Zika Virus and Neurologic Disease

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KEYWORDS

• Zika virus • Neurologic manifestations of Zika virus • Congenital Zika syndrome
• Guillain-Barré syndrome

KEY POINTS

- Although Guillain-Barré syndrome (GBS) is the most frequent Zika-associated neurologic manifestation among adolescents and adults, additional neurologic manifestations have been identified, including myelitis, encephalitis, and sensory neuropathy.
- ZIKV has been identified to disrupt proliferation and migration of neural progenitor cells.
- Long-term management of CZS requires a comprehensive combination of supportive services throughout early development. Early childhood stimulation and rehabilitation programs coupled with psychosocial support are imperative for optimal outcomes.
- Debate remains regarding the neurovirulence of Asian and African ZIKV strains and whether this may have contributed to the severity of the most recent outbreak.
- Although there are more than 40 vaccine candidates in the pipeline, a vaccine will likely not be available for at least 2 years. It is also not known if ZIKV infections lead to lifelong immunity, although the significant decline in cases over the last several months suggests that there is herd immunity.

INTRODUCTION

Zika virus (ZIKV), an arthropod-borne virus, is a single-stranded, positive-sense RNA virus that belongs to the Flaviviridae family, which includes Dengue (DENV), yellow fever (YFV), St. Louis encephalitis, Japanese encephalitis, and West Nile viruses (WNV).[1,2] This emerging infectious disease most recently caused a widespread epidemic throughout the Americas and prompted the World Health Organization

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(WHO) to declare ZIKV a Public Health Emergency of International Concern from February 2016 to November 2016.[1,3,4] According to the most recent WHO ZIKV situation report published in March 2017, a total of 84 countries, territories, or subnational areas had evidence of vector-borne ZIKV transmission.[5] Compared with the peak incidence of ZIKV from November 2015 to February 2016, the number of suspected and confirmed ZIKV cases has recently declined (http://www.paho.org/hq/index.php?option=com_content&view=article&id=11599%3Aregional-zika-epidemiological-update-americas).[6] Many experts attribute the recent decrease in ZIKV cases to the development of a widespread immunity across populations in previous epidemic regions, although it remains unknown whether lifelong immunity exists.[7] Individuals from nonepidemic regions traveling to ZIKV endemic regions and those who are not immune remain at high risk. Although most cases are mild or go undetected, rare severe neurologic effects including congenital ZIKV syndrome (CZS) in neonates and Guillain-Barré syndrome (GBS) in adolescents and adults have been identified.[8,9] The serious neurologic complications associated with ZIKV prompted the declaration of the public health emergency of international concern and are the focus of this review.

EPIDEMIOLOGY

ZIKV was first identified in a febrile sentinel Rhesus monkey in Uganda's Zika forest in 1947, and the first documented human illness caused by ZIKV was reported in Africa in 1952.[3,10] Thereafter, only a dozen additional cases were reported in equatorial Africa and Asia until 2007 when an outbreak occurred on Yap island in Micronesia.[11] Sporadic cases were subsequently found in various Southeast Asian countries, including Thailand, Cambodia, Malaysia, Indonesia, and the Philippines in the late 2000s to early 2010s, at which time no known neurologic manifestations were reported.[3] A second major epidemic, leading to more than 19,000 symptomatic infections, occurred in the French Polynesian archipelago in 2013 and 2014.[1,4] It is suspected that the lack of community-acquired immunity and a large population of mosquito vectors contributed to the widespread outbreak.[3] The ZIKV strain isolated during this outbreak was similar to the Asian lineage strains from Yap Island in 2007 and Cambodia in 2010.[12,13] The concern for a link between ZIKV infection and neurologic complications was first identified in the French Polynesia outbreak, where a significant increase in GBS cases was seen compared with the previous 4 years. In addition, a retrospective analysis found supportive evidence of the potential association between ZIKV infection during pregnancy and microcephaly.[1,2,14–16] The increases in microcephaly and GBS cases were temporally and geographically related to the increase in ZIKV, shedding light on the magnitude of the infection and its potential severe consequences. Outbreaks subsequently followed in other Pacific islands, including the Cook Islands, New Caledonia, and Chile's Easter Island.[10,17] In January 2015, there were reports of an increase in acute febrile illness cases in northeast Brazil accompanied by rash, muscle pain, joint pain, and headache. In 25 patients sampled, all tested negative for Chikungunya (CHIKV), rubella, and measles, whereas 11 were also negative for DENV.[17] It is important to note that CHIKV and DENV are endemic to these regions, are carried by the same vector as ZIKV, and present symptoms that are similar to ZIKV.

The first case of autochthonous transmission of ZIKV in Brazil was reported by a laboratory in Paraná, Brazil on specimens received in March 2015 for patients who initially presented with a "dengue-like syndrome."[18] In April 2015, a preliminary report from a laboratory in the Brazilian state of Bahia heralded the detection of ZIKV in samples, but confirmatory tests were still pending.[17] The WHO confirmed the first case of ZIKV in

May 2015, although the virus was likely introduced more than 12 months before, potentially via the World Cup in 2014.[2,4,18–20] By July 2015, ZIKV transmission was reported in 12 Brazilian states.[17] Colombia confirmed ZIKV cases in October 2015 followed by Suriname, El Salvador, Guatemala, Paraguay, and Venezuela in November 2015.[17] Over the next 2 months leading into the beginning of 2016, 18 additional countries in the Americas and the Caribbean reported cases of ZIKV infection.[17] In February 2016, ZIKV was announced a Public Health Emergency of International Concern by the WHO because of significant reported increases in microcephaly and other neurologic disorders identified in Brazil, and previously in French Polynesia.[17] Overall, transmission spread throughout South and Central America as well as the Caribbean, affecting 48 countries and territories from March 2015 to March 2017.[1,3]

Effective monitoring of ZIKV was enforced because of the concern for sexual transmission, congenital birth defects, and other neurologic manifestations, which led to ZIKV detection outside of the Americas and Caribbean. Cape Verde, an island off the coast of West Africa, reported their first outbreak of ZIKV, caused by the Asian strain, in October 2015. Later analysis revealed that it was most likely imported to Africa from Brazil.[10,21] There was a large concern that ZIKV may spread to the African continent during the most recent outbreak, although there is a lack of evidence currently that neurovirulent strains have emerged in the region. Although ZIKV did not reach the African continent, it did reach the continental United States. According to the Centers for Disease Control and Prevention (CDC), the first known outbreak of ZIKV caused by local mosquito-borne transmission occurred between June 30, 2016 and August 5, 2016 in Florida.[22] Of the 29 individuals who displayed diagnostic evidence of recent ZIKV infection in the affected areas, 4 infections were attributed to likely local mosquito-borne transmission.[22] In the US territories during the 2015 to 2017 time period, there were 37,103 symptomatic ZIKV cases reported (not including congenital disease cases), 611 (2%) of which occurred in 2017.[23,24] During the same time period, there have been 5613 symptomatic ZIKV cases reported in the United States (not including congenital disease cases), 385 (7%) of which occurred between January 1, 2017 and December 20, 2017.[23,24] In 2017, 4 (1%) of these cases were acquired via sexual transmission; 3 (1%) were acquired through presumed local mosquito-borne transmission, and 378 (98%) cases occurred in travelers returning from endemic areas.[23] Two cases of locally transmitted ZIKV by mosquitoes have been reported in the southernmost counties of Texas in 2017.[25] Most recently in November 2017, a single case of presumed local transmission of ZIKV was reported in Miami-Dade County, Florida after an individual, who had not traveled to active ZIKV transmission areas nor had a sexual partner with recent travel history, tested positive for ZIKV.[26] Despite this single case report, there is no current evidence of ongoing, active transmission of ZIKV in Florida at this time.[26]

TRANSMISSION

Transmission occurs primarily through vector routes, predominantly *Aedes aegypti* mosquitoes, which are also largely responsible for transmitting DENV, CHIKV, and YFV.[1,4] Although bites can be acquired throughout the day and night, most tend to occur in the early morning, late afternoon, and early evening.[27] Individuals who live in tropical or subtropical areas, where *Aedes* mosquito vectors are located, are at increased risk for ZIKV.[4] A recent study investigated potential ZIKV transmission via *Aedes albopictus* mosquitoes and revealed that although *A albopictus* had a higher susceptibility to ZIKV infection, *A aegypti* had higher transmission efficiency.[28] Because *A albopictus* mosquitoes are capable ZIKV vectors, they should be closely monitored because this raises potential concern that they may be able to transmit the virus more effectively in the future

through adaptive events.[28] Prevention, treatment, and surveillance of *Aedes* vectors are imperative for optimal disease control. One report highlighted how active community prevention participation in Cuba helped to sustain control of vector-borne diseases, including DENV and ZIKV through treatment with pesticides, which decreased the number of infected female carrier mosquitoes.[29] Along with the primary modes of preventing mosquito transmission (ie, insecticides and breeding site removal), other methods include introduction of *Wolbachia* bacteria and transgenic mosquitoes.[30] Further treatment and prevention measures are discussed later in the "Prevention, Treatment, and Vaccine Development" section.

In addition to vector-borne transmission, maternal-fetal transmission occurs when pregnant mothers infected with ZIKV pass the infection on to their fetus, which may lead to CZS, which is discussed in detail later in the section on "Congenital Zika Syndrome." Unlike other Flaviviridae viruses, sexual transmission has also been documented and has contributed to ZIKV's outbreak potential. Although the first man-to-woman transmission occurred in 2008, the first reported case of woman-to-man sexual transmission occurred in July 2016 in New York City.[31,32] Sexual transmission may occur via vaginal, anal, and oral routes even if individuals are asymptomatic.[33] Between January and April 2016, 9 reported cases of man-to-woman sexual transmission occurred in the United States as a result of recent male travel to outbreak regions.[34] All male travelers had laboratory evidence of a recent ZIKV or unspecified flavivirus infection, whereas all female nontravelers had laboratory-confirmed ZIKV infection.[34] Although not yet documented in the United States, ZIKV has also been transmitted via blood transfusions in multiple cases in Brazil, and laboratory exposure of ZIKV has occurred.[33,35,36] Although ZIKV has been detected in breast milk up to 9 days after delivery, no reports have linked ZIKV infections to breastfeeding.[37] Transmission through organ transplantation is theoretically possible; however, there have been no reported cases to date.[37–39]

NEUROLOGIC MANIFESTATIONS

Adolescent and Adult Neurologic Manifestations

Although rare, various severe neurologic complications are associated with ZIKV infection in adolescents and adults. GBS, an acute autoimmune polyneuropathy, has been the most common neurologic complication associated with ZIKV in those age groups.[8,9,40,41] The first report of GBS associated with ZIKV occurred during the French Polynesia outbreak in November 2013.[42] In a case-control study, 42 cases were identified, a significant increase from the number of annual GBS cases compared with previous years.[43,44] Thirty-seven (88%) patients had a recent history of viral syndrome in a median of 6 days (interquartile range [IQR] 4–10) before neurologic onset with all patients no longer viremic at the time of admission. Most had electrophysiological findings compatible with acute motor axonal neuropathy (AMAN), although incomplete electrophysiological testing was performed.[43] Interestingly, 95% of GBS patients were found to have preexisting DENV immunity. Antibodies against DENV serotypes 1 and 3 were detected during that time. Past DENV history, however, did not significantly differ from either of the 2 control groups (group 1: individuals presenting with a nonfebrile illness; group 2: reverse-transcription polymerase chain reaction [RT-PCR] -confirmed ZIKV, but no neurologic complications; 89% and 83%, respectively).[43]

A study performed in Rio de Janeiro, Brazil between December 5, 2015 and March 18, 2016 found an increased incidence of GBS from approximately 0.6 GBS cases per month in 2013 to 2014 to 5.4 cases per month.[45] In a case series involving

7 geographic locations (Bahia State, Colombia, the Dominican Republic, El Salvador, Honduras, Suriname, and Venezuela) between April 1, 2015 and March 31, 2016, 1474 cases of GBS were reported among 164,237 confirmed or suspected ZIKV infections.[46] Data were analyzed on ZIKV and GBS incidence, and a strong association between GBS incidence was found with 2.0 to 9.8 times higher incidence compared with pre-ZIKA time periods.[46] Across Colombia, approximately 90 GBS cases were documented per month during the peak of ZIKV outbreak, an increase from the mean 20 cases per month from 2009 to 2015.[47] In Puerto Rico, it was predicted that the annual incidence of GBS would be 3.2 to 5.1 times the baseline incidence in 2016 and that long-term care needs would be 3 to 5 times those of the years before ZIKV circulation.[48] Between January 1 and July 31, 2016, 56 suspected GBS cases were identified in Puerto Rico and 34 (61%) had evidence of ZIKV or flavivirus infection (10 confirmed, 16 presumptive ZIKV, 8 presumptive flavivirus infection). All patients were hospitalized and treated with intravenous immunoglobulin.[49] The median age was 55 years; 20 (59%) of patients were women, and out of the 32 GBS patients whose charts were completely reviewed, the most common symptoms included hyporeflexia or areflexia (97%), leg weakness (97%), leg paresthesia (75%), arm weakness (75%), facial weakness (63%), arm numbness (59%), and dysphagia (59%).[49] Twenty-one patients (62%) required intensive care unit (ICU) care; 12 (35%) were required mechanical ventilation, and one succumbed to septic shock.[49]

Both acute inflammatory demyelinating polyneuropathy (AIDP) and AMAN subtypes have been identified in ZIKV-infected individuals, although AMAN has been identified less frequently.[43,47,50,51] Seventy-eight percent (36/46) of GBS patients in a Colombian cohort who received nerve-conduction and electromyography studies from January to March 2016 were found to have AIDP subtype.[47] Thirty-eight patients (56%) were men, and the median time from acute ZIKV symptom onset to GBS symptom onset was 7 days (IQR, 3–10).[47] Sixty-six patients (97%) experienced limb weakness, 56 (82%) presented with ascending paralysis, 52 (76%) experienced paresthesias, and 22 (32%) had facial palsy.[47] When investigating the severity of illness, 40 (59%) required ICU stays, 21 (31%) required mechanical ventilation, 21 (31%) had autonomic dysfunction, and 3 (4%) died of respiratory failure/sepsis.[47] In a separate case-control study in Barranquilla, Colombia during October 2015 to April 2016, 47 GBS cases were confirmed with a median age of 49 years (range, 10–83), and 25 (53%) were women.[52] Thirty-six (77%) had antecedent illness in the 2 months before the onset of neurologic symptoms with a median of 6 days (range, 0–55) from the time of antecedent illness onset to onset of neurologic symptoms.[52] Of the 13 patients who received electrodiagnostic testing, 10 (77%) were consistent with AIDP, 1 (8%) was consistent with AMAN, and 2 (15%) were undefined electrophysiologically.[52] Thirty-two (68%) received intensive care, 11 (23%) required mechanical ventilation, 32 (88%) were discharged home, and 2 (6%) died before discharge.[52] Across the larger studies investigating GBS cases in conjunction with ZIKV, approximately 63% of patients visited the ICU, about 30% were mechanically ventilated, and the mortality rate was about 5%.[47,49,52] In contrast to the case-control study in French Polynesia, but consistent with studies in Colombia, AIDP was found in the 5 GBS patients who underwent electrophysiological testing.[49] Although AMAN has been identified less frequently, a descriptive case series in Cúcuta, Colombia of 19 GBS patients admitted to various ICUs from December 2015 to March 2016 revealed that all patients had AMAN subtype and the median time to neurologic findings following the first viral symptoms was 10 days (IQR, 5–12; range, 2–60).[53]

Complementing the French Polynesian case-control study is a study performed in Salvador, Brazil during 2015 that found a strong correlation between GBS and an

acute exanthematous illness outbreak (AEI) with ZIKV noted as the likeliest underlying cause.[54] Of 17,503 AEI cases, 51 patients were hospitalized with GBS or GBS variants (eg, Miller Fisher syndrome), yielding approximately 1.74 hospitalized GBS cases per 100,000 people during 2015.[54] The peak incidence of GBS occurred 5 to 9 weeks after the peak AEI incidence, which is longer than in other studies.[43,54] Other variants of GBS have been described, including a 35-year-old man in Haiti who presented with the GBS variant facial diplegia with acral paresthesias and later developed the features of Miller Fisher syndrome.[55] Although the patient's ataxia improved, he still required the use of a cane 3 weeks after discharge, and there was only minimal improvement of his bilateral facial weakness.[55] As of March 10, 2017, the latest situation report published by the WHO, 23 countries/territories reported GBS potentially associated with ZIKV infection.[5]

Urine studies for ZIKV may be particularly helpful in detecting ZIKV-associated GBS cases. In a case report in January 2016 from Martinique, urine PCR was used to definitively diagnosis GBS associated ZIKV.[56] Although all RT-PCR tests performed on plasma and cerebrospinal fluid (CSF) were negative for ZIKV, the first patient had a positive ZIKV in urine via RT-PCR 15 days after the onset of neurologic symptom onset, whereas ZIKV was detected in the urine of the second patient via RT-PCR on days 5, 15, and 21 after the development of neurologic symptoms.[56] Similarly, in a study performed in Colombia, of the 17/68 (25%) patients who tested positive for ZIKV, most of the positive results were detected in urine samples (16), whereas there were also 3 positive CSF samples and 1 positive serum sample.[47]

In addition to GBS and its variants, other neurologic manifestations associated with ZIKV infections have been identified, including myelitis, encephalitis, meningoencephalitis, acute disseminated encephalomyelitis (ADEM), sensory polyneuropathy, and optic neuropathy.[9,57–59] ZIKV-associated encephalitis cases have been reported with a neurologic onset varying from 1 to 8 days.[40] In addition, 3 adult cases of ZIKV-associated ADEM and 9 ZIKV-associated myelitis cases have been reported.[40] Various case reports have revealed a range of neurologic manifestations, including an 81-year-old with meningoencephalitis, a 15-year-old from Guadeloupe with acute myelitis, one young adult and one elderly individual who suffered from encephalopathy, an adolescent who suffered cognitive impairment and neuropsychiatric symptoms following ZIKV infection, and an 18-year-old with encephalomyelitis.[60–63] In a recently published single-center observational study in Brazil, ZIKV infection was associated with an increase in the incidence of a diverse spectrum of serious neurologic syndromes. Of the 35 patients (88%) who had molecular and/or serologic evidence of recent ZIKV infection in the serum and/or CSF, 27 had GBS (18 demyelinating, 8 axonal, and 1 Miller Fisher syndrome), 5 had encephalitis (3 with concomitant acute neuromuscular disease), 2 had transverse myelitis, and 1 had chronic inflammatory demyelinating polyneuropathy.

Congenital Zika Syndrome

CZS results from vertical transmission of ZIKV from an infected woman to the fetus during pregnancy. According to the CDC, CZS is categorized by 5 features (**Box 1**), and neuroimaging examples of severe CZS can be found in **Fig. 1**.[64] Other abnormalities of CZS reported by the CDC are displayed in **Box 2**.[64] Children who are impacted by CZS may experience severe neurodevelopmental delay, epilepsy, blindness, hearing loss, and hypotonia.[8,65]

An increase in reported microcephaly cases in Brazil during October 2015 initially raised concern of a potential link between maternal ZIKV and congenital ZIKV.[8] Subsequently, scientific evidence has linked ZIKV with microcephaly (see the section

Box 1
Congenital Zika syndrome (Centers for Disease Control and Prevention)

Five features of congenital Zika syndrome

1. Severe microcephaly in which the skull has partially collapsed
2. Decreased brain tissue with a specific pattern of brain damage, including subcortical calcifications
3. Damage to the back of the eye, including macular scarring and focal pigmentary retinal mottling
4. Congenital contractures, such as clubfoot or arthrogryposis
5. Hypertonia restricting body movement soon after birth

From Congenital Zika syndrome & other birth defects. 2017. Available at: https://www.cdc.gov/zika/hc-providers/infants-children/zika-syndrome-birth-defects.html. Accessed November 10, 2017.

"Neuropathogenesis"). Twenty-seven countries/territories in the Americas have reported confirmed cases of CZS since 2015.[6] A large case series of 602 ZIKV cases in Brazil between November 19, 2015 and February 27, 2016 and of 899 newborns without suspicion of ZIKV found that the ZIKV cases had smaller head circumference and higher first-week mortality.[66] A postmortem case series of 7 RT-PCR–confirmed cases in neonates from Ceará, Brazil reported that all had microcephaly, ventriculomegaly, dystrophic calcifications, and severe cortical neuronal depletion; 6 additionally had arthrogryposis.[67] Importantly, some CZS cases have presented with normal head circumference, which indicates that additional screening measures for CZS are necessary because microcephaly alone is insufficient to detect all affected newborns.[8,68–70] For example, in a retrospective Brazilian study of 13 neonates with laboratory-confirmed ZIKV, all were born without microcephaly, although later neuroimaging revealed brain abnormalities, including decreased brain volume, ventriculomegaly, subcortical calcifications, and cortical malformations in all (**Fig. 2**).[71] Subsequently, slower rates of head growth occurring in 11 of the infants was confirmed as early as 5 months after birth and was accompanied by neurologic dysfunctions (ie, hypertonia, hemiparesis, dyskinesia/dystonia, dysphagia, epilepsy, persistence of primitive reflexes).[71] In addition, a recent report demonstrates how CZS can present with a spectrum of changes, including microcephaly at birth, postnatal microcephaly, or no microcephaly.[72] A retrospective analysis of 77 infants revealed that 19 (24.7%) had evidence of CZS, 16 (20.8%) had microcephaly, and 3 (3.9%) did not.[72] All 3 in the latter group were recognized as having brain impairment a few months after birth and were found to have asymmetric polymicrogyria, predominantly in the frontal lobes; calcifications restricted to the leukocortical region, mild ventricular enlargement, and delayed myelination.[72] Another study that supports the need for improved CZS detection measures was a review of major radiological studies in which the most common abnormalities among 66 fetuses with suspected or confirmed ZIKV were ventriculomegaly (n = 21, 33%), microcephaly (n = 15–17, 24%), and intracranial calcifications (n = 17, 27%).[66] Two novel abnormalities found on neonatal brain MRIs of infants with CZS include enhancement of multiple cranial nerves and chronic ischemic cerebral infarction.[73] A separate contemporaneous case report described a 10-month-old boy who presented with an acute ZIKV infection that was also associated with cerebral infarction.[74] Further investigation is needed to establish the link between ZIKV and strokes in infants. CZS has also recently been associated with hydrocephalus.[64,75–77] The initial report included 21 CZS cases with

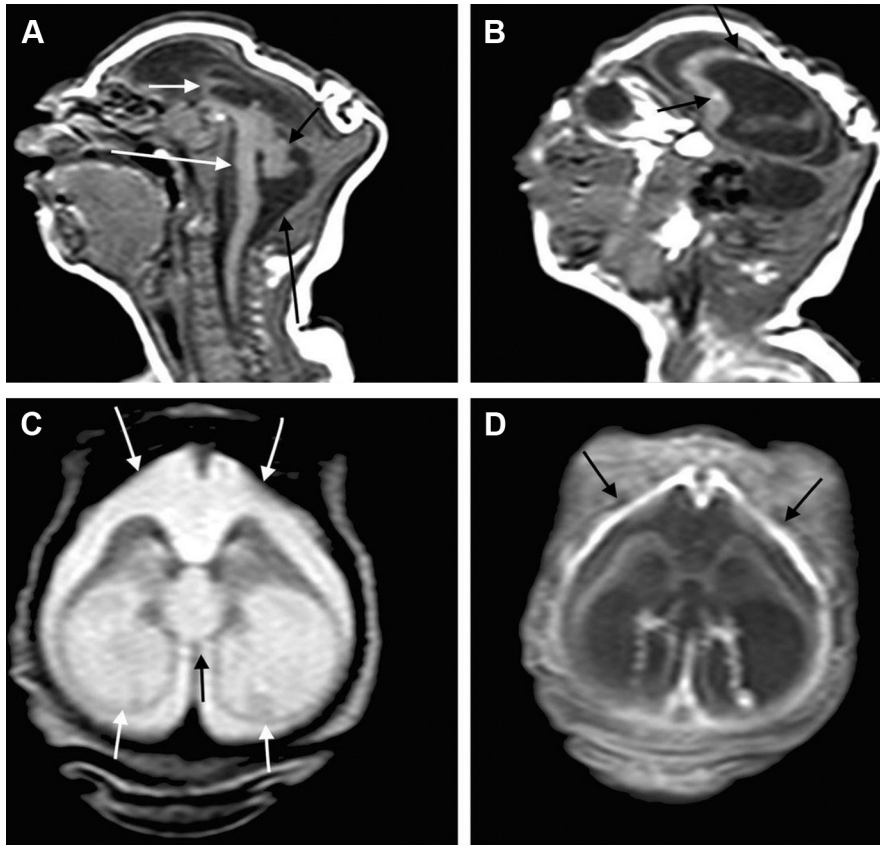

Fig. 1. Images of microcephaly associated with ZIKV infection. Severe microcephaly. Sagittal T1-weighted image (*A*) shows a profound craniofacial disproportion, noticeably hypogenetic corpus callosum (*short white arrow*), and brainstem (*long white arrow*) and cerebellum hypoplasia (*short black arrow*). In addition, the cisterna magna is enlarged (*long black arrow*). Observe the small dystrophic calcifications hyperintense on T1-weighted image (*B*) in the frontal lobe (*black arrows*) and extremely simplified gyral pattern. Axial T2-weighted image (*C*) shows severe ventriculomegaly, mainly at the posterior horn and ventricular atrium (*short white arrows*). Note the bulging walls of the ventricle, the upward dilated third ventricle (*black arrow*), and enlargement of the subarachnoid space (*long white arrows*). Axial T1-weighted image fat-suppression postcontrast (*D*) shows thickness and enhancement of frontal pachymeninges (*black arrows*). These last findings (*C*, *D*) may indicate a blockage in the CSF pathways and/or reduced absorption of CSF owing to impairment of the meninges or injury of arachnoid granulations. (*From* de Fatima Vasco Aragao M, van der Linden V, Brainer-Lima AM, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. BMJ 2016;353:i1901; with permission.)

ventricular enlargement between November 2015 and July 2017, 6 (28.6%) of which required ventriculoperitoneal shunting due to progressive ventricular enlargement complicated by seizures. Postoperative improvements were seen in all cases.[75]

Ocular and hearing abnormalities have also been associated with ZIKV (see **Box 2**). In a recent prospective case series from Cúcuta, Colombia and Maracaibo, Venezuela, of 43 infants evaluated in ophthalmology centers with presumed CZS all

Box 2
Other birth defects of congenital Zika syndrome (Centers for Disease Control and Prevention)

Other abnormalities associated with congenital Zika syndrome:
- Brain atrophy and asymmetry
- Abnormally formed or absent brain structures
- Hydrocephalus
- Neuronal migration disorders
- Excessive and redundant scalp skin

Reported neurologic findings
- Hyperreflexia
- Irritability
- Tremors
- Seizures
- Brainstem dysfunction
- Dysphagia

Reported eye abnormalities:
- Focal pigmentary mottling and chorioretinal atrophy in the macula
- Optic nerve hypoplasia
- Cupping
- Atrophy
- Other retinal lesions
- Iris colobomas
- Congenital glaucoma
- Microphthalmia
- Lens subluxation
- Cataracts
- Intraocular calcifications

From Congenital Zika syndrome & other birth defects. 2017. Available at: https://www.cdc.gov/zika/hc-providers/infants-children/zika-syndrome-birth-defects.html. Accessed November 10, 2017.

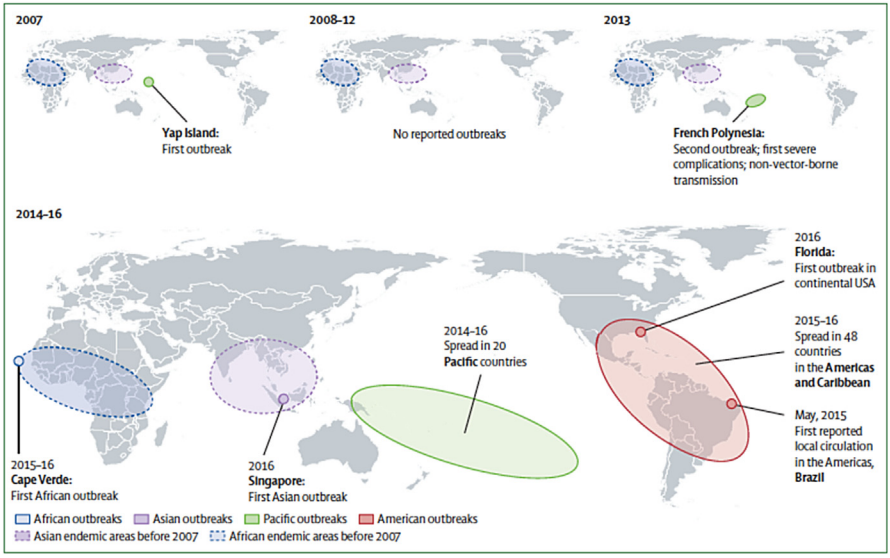

Fig. 2. ZIKV outbreaks 2007 to 2016. (*From* Baud D, Gubler DJ, Schaub B, et al. An update on Zika virus infection. Lancet 2017;390(10107):2101; with permission.)

infants presented with bilateral ocular findings, such as focal macular pigment mottling, lacunar maculopathy, chorioretinal scarring, congenital glaucoma, optic nerve hypoplasia, and other optic disc abnormalities.[78] Although glaucoma is a rare manifestation associated with CZS, the first report of ZIKV-associated glaucoma occurred in an infant 95 days after birth despite no detected signs of glaucoma in the ophthalmologic examination 3 days after birth.[79] In a case series that examined 29 infants with presumed ZIKV exposure in Salvador, Brazil, 10 children (34.5%) experienced ocular abnormalities, including focal pigment mottling of the retina and chorioretinal atrophy, optic nerve abnormalities, bilateral iris coloboma, and lens subluxation.[80] The mechanism behind the ocular abnormalities may be directly induced by ZIKV or may be secondary to cerebral manifestations of CZS (see "Neuropathogenesis").[80–82] A retrospective evaluation of 70 infants with microcephaly and laboratory evidence of ZIKV revealed 5 (7%) with sensorineural hearing loss (3 bilateral, 2 unilateral), although when eliminating an infant who received amikacin before the hearing test, the percentage of ocular abnormalities was 6%.[83]

Between 2015 and December 2017 in the United States and its territories, there were 244 live-born infants with Zika-associated birth defects and 17 pregnancy losses with Zika-associated birth defects.[84] As of December 21, 2017, there were 3715 confirmed congenital ZIKV infections throughout the Americas, 79% (2952) of which were from Brazil.[85] The incidence of reported cases of microcephaly in Brazil dropped from 41.3/10,000 live births before July 2016 to 17.0/10,000 live births after July 2016.[86] Although evidence shows an increased risk of CZS during the first trimester of pregnancy, there remains a risk in the second and third trimesters. One study showed that the earlier a rash occurred during pregnancy, the smaller the mean head circumferences at birth, supporting the claim that there is an increased risk of CZS during the first trimester.[66] Similarly, the CDC reported that approximately 9/60 (15%, 95% confidence interval = 8%–26%) of confirmed ZIKV infections during the first trimester led to ZIKV-related birth defects.[87,88] In this same report, the incidence for other trimesters was not calculated due to small numbers.[88] A report in the US territories found that among pregnant women with confirmed ZIKV infection, 8% of fetuses and infants had evidence of CZS with exposure in the first trimester, 5% in the second trimester, and 4% in the third trimester.[89,90]

DIAGNOSTIC TESTING

RT-PCR is used to detect ZIKV RNA during acute ZIKV infections.[91–94] In specimens that are collected less than 14 days after symptom onset, the CDC recommends nucleic acid testing (NAT) on serum and urine (ie, RT-PCR or any test that detects genetic material of an infecting pathogen).[95] Urine specimens can be useful because reports have demonstrated a relatively long detection time. ZIKV RNA is detected in urine up to 39 days (approximately 6 weeks) after symptom onset, although it has been detected in a man as late as 91 days.[96,97] Because patients with ZIKV may present asymptomatically or with mild symptoms (ie, fever, maculopapular rash, arthralgia, or conjunctivitis), it is challenging to ensure diagnostic testing is conducted during the viremic time frame.[98,99] The median time between ZIKV onset and neurologic manifestations (ie, GBS) often misses the narrow window for ZIKV detection by PCR, complicating the diagnosis further. Therefore, although a positive RT-PCR indicates an acute infection, a negative result does not eliminate the possibility of a ZIKV exposure.[8,91] In specimens that are collected $\geq$14 days after symptom onset or in specimens that are negative by RT-PCR, the CDC recommends ZIKV immunoglobulin M (IgM) serology testing followed by a plaque reduction neutralization test (PRNT) if

the IgM result is nonnegative (ie, positive, equivocal, presumptive positive, or possible positive).[95] ZIKV PRNT ≥10 and DENV PRNT <10 indicate a ZIKV infection but do not distinguish between an active or a prior infection.[95] Although PRNT is highly specific, the test is only performed by a limited number of laboratories across the world because it is expensive, labor intensive, and requires materials not widely accessible to all areas impacted by ZIKV and other flaviviruses.[8,92]

In addition to serum and urine, ZIKV RNA has been detected in other bodily fluids, including whole blood, saliva, semen, vaginal secretions, breast milk, and CSF.[40] ZIKV RNA has been detected in whole blood longer than in serum.[8] ZIKV RNA has been detected in semen up to 188 days after onset of symptoms, although it is still unclear how long one may be infectious.[100] Viral shedding of ZIKV RNA has been detected for up to 14 days in vaginal secretions.[101] In addition, CSF can be used to test for ZIKV IgM.[102]

For pregnant women with a possible exposure to ZIKV and who present with ZIKV symptoms, ZIKV NAT on serum and urine should be performed in addition to ZIKV IgM serology.[102,103] Because ZIKV IgM antibodies can persist past 12 weeks after infection, these results alone are unable to distinguish between an infection that occurred before or during pregnancy.[104] For detailed information about test interpretations, visit https://www.cdc.gov/zika/pdfs/testing_algorithm.pdf.[103]

A major challenge associated with the current diagnostic techniques includes the high cross-reactivity with other flaviviruses due to structural and genetic similarities, including DENV and CHIKV, as well as coinfections in individuals given that many flaviviruses circulate simultaneously throughout various geographic locations.[92,99] DENV and ZIKV, in particular, share many amino acid sequence similarities in the main targets for antibody responses, including the envelope, premembrane proteins, and the nonstructural protein NS1, which makes interpretation of antibody-based testing challenging.[94]

For pregnant women who have evidence of a possible ZIKV infection, prenatal ultrasound is recommended every 3 to 4 weeks to evaluate fetal anatomy.[104] Although ZIKV has also been detected in amniotic fluid using ultrasound-guided transabdominal amniocentesis, the data on its utility and optimal performance time are limited and should be considered on a case-by-case basis.[105] The sensitivity and specificity of RNA testing of amniotic fluid are not currently established at this time, and it is unclear whether infants who test positive for congenital ZIKV via amniotic fluid will present with abnormalities at or after birth.[106] A negative ZIKV RNA result from amniotic fluid does not eliminate the possibility of congenital ZIKV because research has suggested that the detectable viremic time period may be transient.[107]

The complications caused by past exposures, asymptomatic or mild symptom presentation, cross-reactivity between flaviviruses, transient viremic time period in various biological samples, uncertainties involved in prenatal testing and monitoring, and limited resources in various geographic settings make ZIKV diagnosis challenging. Future research is needed to help address those challenges.

NEUROPATHOGENESIS

Viral Lineages and Neurovirulence

Phylogenetic studies have revealed that there are 2 ZIKV lineages, African and Asian, and that the latter was responsible for the 2007 and 2013 Pacific Islands outbreaks as well as the most recent outbreak throughout the Americas.[2,108,109] ZIKV analyzed from the Yap Island provided phylogenetic evidence that the Yap Island outbreak originated in Southeast Asia.[32] Between the African and epidemic Asian strains of ZIKV, most

genetic changes were observed in the NS5 proteins (involved in blockade of type 1 interferon signaling and formation of replication complex of flavivirus genome), NS4, and E (envelope).[41] Nonstructural proteins NS1, NS2B, and NS4A have been identified to contribute to virulence via immune evasion effects.[41] E protein glycosylation at Arg-154 is also seen in epidemic Asian strains but not the African wild type, and it may be involved in assembly and infectivity of flaviviruses.[41]

Debate remains about whether newer strains have evolved to cause neurotropic infections. It is unclear whether the African ZIKV is as capable of the Asian lineage in causing severe neurologic complications in fetuses, neonates, and adults.[8,110] Some research suggests that more neurovirulent strains of ZIKV have evolved via new mutations, while a recent report using organotypic brain slice cultures generated from embryonic mice of various ages reports that all lineages of ZIKV appear to be neurotropic and that even the older strains from 1947 can affect developing brains.[41,111]

A recent study found evidence of antibody-dependent enhancement (ADE) in mice that had antibodies from a previous DENV or WNV infection and experienced more severe manifestations of ZIKV.[112,113] Mice that had been injected with DENV or WNV-convalescent plasma experienced increased morbidity (ie, fever and viral loads in the spinal cord and testes), increased ZIKV antibodies in their testes and spinal cords, and increased mortality compared with controls. Those findings support the hypothesis that ADE may have contributed to the severity of the most recent ZIKV outbreak due to geographic cocirculation of other flaviviruses, including DENV.[113] However, some researchers have expressed concern that the findings of this may not mimic human pathogenesis.[112]

Pathogenesis of Congenital ZIKV Syndrome

Various studies provide evidence that ZIKV disrupts proliferation and migration of neural progenitor cells (NPCs).[110,114–116] The consequent cell death of NPCs prematurely arrests the development of the fetal brain. Studies have shown that ZIKV crosses the placental barrier to infect the developing fetus.[110] One study revealed that when human NPCs and neuronal cells were infected with the Brazilian strain of ZIKV ($ZIKV^{BR}$), there were more viral copies in NPCs and neuronal cells compared with the wild-type African strain ($ZIKV^{AF}$).[114] Both $ZIKV^{BR}$- and $ZIKV^{AF}$-infected NPC cultures showed signs of cell death after 96 hours postinfection.[114] In addition, offspring of pregnant SJL mice (a strain that is immunocompetent but more susceptible to viral infections and has known immune irregularities) infected with $ZIKV^{BR}$ had cortical malformations and thinner cortical layers, analogous to findings of microcephaly in humans.[114] The brain tissue from those offspring also had evidence of viral RNA and neuronal cell death. Further PCR analysis reveals that in those affected offspring, genes related to autophagy and apoptosis were upregulated.[114] In another study consisting of 5 postmortem evaluations of fetal and neonatal cases of CZS, all mothers had symptoms of fever and rash in the first trimester and ZIKV was confirmed in the central nervous system tissue of offspring.[115] On autopsy, histopathological changes were seen in brain and placental tissue but not in other organs. On gross examination of the brain, there were malformations including lissencephaly, alobar holoprosencephaly, and cerebellar hypoplasia.[115] ZIKV antigen was isolated in the placenta, specifically in the chorionic villi.[115] One study demonstrates that ZIKV RNA binds to Musashi-I (MSI1), a translational regulator protein found in neural precursors, retina, and testis that is required for neurodevelopment. This prevents interaction between MSI1 and its target RNAs *MCHP1* and *NUMB*, thereby resulting in defective migration and cell-cycle disruption in the NPCs.[116]

Pathogenesis of Guillain-Barré Syndrome

Hypotheses on the pathogenesis of ZIKV-associated GBS include direct neuropathogenic mechanisms, a hyperacute immune response, immune dysregulation, and molecular mimicry against neural antigens.[8,117] Given the short time period between ZIKV symptoms and GBS onset found in several studies, it is likely that a parainfectious process involving immune-mediated inflammation of neural tissue is involved.[41,51] Molecular mimicry in which infectious molecules resemble membrane molecules in neural tissue as seen in other cases of GBS triggered by infections such as *Campylobacter jejuni* likely also play a pathogenic role in ZIKV-associated GBS.[41] This "mistaken immune attack" may arise because the surface of ZIKV contains polysaccharides that resemble glycoconjugates of the human nerve tissues. There is dual recognition, by a single B- or T-cell receptor, of a microbe's structure and an antigen of the host. ADE of ZIKV infection may also play a role given an observation that patients who developed GBS had higher titers of cross-reacting IgM or IgG antibodies to flavivirus antigens, including DENV infection, although this is confounded by the high degree of cross-reactivity seen in antibody-based testing for flaviviruses.[41]

Prevention, Treatment, and Vaccine Development

Prevention measures

The key measure to interrupt the transmission of ZIKV is through control of the *Aedes* mosquito vector density through mechanisms including proper cleaning and maintenance of water supplies and storage systems, adequate solid waste management systems, and alterations in human behavior and residence systems (**Table 1**).[118] Another vector control strategy is to genetically modify mosquitoes, giving rise to the population of mosquitoes whose offspring are not able to survive.[119] Another strategy that

Table 1
Prevention recommendation

Strategy	Action
Control vector design	• Diligent management and control of environmental factors • Eliminate or reduce vector breeding sites in common areas • Conduct mass sanitation campaigns to educate the public • Ensure mosquitoes are removed within the predetermined radius of critical places like schools, hospitals, transport terminals, using risk stratification paradigms • In areas with viral activity, use mosquito adulticidal sprays to interrupt ZIKA transmission • Ensure proper monitoring and follow-up during integrated actions for vector control
Preventative measure	Individual protection • Encourage individuals to use bed nets • Appropriate clothing to cover exposed skin • Use repellents Household/residential protection • Encourage installation and use of wire-mesh screens on doors and windows • Once per week emptying, cleaning, turning over, and disposal of containers that can hold water inside or outside the houses to reduce any mosquito breeding sites

From Sikka V, Chattu V, Popli R, et al. The emergence of ZIKA as a global health security threat: a review and a consensus statement of the INDUSEM Joint Working Group. J Glob Infect Dis 2016;8:3; with permission.

has been shown to reduce the mosquito-to-human transmission events, particularly with DENV, involves the introduction of *Wolbachia* bacteria into the mosquito population, reducing the transmission of virus to humans from mosquito.[120] Because of the unique traits of *Wolbachia* that cause cytoplasmic incompatibility, the bacteria are useful as a promoter of genetic drive within a population. *Wolbachia*-infected females are able to produce offspring with uninfected and infected males; however, uninfected females are only able to produce viable offspring with uninfected males. Thus, infected females have a frequency-dependent reproductive advantage.

With regards to personal protection, individuals should avoid contact with mosquitoes in areas endemic for ZIKV (see **Table 1**). Individuals living in and traveling to ZIKV-affected regions should refer to the CDC Web site for further guidance on prevention measures (https://www.cdc.gov/zika/prevention/protect-yourself-and-others.html). It is important to advise those living in endemic regions and travelers to ZIKV-affected areas to practice safe sex or abstinence for at least 6 months from exposure and to not donate blood for at least 1 month after returning to reduce the risk of potential transmission.[121] In addition, pregnant women with potential risk of exposure to ZIKV should have fetuses evaluated and monitored closely for CZS. For further information, it is recommended that travelers and pregnant women visit the following CDC Web site for the most up-to-date recommendations: https://www.cdc.gov/zika/pregnancy/protect-yourself.html.[122–124]

Treatment

ZIKV disease is usually mild and requires no specific treatment. People sick with acute ZIKV infection should remain adequately hydrated and treat pain and fever with acetaminophen.[8,125] By use of large screening strategies, several compounds have been found to have in vitro activity against ZIKV, but there are no antiviral drugs that have shown activity against the virus in vivo.[8] Management recommendations for GBS and myelitis as a result of ZIKV include immunomodulatory therapy and supportive care, as per guidelines for management of these respective syndromes triggered by other causes.[126] Long-term management of CZS requires a comprehensive combination of supportive services throughout early development. Early childhood stimulation and rehabilitation programs coupled with psychosocial support are imperative for optimal outcomes. For further guidance on the management ZIKV neurologic complications, including CZS, refer to the WHO Zika Toolkit (http://www.who.int/mental_health/neurology/zika_toolkit/en/).[126]

Vaccine development

A safe, effective, and rapidly scalable vaccine against ZIKV is needed. A recent study describes a purified formalin-inactivated Zika virus vaccine candidate that showed protection in mice and nonhuman primates against viremia after ZIKV infection.[127] Although there are more than 40 vaccine candidates in the pipeline, a vaccine will likely not be available for at least 2 years. It is also not known if ZIKV infections lead to lifelong immunity, although the significant decline in cases over the last several months suggests that herd immunity exists in endemic regions.

SUMMARY

Although most cases of ZIKV are mild or not detected, rare severe neurologic effects have been identified, including but not limited to GBS and CZS. Over the last year, scientific evidence has established a causal link between ZIKV and neurologic manifestations, including congenital birth defects. Diagnostic and treatment challenges remain due to cross-reactivity between flaviviruses, the transient viremic time

period, uncertainties involved in prenatal testing and monitoring, and limited resources for supportive care in various geographic settings. Longitudinal studies are needed to evaluate the long-term effects of ZIKV infection, including the long-term risks in infants exposed to ZIKV in utero. Whether alterations of the Asian strain have led to increased neurovirulence remains under debate. Although herd immunity is suspected, it is unknown at this time whether ZIKV infections lead to lifelong immunity. Thus, prevention efforts, including reduction in mosquito vector transmission and sexual transmission, are required as well as ongoing international efforts for vaccine development.

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