



REVIEW ARTICLE

The Zika virus: Lurking behind the COVID-19 pandemic?

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Abstract

What is known and objective: The sudden and extensive outbreak of coronavirus (SARS-CoV-2) has overshadowed another developing viral threat: the Zika flavivirus. Of particular concern is that pregnant women can pass Zika virus to the foetus, and there is a strong implication of an association between Zika virus infection and foetal microcephaly. Currently, there is no vaccine, and there is no cure.

Methods: Published literature and Internet sources were searched for information related to Zika virus, its transmission, its clinical presentation and sequelae, prevention and implications (practice and regulatory) for healthcare providers. The identified English sources were reviewed, assessed and synthesized. Emphasis was placed on providing an overview of the problem, and identification of unmet needs and future directions.

Results and discussion: Zika virus poses a major challenge for healthcare providers, particularly in areas unaccustomed to it, since it is transmitted to humans by the vector *Aedes aegypti* mosquito. The outbreak impacts every healthcare provider, because every provider is required to report cases of Zika infection to their state or local health agencies—whether the infection is confirmed or merely suspected. Since the virus has become a worldwide crisis, healthcare providers will need to work across national boundaries and medical disciplines in order to educate patients about Zika symptoms and the mosquito vector. Until further information is known, infected patients (male and female) are being advised to avoid conceiving a child.

What is new and Conclusion: Until a vaccine is developed or effective treatment for Zika virus is discovered, healthcare providers must be AVP (aware, vigilant and proactive) in order to lessen the spread and impact of the implicated devastating birth defects (microcephaly) and other neurological disorders (eg Guillain-Barré Syndrome) of this infection. Unfortunately, many knowledge gaps exist. There is an urgent need for a reliable, inexpensive diagnostic test, an effective treatment and an approved and readily available vaccine.

Until a vaccine is developed or effective treatment for Zika virus is discovered, healthcare providers must be proactive to lessen its spread and impact of implicated birth defects (eg, microcephaly) and other neurological disorders (eg, Guillain-Barré

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Syndrome). Unfortunately, knowledge gaps exist. There is urgent need for a reliable, inexpensive diagnostic test, effective treatment and readily available vaccine.

KEYWORDS

Aedes aegypti, Guillain-Barré syndrome, microcephaly, vaccine, Zika virus

1 | WHAT IS KNOWN AND OBJECTIVE

Zika is a single-stranded ribonucleic acid (RNA) flavivirus transmitted to humans primarily by *Aedes aegypti* mosquitoes and sexual contact with infected individuals.¹ Its name derives from the Zika Forest in Uganda, where the virus was first identified in 1947 in a febrile Rhesus monkey.² The first human cases were described in 1952 in Uganda and Tanzania with sporadic case reports since then from Africa and Asia, including a 2007 outbreak on Yap Island in Micronesia.³ From its discovery to the first outbreak in 2007, just 13 naturally acquired cases of Zika infection were reported, all with mild symptoms.⁴ The first large outbreak occurred in 2007 in Micronesia, followed by outbreaks in Polynesia and New Caledonia in 2013 and 2014, respectively. Since 2015, Zika has been spreading with alarming rapidity; with outbreaks reported in 87 countries.^{2,5,6} Some cases in the Americas, including Easter Island, Chile and Mexico, involve autochthonous (person-to-person rather than mosquito-person) circulation of the Zika virus.⁵ By 2015, there were an estimated 1.3 million cases of Zika infection.^{7,8} Rapid globalization facilitates the spread of this and other viruses⁹ (for example, it is speculated that the Zika virus entered Brazil in 2014 during the World Cup games).¹⁰

In October 2015, Brazil declared a national public health emergency owing to a sharp increase in the number of children born with microcephaly in the area of Pernambuco, with the suspicion that it was prenatal exposure to Zika virus that was the culprit.² Monitoring for microcephaly began on 22 October 2015 and from then until 20 January 2016, a total of 3893 suspected cases were documented, of which 512 were clinically investigated and 230 resulted in confirmation of the diagnosis. Zika virus RNA was present in the amniotic fluid of two foetuses with microcephaly on prenatal ultrasound and in the placenta of a woman who had a Zika infection and terminated her pregnancy. The Zika virus was also found by reverse transcription-polymerase chain reaction (RT-PCR) and by immunohistochemistry in four cases of congenital malformation in two miscarriages and two full-term neonates who died shortly after delivery.²

The Zika virus poses a huge public health threat. For example, in the United States,^{11,12} where the most vulnerable to the mosquito-borne illness will likely be Gulf Coast states such as Florida and Texas, the White House asked for extensive funding to fight the Zika virus.^{13,14}

2 | METHODS

A search was conducted of published literature using Internet sites such as PubMed, MEDLINE and other sources. Search terms were

selected to identify basic science and clinical information about the spread, pathology, treatment and prevention of Zika virus, and efforts to ameliorate suffering by preventing its spread. Studies published in the English language (or translations where available) were included. Additional sources were obtained from references within the primary sources. Only peer-reviewed publications were included and integrated into the review.

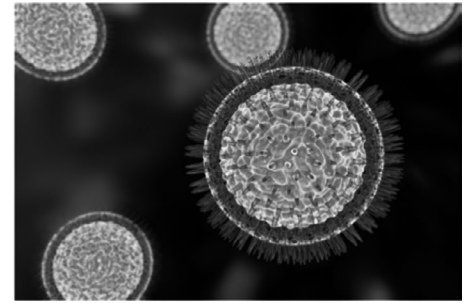
3 | RESULTS AND DISCUSSION

3.1 | The Zika virus

The Zika virus belongs to the family *Flaviviridae* and genus *Flavivirus*. Flaviviruses are a type of arbovirus, a large group encompassing RNA-viruses which often rely on arthropod vectors such as mosquitoes or ticks for transmission. Other arboviruses include dengue, yellow fever, West Nile virus, Japanese encephalitis virus and chikungunya. The Zika virus is enveloped and icosahedral (consisting of identical subunits that make up equilateral triangles arranged symmetrically) with a non-segmented, single-stranded, positive-sense RNA genome which can directly translate into viral proteins. Transmission of the Zika virus can occur by the bite of an infected female *Aedes aegypti* mosquito.⁷ (Figure 1) Historically, the *Aedes aegypti* mosquito was the vector for the transmission of yellow fever, which is much less of a threat today owing to effective vaccines.¹⁵ In the case of Zika, the virus replicates in the mosquito's epithelial cells and then its salivary glands. About five to 10 days after it infects a mosquito, the Zika virus is detectable in that mosquito's saliva and can be transmitted to humans. If the mosquito's saliva can be inoculated into human skin, the virus infects epidermal keratinocytes, skin fibroblasts and the Langerhans cells. The pathogenesis of the Zika virus in humans remains to be elucidated, but it is thought to spread next to the lymph nodes and then into systemic circulation.¹⁶ It is not clear if and how other means of transmission can occur, but it appears that the virus can be transferred by mother to foetus, by sexual contact with an infected man, and by blood transfusion.¹⁷⁻¹⁹

When humans encroach on the natural habitat of other species, the result is either extinction of the invaded species or commensalism, that is, the invaded species continues to breed in a human-dominated environment. In the case of the *Aedes aegypti* mosquito, which requires a vertebrate source of blood, the mosquito develops a preference for the most readily available source of that blood, namely humans.^{15,20} Humans occupy the largest range of terrestrial habitations and when a species, such as *Aedes aegypti* evolves abilities

FIGURE 1 The female *Aedes aegypti* mosquito (left), active in the daylight hours, is the vector for the Zika virus (right). Images purchased from iStock



to survive together with humans, their territories may expand with human mobility.¹⁵

3.2 | Clinical presentation

Deceptively, the majority of people infected with Zika virus will not develop serious clinical symptoms.^{3,21,22} The incubation period is currently thought to be about three to 12 days, and the illness itself lasts about 2–7 days.²³ The main symptoms are an eruptive skin rash (exanthema) (90% of patients), arthralgia (65%), nonpurulent conjunctivitis (55%) and headache.³ The exanthem may be morbilliform or be comprised of tiny papules, and it tends to descend, that is, start on the upper portion of the body and move down as the illness progresses.²⁴ If fever is present, it is low. Diffuse symptoms, such as retro-orbital pain, abdominal pain, nausea, vomiting, diarrhoea and constipation, may occur. However, as is often the case with outbreaks of illness at different locations, a somewhat different constellation of symptoms may appear in various locations. From November 2015 to February 2016, 93 cases of Zika virus infection were evaluated by the Epidemiological Surveillance System for Zika Virus in Mexico and the main clinical symptoms reported in these cases were fever (97%), rash (93%), nonpurulent conjunctivitis (89%), headache (85%) and myalgia (84%), with no deaths reported.⁵

There are a few case reports in the literature describing the presentation of Zika infection. A male patient returning from a vacation in Puerto Rico experienced headache and lethargy, and the next day noticed erythematous eruptions on his hands and arms.²⁴ Within 24 h, the eruptions became more prominent and spread to his trunk but he never experienced pruritus. His eyes were red, and on the third day he had skin eruptions on his knees and feet along with burning pain in his feet. Joint pain of the wrists, knees and ankles was noted on the fourth day, and these symptoms continued until they resolved spontaneously on the eighth day. He did not have fever, cough, sore throat or any gastrointestinal symptoms. Tiny pink and red erythematous papules were noted on his head, neck, trunk and extremities along with petechiae on the hard palate. Lymph nodes were not palpable.

In a study of pregnant women infected by the Zika virus reported as a case series in Brazil, the most frequently reported symptoms were rash (72%), fever (45%), arthralgia (38%), headache (17%) and

pruritus (14%).²⁵ However, this is a case series and these statistical findings cannot be extended to all populations.

3.3 | Diagnosis of Zika virus infection

Zika virus infection can result in a clinical syndrome that produces no symptoms, diffuse symptoms or symptoms similar to those of dengue or chikungunya viruses. For that reason, diagnoses must rely on more than clinical criteria.⁹ The presence of the above-described symptoms (rash, low fever, joint pain and headache) should be considered, as well as historical factors, such as recent travel to an affected area.²² Other similar diseases, such as malaria, chikungunya and dengue fever should be ruled out.

The Zika virus can be definitively diagnosed by RT-PCR tests on the blood or other body fluids (urine, saliva), a test that is rapid to administer, highly specific,²⁶ but with low sensitivity. Nucleic acid amplification assays may have low sensitivity with blood samples because the viremia period (time from the point at which the virus enters the blood stream until it is present at the first site of infection, before spreading to other tissues) is only about 1–5 days after onset of symptoms.⁹ Thus, Zika virus RNA is difficult if not impossible to detect in the serum after the first week of illness.²⁶ Virus-specific IgM and neutralizing antibodies develop towards the end of the first week of the illness. The best results are obtained when the test is administered early in the acute phase of the illness. Serum antibody testing may be challenged by cross-reactivity with other arboviruses, such as dengue.²⁷ The US Food and Drug Administration (FDA) has authorized the emergency use of RT-PCR kits to be used to detect the Zika virus in the blood.²⁸

Diagnoses based on molecular biology may result in a high rate of false-negatives because the Zika virus genome is made of RNA which is extremely fragile. It is possible, but in many cases cost prohibitive, to isolate the Zika virus in cell cultures such as Vero cells and identify them by indirect immunofluorescence.²⁹

Urine testing may be more reliable for Zika virus infections than blood tests. For example, the Florida Department of Health, Bureau of Public Health Laboratories, tested specimens from 913 persons who met criteria for Zika virus testing and of these, 91 had confirmed or probable Zika virus infection; all cases were related to travel. Investigators then tested the Zika patients using different test modalities on different days to assess the most sensitive, specific

and efficient testing algorithm. Over 90% of those with an RT-PCR confirmed Zika diagnosis tested positive with urine tests but results were much lower with blood and saliva testing.³⁰ New point-of-care diagnostic assays are being developed for commercialization.³¹ Ideally, these tests should be easy to administer, cost-effective and provide highly specific and highly sensitive test results.

3.4 | Treatment

At present, *there are no vaccines and no antiviral agents to treat the Zika virus.*³² Zika infection is usually relatively mild, self-limiting and rarely fatal. Symptoms may persist for a few days to a week. Many people infected by the Zika virus do not seek medical treatment and may not even be aware that they have the disease since they may be asymptomatic or have only mild or diffuse symptoms. Although the Zika infection presents in similar fashion as dengue fever, in general Zika infections are milder than dengue infections.

When patients present with symptoms (*viz.*, rash, arthralgia, fever, nausea, headache), treatment focuses on relieving pain, reducing fever (if present) and addressing other symptoms such as administering antihistamines to treat pruritus. Nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates (aspirin) should not be used because of an increased risk of haemorrhagic syndrome.²¹ Pregnant women who test positive for Zika infection should receive high-risk prenatal care with serial foetal ultrasound monitoring every 3–4 weeks to monitor foetal anatomy and growth.³³

3.5 | Microcephaly

Zika virus can induce autophagy in infected neural cells. Murine studies suggest that the virus may increase apoptosis, improper

neural stem cell orientation and premature neuronal differentiation, and decrease progenitor cells, which, in turn, reduces grey matter and thus brain size and thereby leads to microcephaly (Figure 2).^{34,35} Microcephaly, a birth defect associated with abnormal brain development and manifesting as a head of small circumference, is associated with neurological problems such as hypertonia, spasticity, hyperreflexia and seizures.³⁶

The Zika virus has been found in foetal brain tissue.⁸ The first association between the virus and microcephaly was reported in Brazil in 2015.³⁷ More recent studies indicate significant cellular death of neural stem cells infected by the Zika virus, which supports the hypothesis that the Zika virus inhibits foetal brain development.³⁸ By 22 March 2016, the Brazilian Ministry of Health reported that it had been notified of 6671 cases of microcephaly, of which 4293 were being investigated with 907 already confirmed.³⁹

The Ministry of Health in Brazil investigated the number of cases of microcephaly and found that the previously reported rate of about 0.5 cases per every 10,000 live births had increased about 20-fold after the Zika outbreak.⁴⁰ The Pan American Health Organization reported viral genome identification using real-time RT-PCR in the amniotic fluid from two pregnant women who had prenatal ultrasound monitoring which determined that their foetuses had microcephaly.⁴⁰ A neonate with microcephaly who died shortly after birth was determined to have Zika virus RNA in brain tissue.⁴⁰ These events led to the Ministry of Health in Brazil, the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC) to attribute an association between Zika infection and microcephaly.⁴¹ However, definitive causality was not established—it is currently under intense study.^{42–44}

Using embryonic stem-cell-derived cerebral organoids to recapitulate first trimester foetal brain development, it was shown that

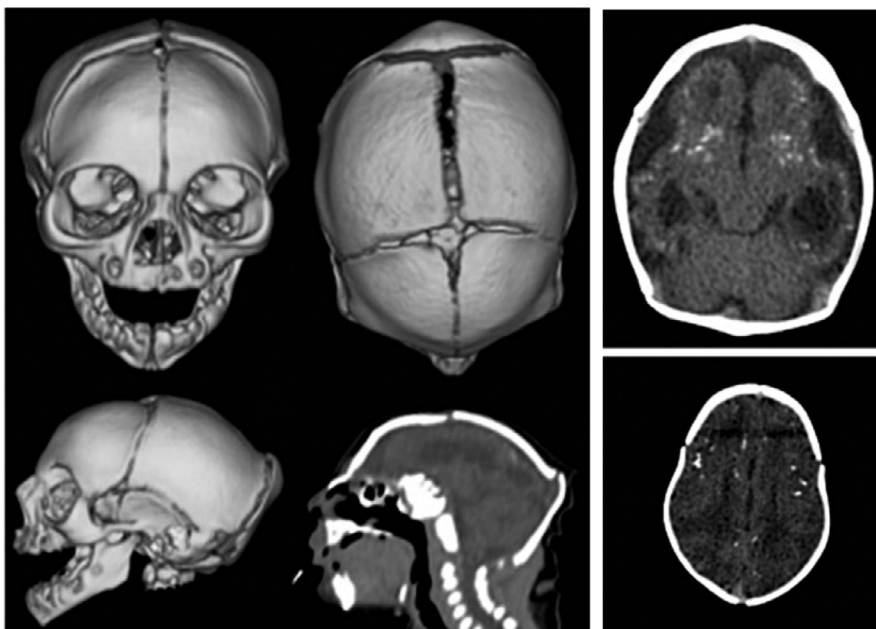


FIGURE 2 Congenital Zika syndrome. From Moreira and Richtmann (2019)⁷⁹ with permission

the Zika virus infects organoids, resulting in a decrease in overall organoid size. The innate immune receptor toll-like-receptor 3 (TLR3) is upregulated following Zika infection, and TLR3 inhibition reduces the phenotypic effects of Zika infection. It appears that the gene expression changes that occur during TLR3 activation involve over 40 genes associated with neuronal development, thus implicating disrupted neurogenesis.^{45,46} Evaluation using immune-cytochemistry and electron microscopy shows that the Zika virus targets human brain cells and reduces their viability and growth.⁴⁷

3.6 | Guillain-Barré syndrome

Increases in the number of cases of Guillain-Barré Syndrome (GBS) have been observed in some of the same places and at the same times as the Zika virus epidemics, suggesting a possible association.^{2,48} GBS is a neurological disease characterized by an acute autoimmune inflammatory demyelinating polyneuropathy that can result in flaccid paralysis.⁴⁹ Its global incidence is usually about 1 to 4 cases per 100,000 people,⁴⁹ but during the Zika epidemic in French Polynesia in 2013, the incidence increased 20-fold.⁵⁰ And it has been reported that significantly more GBS patients have serological evidence of prior Zika infection than controls (100% vs. 56%, $p < 0.0001$).⁵¹ But epidemiological studies in other parts of the world, such as in Mexico, do not support an increased incidence in GBS.⁵ Thus, a link between the Zika virus and GBS has been postulated, but not confirmed.⁵⁰

3.7 | Knowledge gaps

- Prior to the recent outbreaks, the infection due to Zika virus was known as an obscure, mild infection with only about a dozen reported cases worldwide. The recent outbreaks in Polynesia and now Brazil were sudden, unexpected and widespread, which raises troubling questions as to whether or not certain changes—such as virus mutation or improved vector competence—might be driving this new epidemic. There is much that is not yet known about the Zika virus: its basic reproduction number and attack rate, or whether infection confers long-term immunity. It appears to be associated with microcephaly, but what about other developmental abnormalities?
- Non-vector transmission of the Zika virus has been postulated, including perinatal transmission, sexual transmission and transmission via a blood transfusion.^{52,53} This may impact blood supplies in affected areas.⁵⁴
- It is also unclear why after decades of relative quiescence, Zika is now resulting in epidemics in far-flung locations.⁴² Certainly increased travel opportunities and globalization may play a part. Or the current virus may have evolved changes that allow for more rapid or efficient replication, or it is better able to counteract host

immune response (leading to greater virus production and more severe disease).⁵⁵

- Limited prior study of the Zika virus means that there is limited knowledge about its genetic diversity.⁴⁰ The US Army Medical Research Institute of Infectious Disease and the University of Texas Medical Branch have recently completed genome sequences of five Zika isolates.⁵⁶ Of these genomes, four belong to the African lineage (they were isolated in Senegal and Uganda) and one is Asian (isolated in Cambodia). Complete genomes have been sequenced from the blood of patients in the Philippines and Thailand.⁵⁷ There is little information about its genomic structure and genetic variations associated with the recent Zika virus outbreaks in the Americas. It is thought that the major viral proteins of the Zika virus likely share structural and functional features with other flaviviruses.⁵⁸ Phylogenetic analysis suggests that all of the Zika virus strains currently in circulation in the Americas form a unique clade within the Asian lineage of the Zika virus. Some conserved amino acid residues differentiate the Asian strains from the current American strains and each of these from the African strains.⁵⁸
- As in any global health crisis, there are problems of translation. Differences in culture, healthcare utilization patterns and even diagnostic criteria make it difficult to compare information from one country to another. The real number of persons infected and the extent of transmission into various countries cannot be fully known owing to incomplete surveillance data, undiagnosed cases and differences in reporting.²³ This is a factor needing improvement.
- Risk assessment is difficult with the Zika virus, in that it is not known how many people in an epidemic region will be infected and of those infected, how many will be symptomatic and/or how many will be pregnant women. It is not known how many pregnant women infected with the Zika virus will pass the infection along to the foetus and it is further unknown how many Zika-infected newborns will exhibit neurodevelopmental abnormalities. It is also unclear if Zika infection at a particular gestational age is more, or less, dangerous to the foetus than infection at other times. Thus, providers and public health experts may be underestimating or overestimating the public health threat.

3.8 | Readiness

In theory, the Zika virus can be transmitted wherever the mosquito vector exists. For example, in the United States, this encompasses a large area for seasonal transmission and a smaller area, around the Gulf Coast, for year-round transmission.⁵⁹ The Zika outbreaks thus far have placed great burdens on local populations that were unprepared to meet the threat. Urgently needed in such situations are reliable diagnostic methods (which is complicated by cross-reactivity with other types of flaviviruses, such as dengue), initiatives to limit the mosquito vectors, public health awareness campaigns to

increase prevention, a comprehensive action plan that consists of health promotion, reproductive health recommendations for antenatal control and epidemiological surveillance.⁵

Since Zika cannot be treated once it starts and since there are currently no vaccines to prevent infection, the best methods at our disposal involve aggressive prevention. This would include mosquito control, public awareness campaigns, limiting travel by pregnant women to locations where Zika is particularly prevalent and clinician education. Aggressive educational campaigns targeting pregnant women and women who could become pregnant are needed. *Aedes* mosquitoes³⁷ are present in many tropical and subtropical regions and are expanding their territory into more subtropical regions.⁶⁰ *Aedes aegypti* is known to transmit the Zika virus, and *Aedes albopictus* could possibly be a vector as well.^{61,62}

The Zika virus is a nationally notifiable condition in the United States, and clinicians should be aware that they need to report confirmed and even suspected cases of Zika viral infection to the state or local health departments.⁹

3.9 | Means of transmission and special populations

3.9.1 | Blood transfusions

Arboviruses transmitted by blood transfusion pose a serious problem for the healthcare system. It has been proposed that nucleic acid testing (NAT) or pathogen inactivation (PI) could be used to secure the blood supply. NAT can be done relatively easily in areas where one arbovirus is in circulation and commercial tests are available—this was done in North America for the West Nile virus.⁶³ For multiple arboviruses (such as Zika, dengue, chikungunya and others), new tests may be required. A cost-effective multiplex assay would be ideal. PI can be implemented using amatosalen-UVA illumination.^{63,64} Two transfusion-related Zika virus transmissions have been reported from Brazil.²³

3.9.2 | Sexual transmission

Sexual transmission of the Zika virus (from infected male to female) has been described in the US and other countries but is thought to be rare⁶⁵ and its epidemiological importance unclear.⁶⁶ It is not known if men with asymptomatic Zika infection can transmit the virus through sexual contact.⁶⁷ Testing asymptomatic men is not recommended as it is unclear at present whether positive blood test results mean the virus is present in semen and, conversely, whether negative blood test results mean it is not.⁶⁷

3.9.3 | Pregnant women

Clinicians should educate all women of childbearing potential, particularly those in vector-rich areas, about the risk contracting the

Zika virus and ways to protect themselves.⁶⁷ This education should include basic facts about the infection, common symptoms of infection and ways to protect against mosquito bites. Women of childbearing age who may have been exposed to the Zika virus and have had symptoms (such as fever, rash, arthralgia or conjunctivitis) should have a blood test for Zika infection.⁶⁷ Women with diagnosed or suspected Zika infection who are not pregnant should wait at least 8 weeks after the onset of symptoms before attempting to conceive a child; men should wait at least 6 months.⁶⁷

The Zika infection may be asymptomatic or result in only mild or vague symptoms that are overlooked. Thus, women may have been infected with the Zika virus and not know it. The risk of congenital infection in pregnant women with an asymptomatic Zika infection is unclear.⁶⁷

When pregnant women travel to or reside in areas where the Zika virus is prevalent and develop symptoms congruent with Zika infection, serum blood tests are recommended to identify Zika infection.⁶⁷ Children born to mothers who test positive (or inconclusive) for the Zika virus should also be tested. Neonates with evidence of potential Zika virus infection should be clinically evaluated and monitored over time, specifically in terms of measurements of head circumference, length, weight and assessment of gestational age. Neurological abnormalities, rashes, dysmorphic features, splenomegaly, hepatomegaly and ophthalmologic and otoacoustic examination are recommended within the first month of life.⁶⁸ Infants with microcephaly or intracranial calcifications should be referred to a paediatric neurologist.⁶⁹

It is not known if the Zika virus causes miscarriage.^{70,71} In a study of 88 pregnant women with rash, women infected with the Zika virus had significantly more adverse pregnancy outcomes (up to and including foetal death) than those without Zika infection (29% vs. 0).⁷² In a small case series ($n = 9$), Zika virus infection was more likely to be associated with adverse pregnancy outcomes when it occurred in the first trimester versus later in the course of the pregnancy.⁷³ Pregnant women with Zika symptoms who test positively for the disease should be referred to specialists and counselled. The appropriate role of amniocentesis for pregnant women with the Zika virus must be evaluated individually. The sensitivity and specificity of RT-PCT of amniotic fluid for congenital Zika virus infection are not established, that is, it cannot be said at present that a positive amniocentesis test predicts foetal developmental abnormalities.⁶⁷ Furthermore, it is not known at what gestational age amniocentesis is most reliable for Zika virus testing.

3.9.4 | Pregnancy, labour, delivery

Healthcare professionals who work in obstetrics must take special precautions to avoid infection with Zika, which may be present in body fluids, including blood and amniotic fluid. During routine, uncomplicated delivery, a pregnant woman may lose 500 ml of blood and a greater volume than that of amniotic fluid. Gloves and a surgical mask should be worn if a catheter is placed or a needle is inserted

for epidural injection.⁷⁴ These precautions should be observed routinely, even if the patient is not diagnosed with or suspected to have a Zika infection, since the infection may be asymptomatic. All healthcare workers associated with labour and delivery should use standard precautions, including gloves, a mask, eye protection and an impermeable gown.

3.9.5 | Lactation

Zika viral RNA can be detected in breast milk, but there is no evidence that the virus can be transmitted in this way.¹⁷

3.9.6 | Fertility treatment

Although there is no documented case of Zika virus transmission through fertility treatments (such as donated embryos or gametes), it seems medically possible that this could occur, in that it is unlikely the cryopreservation process would destroy the Zika virus. The FDA has recommended that anonymous donors to fertility clinics be declared ineligible if in the last 6 months they have been diagnosed with the Zika virus, have lived or travelled to an area with active Zika virus transmission or have had sex with a male partner who has been diagnosed with the Zika virus or travelled to an area of active Zika virus transmission.⁶⁷ Directed donors must meet the same eligibility criteria as anonymous donors, but these recommendations would not apply to sexually intimate couples.

4 | WHAT IS NEW AND CONCLUSION

4.1 | Unmet needs

Although work is ongoing for a vaccine against Zika, none is currently available.^{2,32} Furthermore, vaccines need to be inexpensive in order to assure proper distribution in epidemic-plagued areas, which may not be well-developed economically. Control of vectors can help reduce the spread of these viruses but also requires considerable resources. These might include biological control of mosquito larvae, the use of *Wolbachia*-infected or transgenic mosquitoes, and traditional methods to avoid mosquito bites (netting, insecticides). Mosquito control can be further improved by changes in urban sanitation, water supply and housing to reduce the opportunities for them to breed. Promising results have been reported by the CDC, which have developed an autocidal gravid ovitrap (AGO) to attract and capture *Aedes aegypti* mosquitoes. For example, in Puerto Rican communities where the AGO traps were deployed, the incidence of chikungunya virus infection was reduced.⁷⁵ As the AGO traps are simple, inexpensive and low-maintenance devices that require no pesticides, these may represent an important and economically viable weapon in the fight against the Zika virus and other mosquito-borne diseases.

Reliable, cost-effective test measures are urgently needed to better define and thus monitor the Zika-infected population.

4.2 | Future directions

In vitro testing has demonstrated that the viral polymerase inhibitor 7-Deaza-2'-C-methyladenosine (7DMA) inhibits Zika virus replication.⁶⁰ When IFN- α/β and IFN- γ knockout AG129 mice were infected with the Zika virus, they developed acute neutrophilic encephalitis with an accumulation of viral antigens in brain and spinal cord neurons. High levels of viral RNA were found in the spleen, liver and kidney of these mice and there was a systematic increase in the serum levels of IFN- γ and IL-18 in infected mice. The virus was also detected in mice testicles. 7DMA was also shown to reduce viremia and delayed virus-induced morbidity and mortality in infected mice.

Future work may involve repurposing the seasonal influenza vaccine for prevention of Zika virus infection.⁷⁶ A potential target for therapeutic antibodies against the Zika virus may be an E protein fusion loop epitope. The flavivirus has an envelope (E) glycoprotein that is responsible for virus entry and represents a good target for neutralizing antibodies for other flaviviruses.⁷⁷ The crystal structure of the Zika virus helicase may be a target for drug development.⁷⁸

4.3 | Frontline responses

Clinicians on the frontline of health care must take a proactive role in talking to their patients about the Zika virus, the potential risks of infection, and associated symptoms. Women of childbearing potential in particular should be educated about Zika and its symptoms, told about its risks and provided with instructions on how to reduce the risk of mosquito bites. These patients should be advised to wear protective clothing and use mosquito repellent when going outdoors.

Large international and national agencies need to mobilize forces to combat the Zika virus. Local authorities should begin initiatives to reduce mosquitoes in their localities, either through spraying and other ongoing efforts, or through public awareness campaigns that ask local citizens to be aware of potential mosquito breeding grounds (areas where water pools or collects) and to drain them.

Healthcare providers should keep abreast of the latest developments in Zika virus diagnosis and treatment. Pregnant women who are suspected of being infected with the Zika virus should be promptly referred to specialists. As much as possible, clinicians should share knowledge with each other about outbreaks, symptoms and specific cases.

5 | CONCLUSION

The Zika virus is an under-the-radar epidemic and one that may challenge our abilities to work in multinational, multidisciplinary teams.

Work is advancing rapidly to better understand, diagnose and treat the Zika virus. The FDA, CDC, the World Health Organization (WHO) and other agencies around the world are taking proactive and aggressive steps to contain the Zika virus. Healthcare providers should educate patients on the risks of the Zika virus and how to prevent it. Further study, better diagnostic tools, more treatment options and vaccinations are urgently needed.

CONFLICT OF INTEREST

None declared.

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