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Selected mosquito borne illnesses – Zika

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Introduction

The arbovirus Zika Virus (ZIKV) (Fig. 1) is a Flavivirus, often transmitted by the bite of infected Aedes aegypti and other Aedes mosquitoes.[1–9] It can also be transmitted by blood and sexual contact.

ZIKV was initially identified in Uganda, from a rhesus macaque, in 1947, and by 1952 human disease was detected in Uganda and Tanzania.[2,3,10,11] The first documented outbreak of ZIKV occurred in Micronesia in 2007. Subsequent outbreaks have occurred in Yap Island and French Polynesia.[2,5,10] Zika is now endemic in the African and Asian continents. Most recently Zika came to public attention owing to infections in Brazil 2015 prior to the Summer Olympics which were planned to occur in that region. It has since spread into the Americas, and poses a risk to North America.[3,12–16]

Arboviruses as endemic pathogens have been increasingly recognized as a major cause of significant global illnesses over the last several decades. Of concern in recent years there has been a dramatic change in the epidemiology of several arboviruses, and the emergence in regions heretofore unaffected. Recently emerging in the Americas, including Brazil, as well as the Caribbean, includes the arboviruses dengue virus (DENV), Chikungunya virus (CHIKV), and Zika virus (ZIKV).[2]

Other areas with past outbreaks of Chikungunya and dengue are considered at higher risk for Zika. These include U.S. territories like Puerto Rico, the U.S. Virgin Islands, and Guam. Local outbreaks have also been reported in parts of Hawaii, Florida, and Texas. Local mosquito-borne Zika virus transmission has also been reported in the continental United States. Many areas in the United

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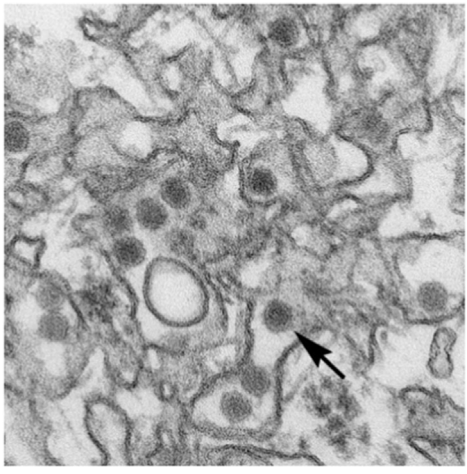

Fig. 1. Transmission Electron Micrograph (TEM) of Zika virus https://phil.cdc.gov/phil/details.asp?pid=20487 Note the round 40 um particles (arrow lower right corner).

States have the type of mosquitoes that can become infected with and spread Zika, Chikungunya, and dengue viruses.

These RNA viruses demonstrate genetic plasticity with high mutation capacity, with adaptability to infect vertebrate and invertebrate hosts.[2,17] Whether West Nile Virus that causes epidemics in suburban and urban settings, Yellow Fever (a reference to the jaundice caused), Dengue, Zika or Chikungunya, expanded geographic regions, including sections of the United States that can support the various mosquitoes suitable for these arboviruses should be expected.[14] Given the viral co-circulation in the America's, including Brazil, raises the potential for co-infection, such that anyone infected with ZIKV should be tested for DENV, and other arboviral illness if signs and symptoms guide beyond the biodrome (cascade of symptoms) that usually characterize a particular arbovirus. Moreover, there is at least a theoretical potential that could influence the immune response, resulting in perhaps more intense viremia, or even trigger autoimmune reaction, including Guillain-Barre' Syndrome (GBS).[3,18–23]

In spite of numerous cases and exhaustive research,[24–26] to date there are no FDA approved vaccines or antiviral treatments for Zika virus infection. However sofosbuvir, an antiviral FDA approved nucleotide polymerase inhibitor for hepatitis C virus has shown promise against Zika in early studies.[24] Cell culture studies established that sofosbuvir efficiently inhibits replication and infection of several ZIKV strains in multiple human tumor cell lines and isolated human fetal-derived neuronal stem cells without significant drug toxicity. Moreover, oral treatment with sofosbuvir protected against ZIKV-induced death in mice.[24]

Clinical

The incubation period of Zika according to the World Health Organization (WHO) is still not fully characterized, but likely a few days from exposure to symptoms. Zika infection is characterized by fever, rash, arthralgias, muscle pain, headache, and occasionally conjunctivitis (Fig. 2). Symptoms in many cases are usually limited and last between 2- 7 days.[3,5,27] Among symptomatic cases, maculopapular rashes occur in more than 90% of patients according to one study.[28] Laboratory findings are variable, and include mild neutropenia, mild lymphopenia, and mild to moderate thrombocytopenia.[29] Neurological manifestations can occur, including Guillain-Barre' Syndrome (GBS) which includes damage to peripheral nervous system, myelin insulation is lost, resulting in facial palsy, muscle dysfunction, and myalgia, along with paralysis and possible pulmonary decline requiring mechanical ventilation.[2,5,18,19,21] Infection during pregnancy can result in severe congenital

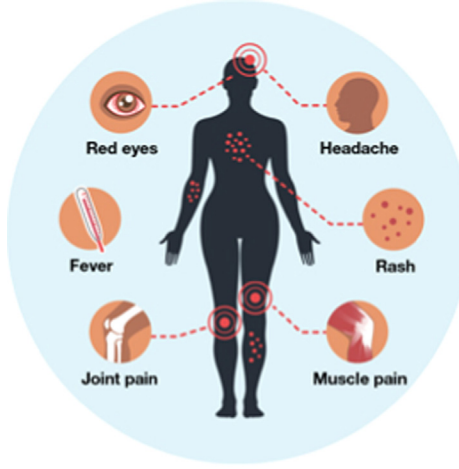

Fig. 2. Symptoms associated with Zika https://www.cdc.gov/zika/about/overview.html.

birth defects, including microcephaly (Fig. 2).[14,18–22] The epidemiology of asymptomatic or minimally symptomatic patients is unknown, but like other arboviruses, subclinical disease can occur.

Although initially considered an infection that merely caused a rash and fever but otherwise benign disease, with the advent of outbreaks from 2013 to 2014 in French Polynesia, resulting in nearly 30,000 cases – severe neurological symptoms were reported, including encephalitis, myelitis, and peripheral paralysis. Notably the number of GBS patients was 8 times in the region during the time of the epidemic than baseline. It is not unreasonable to attribute at least some of that dramatic increase to ZIKV. Further data supporting Zika associated with GBS, fatal encephalitis, deaths of fetuses, microcephaly (Fig. 3), and other malformations have been described in Brazil.[30,31]

Fever is a common clinical symptom; in a returning traveler or someone who has a cascade of symptoms suggestive of a more complex illness, it warrants further examination and testing. Most of the arboviruses of concern cause fever and rash. The severity of fever can suggest the significance of illness with the caveat that the elderly or those taking temperature reducing medications may not mount a febrile response commensurate with the nature of infection. A detailed travel and occupational history are necessary.

A recent study revealed 28% of 24,920 patients who presented to travel clinics on their return home revealed fever was the chief symptom.[32,33] The severity and rapidity of onset may be clues. Unfortunately the incubation period for many of these arboviruses is similar, usually 2 to 7 days. The distinguishing clues include other signs and symptoms in the biodrome.

Of note, increasingly it is becoming evident that Zika and Dengue have neuroinfectious disease capabilities, which may not be the presenting symptoms, but should be watched for.

Infection with Zika virus may be suspected based on symptoms and recent history of travel (e.g. residence in or travel to an area with active Zika virus transmission). A diagnosis of Zika virus infection can only be confirmed through laboratory tests on blood or other body fluids, such as urine, saliva or semen.

The differential diagnosis, especially for persons returning from tropical regions is lengthy, and dengue, leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles, and parvovirus, enterovirus, adenovirus, and alphavirus infections such as Chikungunya, Mayaro, Ross River, Barmah Forest, o'nyong-nyong, and sindbis viruses.[34]

Preliminary diagnosis is based on the patient's clinical features, places and dates of travel, and activities. Laboratory diagnosis is generally accomplished by testing whole blood, serum, or plasma to detect virus, viral nucleic acid, or virus-specific immunoglobulin M and neutralizing antibodies.[34]

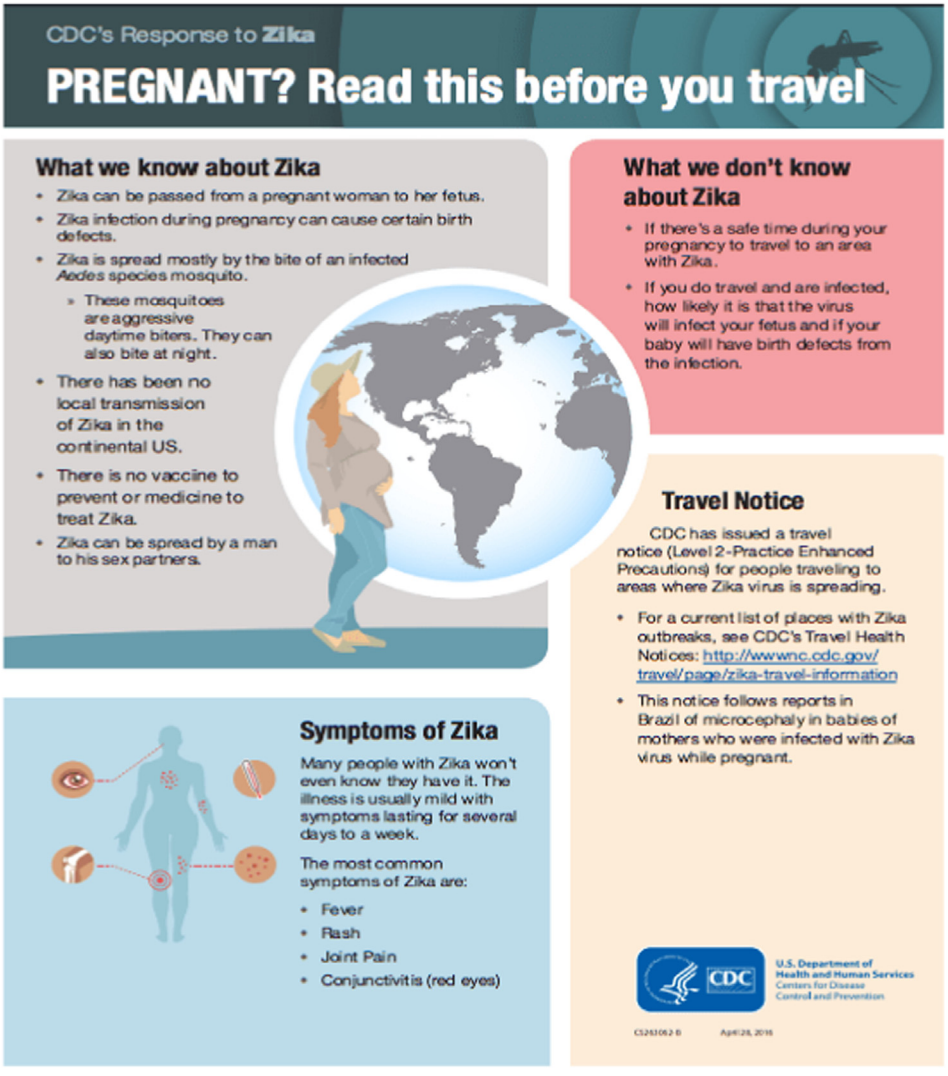

Fig. 3. CDC guidance for pregnant travelers to Zika region (www.cdc.com).

Women who are pregnant, and persons with underlying comorbidities, including HIV, and neurological diseases, as well as the elderly may require additional, and specialist care.

According to the CDC as an arboviral disease, Zika virus is a notifiable infection. Healthcare providers are encouraged to report suspected cases to their state or local health departments to facilitate diagnosis and mitigate the risk of local transmission. State or local health departments are encouraged to report laboratory-confirmed cases to CDC through ArboNET, the national surveillance system for arboviral diseases.[34]

Guillain Barre' Syndrome (GBS)

The exact etiology of GBS remains elusive, but the disorder is thought to result from the immune system attacking neurotissue.[2,5,18–21,35] GBS is often preceded by an infectious illness.

Symptoms of GBS

There are a variety of presentations of GBS.[2,18–21,35] The occurrence of symptoms usually follows an infection by days or weeks. Weakness and tingling in the extremities are usually the first symptoms in the most common forms.

The main types are[35]:

- **Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)**
  a. The most common form in the U.S.
  b. The myelin sheath is damaged
  c. The most common sign of AIDP is muscle weakness

- Starts in the lower part of your body and spreads upward.

- **Miller Fisher syndrome (MFS),**
  a. Paralysis starts in the eyes.
  b. MFS is also associated with unsteady gait.
  c. MFS occurs in about 5 percent of people with Guillain-Barre syndrome in the U.S.
  d. More common in Asia.

- **Acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN),**
  a. Less common in the U.S.
  b. More frequent in China, Japan and Mexico.

Sensations of numbness and tingling, along with frank weakness or paralysis can quickly spread, eventually paralyzing the entire body. As the muscle involvement expands, respiration can be compromised, requiring mechanical ventilation. Severe Guillain-Barre syndrome is a medical emergency; this will require hospitalization. Of note, some patients experience severe nerve pain that may require aggressive analgesic management.

The following are clues that aggressive management is required:

- Rapidly ascending numbness/tingling moving from distal (toes) to proximal (knees, thighs)
- Progressive ascending or descending paralysis
  a. Of note acute asymmetric flaccid paralysis should be evaluated for neurovascular/cerebrovascular emergency

- Weakness that is spreading rapidly
- Choking on saliva
- Orthopnea, dyspnea, especially rapidly progressive

Risk factors for GBS include advanced age, and male gender.

In addition to Zika infection, the following are associated with increased for GBS infection:

Guillain-Barre syndrome may be triggered by:

- Infection with campylobacter (bacteria found in undercooked poultry)
- Influenza virus
- Epstein-Barr virus
- HIV
- Mycoplasma pneumonia
- Surgery
- Hodgkin's lymphoma
- Rarely, influenza vaccinations or childhood vaccinations

Presumptive diagnosis should be assessed aggressively by specialists. Testing for GBS can include lumbar puncture, electromyography, and nerve conduction studies.

Treatment is largely symptomatic and supportive. Plasmapheresis and immunoglobulin therapy may enhance recovery.[35]

Zika treatment

Currently there are no FDA approved antivirals for the treatment of Zika. Therefore, symptomatic and supportive care is recommended. As with patients infected by Chikungunya, given the risk of co-infections, aspirin and NSAIDs should be avoided until Dengue hemorrhagic fever virus is ruled out. Acetaminophen is recommended for fever and mild to moderate joint or muscle pain. More aggressive pain management may be required, although the severity is not generally that of Chikungunya arthropathy. Fluid replacement is important, along with rest.

Zika testing

The CDC recommends Zika virus testing for the following situations[34]

- Anyone with possible Zika virus exposure* who has or recently experienced symptoms of Zika.
- Symptomatic pregnant women with possible Zika virus exposure
- Asymptomatic pregnant women with ongoing possible Zika virus exposure
- Pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection

Zika testing may be considered for

- Asymptomatic pregnant women with recent possible but no ongoing exposure to Zika virus (i.e., travelers)

Zika virus testing is not recommended for

- Non-pregnant asymptomatic individuals
- Preconception screening

Testing guidance for non-pregnant symptomatic individuals

Non-pregnant symptomatic individuals with possible exposure to Zika virus should receive testing of serum and urine by Zika virus ribonucleic acid (RNA) nucleic acid testing (NAT) and Zika virus and/or dengue virus IgM testing of serum. NAT testing is dependent on the timing of specimen collection. NAT testing should be performed on specimens collected < 14 days after symptom onset. Zika virus and dengue virus IgM serology testing should be performed on NAT negative samples collected < 14 days after onset of symptoms or on samples collected ≥14 days after onset of symptoms. NAT testing is not recommended on specimens collected ≥ 14 days after symptom onset.

Testing guidance for symptomatic pregnant women

Symptomatic pregnant women with possible Zika virus exposure should receive concurrent testing of serum and urine by NAT and Zika virus IgM testing of serum as soon as possible, up to 12 weeks after symptom onset.

- A positive NAT result on both serum and urine, regardless of IgM results, should be interpreted as an acute maternal Zika virus infection.

- A positive NAT result on either serum or urine, in conjunction with a positive Zika IgM, should be interpreted as evidence of acute Zika virus infection.
- A negative NAT result in conjunction with a non-negative Zika virus IgM test result should be followed by plaque reduction neutralization test (PRNT). See laboratory interpretation[PDF – 1 page](https://www.cdc.gov/zika/pdfs/lab-table.pdf) in the absence of PRNT testing.

Testing guidance for asymptomatic pregnant women

- **Asymptomatic pregnant women with ongoing possible Zika virus exposure (i.e., residence in or frequent travel to an area with risk of Zika)** should be tested. NAT testing is recommended three times during pregnancy. IgM serology testing is not routinely recommended. Recommendations for the timing of NAT testing are at the initial prenatal care visit, followed by two additional NAT tests performed during pregnancy, coinciding with non-consecutive prenatal visits. Timing of additional NAT testing may be informed by jurisdictional trends in Zika virus transmission, the expected length of Zika virus nucleic acid detection in serum, and the duration of exposure during pregnancy. Although not routinely recommended, after pre-test counseling and individualized risk assessment, physicians and patients, through a shared decision-making model, may collaboratively elect to have IgM testing performed concurrent with NAT testing. For women who have a positive NAT test during pregnancy, additional NAT testing is not recommended. If a patient has previously been confirmed positive for Zika virus infection, no additional IgM serology testing is recommended.

- **Asymptomatic pregnant women with recent possible exposure to Zika virus but no ongoing exposure** (i.e., travelers) may be considered for testing. Although not routinely recommended, testing may be considered on a case-by-case basis using a shared physician-patient decision-making model and in line with jurisdictional recommendations. If testing of asymptomatic pregnant women is performed, the same algorithm as for symptomatic pregnant women should be followed using the timeframe from the last possible exposure to Zika virus.

Note: Jurisdictions may take into account local epidemiologic considerations (e.g., seasonality, geography, and mosquito surveillance and control factors) in making recommendations for Zika virus testing for this group of pregnant women; therefore, testing recommendations for this group of pregnant women may differ by jurisdiction. Please contact your state, tribal, local, or territorial health department for jurisdiction specific guidance.

- **Pregnant women with possible exposure to Zika virus and who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection** should be tested. NAT and IgM testing should be performed on maternal serum and urine following the algorithm for symptomatic pregnant women. If amniocentesis is being performed as part of clinical care NAT testing of amniocentesis specimens should also be performed. Testing of placental and fetal tissues may also be considered.

Testing blood supply

The U.S. Food and Drug Administration in October 2017 approved the cobas Zika test, a qualitative nucleic acid test for the detection of Zika virus RNA in individual plasma specimens obtained from volunteer donors of whole blood and blood components, and from living organ donors. It is intended for use by blood collection establishments to detect Zika virus in blood donations, not for the individual diagnosis of Zika virus infection.[36]

In August 2016, the FDA issued a final guidance document recommending that all states and territories screen individual units of whole blood and blood components with an investigational

blood screening test available under an investigational new drug (IND) application, or a licensed (approved) test when available

The test's clinical specificity was evaluated by testing individual samples from blood donations at five external laboratory sites, resulting in clinical specificity of more than 99 percent.

The cobas Zika test is intended for use on the fully automated cobas 6800 and cobas 8800 systems. The cobas Zika test, cobas 6800, and cobas 8800 systems are manufactured by Roche Molecular Systems, Inc.

Zika transmission

Not unlike other arboviral infections, are transmitted by a variety of mosquitoes, including *Aedea aegypti* and *Aedes albopictus*.[2,3,5,19,37]

Aedes aegypti or *Aedes albopictus* mosquitoes can cause an outbreak, if all of the following happens:

a. People get infected with a virus (like Zika, dengue, or Chikungunya).
b. An Aedes aegypti or Aedes albopictus mosquito bites an infected person during the first week of infection when the virus can be found in the person's blood.
c. The infected mosquito lives long enough for the virus to multiply and for the mosquito to bite another person.
d. The cycle continues multiple times to start an outbreak.

It can also be transmitted through sexual contact, blood transfusions, even laboratory exposures. ZIKV has been demonstrated to persist in bodily fluids, especially semen, where virus can be detected upwards of 6 months after infection.

As Zika virus can be sexually transmitted, advise all men who travel to a Zika affected area with a pregnant partner to abstain from sexual activity or use barrier methods for the duration of the pregnancy. Pregnant women as well as women who intend to become pregnant are advised to avoid traveling to places where the virus is currently circulating. If already travelling in such a region, protect against mosquito bites as much as possible and avoid becoming pregnant for 8 weeks after leaving the affected country. If the male partner has also travelled to a Zika area, the advice is to use condoms or abstain from sexual activity for 6 months post leaving a Zika affected area.

Prevention

Whenever possible, avoiding regions endemic or with active epidemics is suggested. Failing that, patients should be alert to mosquito dense areas.

In addition to receiving travel related vaccines appropriate to the regions planned, taking mosquito precautions, the CDC recommends women who are pregnant or plan to become pregnant in the near term to review their guidance poster (Figure). Also the astute clinician will advise patients to seek out pre and post travel clinic guidance when considering travel, especially to Zika endemic regions.

Vaccine

Although currently there are no FDA approved vaccines to prevent Zika transmission, recently a new generation DNA-based Zika vaccine has been found safe and effective at eliciting an immune response against the virus in early human clinical trials, scientists say. Designated GLS-5700, this vaccine contains synthetic DNA that assists the host to develop an immune response against specific Zika antigen. In the Phase 1 open label study, the safety and immunogenicity of GLS 5700 was evaluated; 40 participants were enrolled between August and September 2016. Two groups of 20

participants received two different doses of the vaccine candidate intradermally at zero, four, and 12 weeks. Each dosage was followed by Cellectra delivery at the site, which generates small, directional electric currents into the skin to facilitate optimal vaccine uptake, production of the intended antigen, and immune responses.[3]

At baseline none of the subjects had ELISA measurable antibody to Zika, but four weeks after the initial dose of GLS 5700 41% of participants had antibody responses, and at week 6 (2 weeks after the second dose) there was a 74% overall response rate. The end results demonstrated study participants developed Zika-specific antibodies, and a significant percent developed significant neutralizing antibodies against the virus. After a 3 dose vaccination protocol 100% of participants had binding antibodies. Of note 95% had binding antibodies after two doses. Moreover serum obtained from the study participants was able to protect immunocompromised mice from developing the disease after infection with Zika virus. This suggests the vaccine-induced antibodies can prevent infection. The vaccine was also well tolerated

GLS 5700 is one of several vaccines under development against Zika. Some are based upon DNA and messenger RNA (nucleic acid based vaccines), as well as viral vectored, inactivated, and live-attenuated vaccine candidates. GLS 5700 is a synthetic DNA vaccine designed to express a consensus

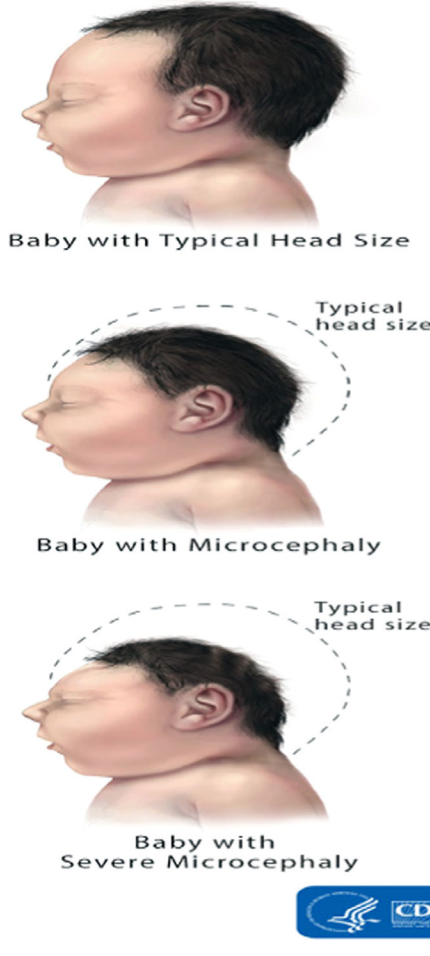

Fig. 4. CDC Microcephaly https://www.cdc.gov/ncbddd/birthdefects/microcephaly.html.

Zika premembrane and envelope antigens. This platform may allow more rapid development of vaccines against other viruses due to the rapidity of designing novel antigens.

Conclusion

Zika is another emerging arbovirus that has gained significant penetration in the South America and threatens North America, given the prevalence of vectors (Aedes mosquitoes) in many parts of the United States. Moreover with the extent of our patients undergoing business and personal travel to regions where Zika is endemic, makes it a likely possibility we will be called upon to identify imported cases. Although initially considered a minor infection, as the number of cases expand through recent outbreaks, the potential severity, especially in terms of adverse neurological events, along with the risk to pregnant women, makes early diagnosis important. Moreover there remains a critical need for vaccines, and antiviral medications. ssssIn the interim being alert for Zika, and arbovirus co-infection, early diagnosis, and aggressive symptomatic and supportive care remain the mainstay of treatment (Fig. 4).

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