]
- **March 4:** The White House and the CDC announce plans to gather state and local officials on April 1 to urgently craft a plan to attack the Zika virus. Federal health officials say they expect the first locally transmitted cases of ZVI in the continental U.S. by June or July.[129] The WHO reports that there is "accumulating evidence" linking ZVI to microcephaly and Guillain–Barré syndrome.[130] Scientists in Brazil discover that a mosquito more common than the one primarily known to transmit Zika may be able to carry the virus. *Ae. aegypti* is recognized as the main transmitter of ZVIs, but the scientists were able to infect another species, *Culex quinquefasciatus*, with the virus in a laboratory. Outside Brazil, *C. quinquefasciatus* exists in more-temperate climates, including the southern U.S., where it is known to carry the West Nile virus and can survive the winters.[131]
- **March 9:** The WHO warns that mosquito spraying may not stop the spread of Zika virus. The agency also says that vaccine trials may come too late for the current outbreak.[132] The CDC's director calls Zika in Puerto Rico a "challenge and crisis."[133] Brazil announces that the number of microcephaly cases linked to ZVI has risen to 4,976.[134]

of life 1) whose mother traveled to or resided in an affected area within two weeks of delivery, and 2) who has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia.[112,145]

According to the CDC guidelines, the evaluation of infants and children for acute ZVI (symptom onset within the past seven days) should include the testing of serum and, if obtained for other reasons, cerebrospinal fluid specimens for evidence of Zika virus RNA using RT-PCR. If Zika virus RNA is not detected and symptoms suggestive of ZVI have been present for at least four days, the patient's serum may be tested for Zika virus immunoglobulin M (IgM) and neutralizing antibodies as well as for dengue virus IgM and neutralizing antibodies. Laboratory evidence of ZVI in a clinical specimen from an infant or child would include detectable Zika virus in culture, Zika virus RNA or antigen, or a clinical specimen positive for Zika virus IgM with confirmatory neutralizing antibody titers at least fourfold higher than dengue virus neutralizing antibody titers. If Zika virus antibody titers are less than fourfold higher than those for dengue virus, test results for Zika virus are considered inconclusive.[145]

The CDC has also issued guidance for health care providers caring for pregnant women and women of reproductive age who may have been exposed to Zika virus.[96] Testing is recommended at the time of illness for pregnant women experiencing symptoms consistent with ZVI. For pregnant women not experiencing such symptoms, testing is recommended when they begin prenatal care. Follow-up testing around the middle of the second trimester of pregnancy is also recommended because of an ongoing risk of Zika virus exposure. Pregnant women should receive routine prenatal care, including an ultrasound during the second trimester of pregnancy. An additional ultrasound may be performed at the discretion of the health care provider. Pregnant women without symptoms of ZVI can be offered testing two to 12 weeks after returning from areas with ongoing Zika virus transmission.

STEPS TO PREVENT VIRUS TRANSMISSION

In response to the growing evidence that ZVI is sexually transmissible, the CDC has recommended that men who reside in or have traveled to an area of active Zika virus transmission

and who have pregnant sex partners should consistently use latex condoms during sex (vaginal, anal, or oral) or abstain from sexual activity for the duration of the pregnancy.[96]

Blood donations are another potential source of Zika virus transmission. The FDA recommends that individuals be deferred from donating blood if they have been to areas with active Zika virus transmission, have potentially been exposed to the virus, or have had confirmed ZVI.[23] In areas without active Zika virus transmission, the FDA recommends that donors at risk for ZVI be deferred for four weeks. Individuals considered to be at risk include those who have had symptoms suggestive of ZVI during the past four weeks; those who have had sexual contact with a person who has traveled to or resided in an area with active Zika virus transmission during the prior three months; and those who have traveled to areas with active transmission of Zika virus during the past four weeks.

In areas with active Zika virus transmission, the FDA recommends that whole blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved pathogen-reduction device is used. The agency's guidance also recommends that blood establishments update donor-education materials with information about the signs and symptoms of ZVI and ask potentially affected donors to refrain from giving blood.[23]

The FDA has also identified human cells, tissues, and cellular and tissue-based products (HCT/Ps) as another potential source of Zika virus transmission.[124] The agency's guidance addresses the donation of HCT/Ps from both living and deceased donors, including donors of umbilical cord blood, placenta, or other gestational tissues. HCT/Ps include corneas, bone, skin, heart valves, hematopoietic stem/progenitor cells (HPCs), gestational tissues (such as amniotic membrane), and reproductive tissues (such as semen and oocytes).

THERAPEUTIC APPROACHES

No specific treatments are available for patients with ZVI.[23,134,139] Supportive therapy includes rest and the use of acetaminophen to relieve fever and pain.[23] Aspirin should not be given to patients younger than 12 years of age with ZVI because of the risks of bleeding and of developing Reye's syndrome.[135] Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should also be avoided in patients with unconfirmed ZVI in case the symptoms are actually caused by dengue or chikungunya—two infections in which NSAIDs are contraindicated.[135] Pruritus may be controlled with antihistamines,[135] and patients should drink plenty of fluids to prevent dehydration from sweating and/or vomiting.[23,135]

According to the CDC, infants with a typical head size, normal ultrasounds, and a normal physical examination born to mothers who traveled to or lived in areas with Zika virus do not require special care beyond what is routinely provided to newborns.[112]

Researchers have taken tentative steps toward finding a pharmacological treatment for patients with established ZVI. At Utah State University, for example, investigators have evaluated the antiviral activity of ranpirnase, a cancer chemotherapeutic agent, in a cell model of ZVI.[146] Overall, the study showed that ranpirnase was active in blocking Zika virus compared with a control. Ranpirnase for injection has been safely administered to more than 1,000 subjects in oncology trials. In another cell-based study, conducted in France, Zika virus appeared to be sensitive to the antiviral effects of both type I and type II interferons.[147] But investigators have run into another roadblock: To date, there are no practical animal models against which potential Zika drugs may be screened.[148]

THE RACE FOR A VACCINE

Although scientists around the world are playing catch-up with the Zika virus,[149] they are well versed in the ways of Zika's relatives, dengue and West Nile. This knowledge has provided a valuable springboard for the development of potential vaccines.[150]

Brazil's Butantan Institute, based in São Paulo, was the first group off the starting block, announcing in January that it planned to develop a Zika vaccine "in record time"—although its director warned that the project would likely take three to five years.[151] The scientists in São Paulo plan to use animals to produce antibodies to combat the virus. A similar approach was used to develop a treatment for Ebola.[152] The National Institutes of Health in the U.S. and the Public Health Agency of Canada have also begun looking for vaccine candidates.[149] In January, a Canadian scientist at Laval University in Quebec told Reuters that work on a Zika vaccine could begin as early as August and that, if successful, the vaccine could be available for emergency use as early as October or November 2016, although full regulatory approval would take years.[149,153] Also in January, vaccine developer Hawaii Biotech Inc. announced that it had started a formal program to test a Zika virus vaccine in fall 2015, when the virus was first making headlines in Brazil, but the company said it had no timetable for initiating clinical trials.[154] Similarly, Inovio Pharmaceuticals, based in Pennsylvania, announced in early 2016 that it had been working on a DNA-based vaccine for the Zika virus since December 2015. In that time, the company has created a DNA strand that could potentially stop the virus, using knowledge acquired from its dengue virus program. Inovio said it planned to move into phase 1 testing in humans by the end of 2016.[155]

Some heavy hitters on the pharma scene have also entered the vaccine race. In early February, Pfizer, Johnson & Johnson, and Merck said they were evaluating their technologies or existing vaccines for their potential to fight the Zika virus. In Europe, Sanofi announced that it would launch a Zika vaccine program, while in Japan, Takeda said it had formed a team to investigate how it might help make a vaccine.[156]

In India, biotechnology company Bharat Biotech said that it had started work on a Zika virus vaccine in 2015 while developing vaccines for chikungunya and dengue. The company is now actively developing two vaccine candidates. One is recombinant (i.e., created by genetic engineering), and the other is inactivated. Both are undergoing preclinical trials.[157]

Meanwhile, at the National Institute of Allergy and Infectious Diseases (NIAID), scientists are working on a DNA-based Zika vaccine that uses a strategy similar to that of an investigational flavivirus vaccine developed by the agency for West Nile virus. The latter vaccine was able to provoke an immune response in a phase 1 study. The NIAID is also investigating a live-attenuated Zika vaccine, building on an approach used in creating a closely related vaccine for dengue virus. In other work, the agency is

using a genetically engineered version of vesicular stomatitis virus—which primarily affects cattle—to develop a third Zika vaccine, which is being evaluated in tissue culture and animal models. The NIAID said it was possible that a vaccine could be ready for early-stage human trials before the end of 2016.[150]

Currently, the primary target group for Zika vaccines appears to be pregnant women, in view of growing evidence linking the infection to severe birth defects. This may complicate vaccine testing, however, since pregnant women are commonly excluded from clinical trials until the safety of a vaccine or drug has been established in other populations. Moreover, effective vaccines work by provoking an immune response that is sufficiently strong to weaken or destroy the targeted pathogen but not so strong that it sickens the patient. Currently, there is no simple way to determine the optimal immune response for warding off Zika virus.[149] Most challenging of all: Since epidemics occur sporadically and with little or no warning, pre-emptively vaccinating large populations in anticipation of Zika outbreaks may be prohibitively expensive.[137]

ENVIRONMENTAL CONTROL EFFORTS

Ultimately, lasting progress won't be made in the Zika war until the threat is eliminated at its source: virus-carrying mosquitoes. Thus, the prevention and control of ZVI involves two basic strategies: 1) removing or modifying mosquito breeding sites, and 2) eliminating or reducing contact between mosquitoes and people.[139] According to the WHO, the latter objective may be achieved by using insect repellent regularly; by wearing clothes (preferably light-colored) that cover as much of the body as possible when outdoors; by using physical barriers, such as window screens and closed doors and windows; and, if needed, by taking additional precautions, such as sleeping under mosquito nets during the day. Insect repellents should contain DEET (N, N-diethyl-3-methylbenzamide); IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester); or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). During outbreaks, health authorities may elect to spray insecticides in affected areas.

In addition, outdoor containers that can hold water, such as buckets and pots, should be emptied and cleaned on a regular basis or covered. Other mosquito-breeding sites, such as roof gutters or used car tires, should be cleaned or removed.[139]

Several inventive methods are being developed to reduce mosquito populations. In Brazil, researchers are planning to zap millions of male mosquitoes with gamma rays to sterilize them using a device called an irradiator, which has been used to control fruit flies on the Portuguese island of Madeira. The government's plan is to breed up to 12 million male mosquitoes each week and then sterilize them with the cobalt-60 irradiator. The sterile males will be released into target areas to mate with wild females, which will lay eggs that produce no offspring.[158] Releasing sterile irradiated male mosquitoes is a technique that was first developed by the United Nations' International Atomic Energy Agency to control tsetse flies in Africa.[159]

Another promising tool is a genetically modified prototype mosquito developed by a British company, Oxitec. The male mosquitoes are modified so that their offspring will die before reaching adulthood and before they are able to reproduce. A WHO advisory group has recommended further field trials of the technique, following promising tests in the Cayman Islands.[159]

An alternative approach uses *Wolbachia* bacteria, which prevent the hatching of eggs from female mosquitoes that have mated with infected males. The bacteria do not infect humans. *Wolbachia* bacteria have been shown to reduce mosquitoes' ability to transmit the dengue virus. In February, the WHO announced that large-scale field trials of *Wolbachia* bacteria would start soon.[159] Tests of *Walbachia* bacteria for both Zika- and dengue-carrying mosquitoes are already under way in Indonesia, where scientists are hoping to recruit 100,000 people in 2016. The investigators are faced with two key challenges, however: convincing the public that the trials are safe and securing funding from the government. They estimated that it will take at least three years before results are seen in the field.[160]

CONCLUSION

As the Zika virus sweeps across Africa, Southeast Asia, and the Americas, ZVI has undergone a correspondingly rapid change from a mild, endemic illness to a world-threatening infection linked to neurological disorders and severe birth defects.[3] The transmission of ZVI may be expected to evolve beyond the virus' mosquito vector to involve person-to-person contact on a global scale, with international travel playing a pivotal role in spread of the disease.[3] Pharma companies and research centers around the globe are working feverishly to develop Zika vaccines, although a vaccine worthy of regulatory approval could take years to reach the market.[149,151,153]

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Vaccine Spotlight: Quadracel

continued from page 240

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