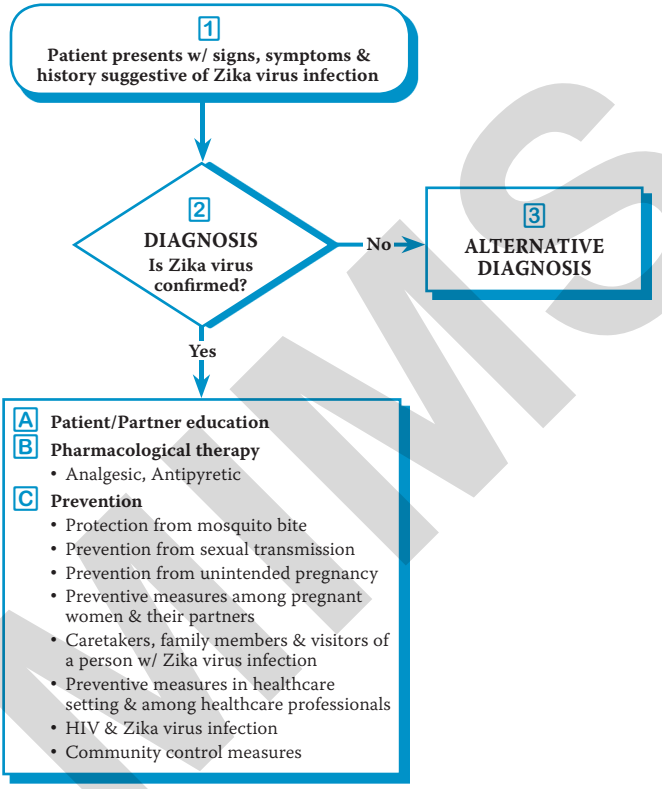
Zika Virus Infection (1 of 7)



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1 ZIKA VIRUS INFECTION

- Zika virus infection is an arboviral & a notifiable disease
- All healthcare professionals are encouraged to report suspected cases to the state & local health departments to facilitate the diagnosis & mitigate the risk of transmission

Etiology

- Zika virus is an icosahedral, enveloped, single-stranded RNA virus that comes from the *Flaviviridae* family & genus *Flavivirus*
  - Its lipid envelope is covered w/ dense projections consisting of membrane & glycoproteins

Mode of Transmission

- It can primarily be transmitted in humans through a bite of *Aedes aegypti* & *Aedes albopictus* mosquitoes
  - Other *Aedes* species that can transmit infection are *Aedes africanus*, *Aedes luteocephalus*, *Aedes vittatus*, *Aedes furcifer*, *Aedes hensilli* & *Aedes apicoargenteus*
    - These mosquito vectors breed in domestic water-holding containers
    - They are aggressive daytime biters
    - Peak biting hours: Early in the morning & late afternoon/evening
    - Feed both indoors & outdoors especially near dwellings
    - Main reservoirs of the virus: Nonhuman & human primates
    - During outbreaks, anthroponotic transmission (human-to-vector-to-human) may occur
- Other possible modes of transmission:
  - Perinatal
  - Sexual (anal, vaginal & oral)
    - May be transmitted from male-to-male, male-to-female- & female-to-male sex partners
    - At present, female-to-female transmission has not been documented
    - Women infected w/ Zika may pass the virus through vaginal fluid & menstrual blood
  - Blood transfusion
  - Organ transplantation
  - Laboratory exposure

Epidemiology

- First identified in the Zika forest of Entebbe in Uganda in 1947 in a Rhesus monkey & isolated in humans in 1952 in Uganda & Tanzania
- It was in 2007 that the first outbreak happened in the Yap Islands of Micronesia that affected >70% of the population aged 3 years old & above
- In 2013 to 2014, the second outbreak occurred in French Polynesia which affected ⅓ of the population
  - 3% of the donated blood samples tested were positive for Zika virus
- Countries & territories that are known to have local mosquito-borne transmission of Zika virus are: East Timor, Ecuador, El Salvador, Fiji, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Indonesia, Jamaica, Kosrae (Federated States of Micronesia), Laos, Malaysia, Maldives, Marshall Islands, Martinique, Mexico, Myanmar, New Caledonia, Nicaragua, Palau, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Saba, Samoa, Saint Barthélemy, Saint Kitts & Nevis, Saint Lucia, Saint Martin, Saint Vincent & Grenadines, Singapore, Saint Eustatius, Saint Maarten, Suriname, Thailand, Tonga, Trinidad & Tobago, Turks & Caicos, United States, Venezuela, Vietnam, Anguilla, Antigua & Barbuda, Argentina, Aruba, Bahamas, Barbados, Belize, Bolivia, Bonaire, Brazil, British Virgin Islands, Brunei, Cambodia, Cape Verde, Cayman Islands, Colombia, Costa Rica, Cuba, Curaçao & Dominica & Dominican Republic
- It was in early 2015 that Zika virus was first identified in Brazil
  - This was also when the Zika virus has rapidly spread throughout the Americas
- In mid to late 2015, cases of microcephaly & Guillain-Barré syndrome were increased & reported in northern Brazil
- In May 2015, the first local transmission of Zika virus in the Western Hemisphere was reported by World Health Organization (WHO)
- In February 2016, the Zika virus infection was declared by the World Health Organization (WHO) as an international health emergency
- On September 7, 2016, the first Zika infection in pregnancy was reported in Malaysia

Signs & Symptoms

- Zika virus infection is mild & self-limiting
- Incubation period is 3-14 days
- May present w/:
  - Arthralgia (eg particularly on the small joints of the hands & feet) & muscle pain
  - Skin rash (eg fine & diffusely distributed maculopapular rashes on the face, trunk, extremities, palms & soles)
  - Conjunctivitis
  - Acute onset of mild or low-grade fever
  - Headache
  - Retro-orbital pain
- Symptoms may appear on the 1st week of illness, last for up to 2-7 days & occur for 2 weeks, though some individuals w/ Zika virus infection may be asymptomatic
- May overlap w/ other arboviral infections but presence of maculopapular & immune-mediated rash predominates

Risk Factor

- Zika virus transmission & infection are increased in patients w/ Guillain-Barré syndrome

2 DIAGNOSIS

- The preliminary diagnosis of a patient suspected w/ Zika virus infection should be based on clinical features, date & place of travel as well as the patient's activities

History

Important points in the clinical history of patients w/ suspected Zika virus infection:

- History of recent travel to places w/ active Zika virus transmission
- Unprotected sexual contact w/ a person who has recent exposure to Zika virus (may be vaginal, anal, oral &/or sharing of sex toys)

Ultrasound

- First trimester ultrasound can detect intrauterine growth retardation at 18 weeks & CNS abnormalities at 19 weeks

Laboratory Tests

RNA Nucleic Acid Test (NAT) for Non-Pregnant Women

- The RNA in Zika virus may be detected earlier in patients who are symptomatic
- RNA NAT should be performed 2 weeks from the onset of symptoms
  - Should be conducted on urine samples collected <14 days after the onset of symptoms
- If there is positive result in any of the samples that have been collected, no additional tests are needed & is indicative of current infection
- If the result is negative, then the serum collected should be further analyzed using the immunoglobulin M (IgM) antibody testing

RNA NAT for Pregnant Women

- For symptomatic pregnant women who have exposure to Zika virus, RNA NAT testing of the serum & urine is recommended for up to 2 weeks after the onset of symptoms
- RNA NAT of serum & urine is recommended for those asymptomatic pregnant women w/ <2 weeks of exposure who live in areas without active Zika transmission & were evaluated 2-12 weeks after exposure who turned out to be IgM-positive
  - Whole blood may also be tested
- For asymptomatic pregnant patients who traveled in high-risk areas, RNA NAT testing is recommended on both serum & urine samples within 2-12 weeks from the date of last possible exposure
  - Recommended for those who present for care ≥2 weeks from being exposed & are IgM positive
- As part of the obstetric care, asymptomatic pregnant patients are advised to have IgM testing on the 1st & 2nd trimester of pregnancy especially in areas w/ active virus transmission
- For those who are IgM positive, a subsequent test known as reflex RNA NAT should be included

Trioplex Real-Time RT-Polymerase Chain Reaction (PCR) Assay

- Used for the qualitative detection & differentiation of RNA from Zika, dengue & chikungunya virus found in human sera, whole blood (EDTA) or cerebrospinal fluid (CSF)
- Also used for the qualitative detection of Zika virus RNA in urine & amniotic fluid
- Negative results do not rule out Zika virus infection; thus, it should not to be used as sole basis for making management decisions

Serologic Tests

- Zika virus-specific IgM & neutralizing antibodies
  - Develop towards the end of the 1st week of illness
  - The IgM antibodies are positive on the 4th day up to 12 weeks after the onset of symptoms
  - For serum samples that have been collected ≥14 days from the onset of symptoms, it is recommended that these samples be tested for anti-Zika virus IgM antibodies
- Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA)
  - Detects IgM antibodies in serum or CSF
  - If the test is presumed to be positive, equivocal or inconclusive, it should be confirmed by plaque-reduction neutralization testing (PRNT)

COMPLICATIONS

- Adults & children are at increased risk of neurologic complications (eg Guillain-Barré syndrome, myelitis, neuropathy) associated w/ Zika virus infection
- Reproductive-aged & pregnant women are the most susceptible to the adverse effects of Zika virus infection

COMPLICATIONS (CONT'D)

- Pregnant women infected by Zika virus may have complications such as stillbirth, preterm birth or miscarriage or may pass their infection to the developing fetus & may cause birth defects (congenital Zika syndrome) such as:
  - Hypoplasia of the cerebellum, brainstem or dermis
  - Thinning or hypoplasia of the corpus callosum & cortical atrophy & malformation
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
  - Extra-axial fluid
  - Limb contractures & hypertonia
  - Polymicrogyria
  - Decreased brain parenchymal volume
  - Delayed myelination
  - Visual defects
  - Hearing loss
- Congenital malformations develop after syptomatic & asymptomatic infection

3 ALTERNATIVE DIAGNOSIS

- Dengue fever
  - Zika virus & dengue virus infections have similar clinical manifestations & are both transmitted by the same mosquito vector
  - In dengue, the fever is usually high grade, muscle pain is severe & not usually associated w/ conjunctivitis
  - In Zika, the fever is usually mild & acute in onset, muscle pain is mild & usually associated w/ non-bacterial conjunctivitis
  - Both infections may present w/ headache
- Chikungunya
  - Both Zika & chikungunya have similar manifestations & mosquito vector
  - In chikungunya, the fever is high associated w/ intense joint pain in the hands, feet, knees & back, as well as conjunctivitis
  - Some patients w/ chikungunya may not be able to bend or walk or even perform simple task
- Leptospirosis
  - May present w/ fever, rigor, myalgia, conjunctival suffusion, headache & jaundice
  - Patients w/ Zika virus infection do not present w/ jaundice
- Malaria
  - Characterized by fever, nausea & vomiting, myalgia, malaise, abdominal pain, diarrhea & anemia
  - Establishment of the diagnosis is through the visualization of parasites on peripheral smear
- Measles
  - Also presents w/ fever, cough, sore throat, coryza, conjunctivitis & lymphadenitis
  - Koplik spots precede generalized rash which is absent in patients w/ Zika virus infection
- Rickettsia
  - Patients w/ Rickettsia have similar symptoms w/ Zika virus
  - The characteristic presence of an eschar at the tick-bite site of inoculation w/ associated lymphadenopathy in Rickettsia is not present in Zika
- Group A Streptococcus (GAS)
  - Group A streptococcus causes skin & soft tissue infections (eg cellulitis, erysipelas, pyoderma, injection drug use, burns, varicella virus infection & spontaneous gangrenous myositis)
  - Zika virus infection does not cause soft tissue infections & the symptoms are usually milder
- Rubella
  - Characteristics of rubella are coryza, pinpoint & pink maculopapular rash that begins on the face then spreads caudally to the trunk & extremities that becomes generalized within 24 hours, arthritis (primarily involves the knees, wrists & fingers) & lymphadenopathy (involvement of the posterior cervical, posterior auricular, & suboccipital lymph nodes) that concurrently occur w/ low-grade fever
  - In Zika virus infection, the arthralgia may be noted on the small joints of the hands & feet while the rashes are characterized by pruritic macules & papules that appear on the trunk, extremities, palms & soles
  - Zika virus infection also presents w/ low-grade fever but without lymphadenopathy
- Parvovirus
  - May present w/ acute & symmetric arthralgia or arthritis (involvement of the small joints of the hands, wrists, knees & feet)
  - Rash in parvovirus may be present or absent while in Zika, maculopapular rashes are present
- Other viruses that may be considered in ruling out Zika virus infection:
  - Enterovirus
  - Adenovirus
  - Alphavirus (eg Mayaro, Ross River, Barmah Forest, o'nyong-nyong & sindbis virus)

A PATIENT/PARTNER EDUCATION

- Both men & women (pregnant or non-pregnant) should be counseled on the possible risk & outcome of Zika virus transmission
  - Symptomatic men are advised to wait at least 6 months from the onset of symptoms before having unprotected sex
  - Asymptomatic men are advised to wait at least 6 months from the last date of possible exposure before having unprotected sex
  - Symptomatic women are advised to wait at least 8 weeks after the onset of symptoms before having unprotected sex
  - Asymptomatic women are advised to wait at least 8 weeks from the last date of possible exposure before having unprotected sex
- Longer precautionary period is recommended for men because:
  - The RNA of the virus still persists in the semen of an infected man after his recovery from the illness
  - It is still unknown for how long will it take an infected man's semen to clear the virus
  - There is no documentation about a good evidence on the difference between symptomatic & asymptomatic men
- For patients who are trying to get pregnant, taking folic acid supplement for 28 days should be advised

B PHARMACOLOGICAL THERAPY

Principles of Therapy

- There is no specific treatment for Zika virus infection; thus, supportive & symptomatic treatment are given
- Infected patients should be protected from further exposure to mosquito especially during the first few days of illness in order to prevent the other mosquitoes from becoming infected & to reduce local transmission
- Supportive care, which includes bed rest, increased fluid intake & use of analgesic (only when fever & pain are present) are advised
- For patients w/ Guillain-Barre syndrome, optimal care including neurologic exam, vital signs & respiratory function monitoring should be done frequently

Antipyretics & Analgesics

- Paracetamol is used for fever & pain relief
- Avoid Aspirin & other salicylates since these may cause gastritis, bleeding & acidosis
- Patients are also advised to avoid taking Aspirin & nonsteroidal anti-inflammatory drugs (NSAIDs) until dengue has been ruled out in order to decrease the risk of hemorrhage
  - Pregnant women at ≥32 weeks age of gestation (AOG) are advised to avoid taking NSAIDs in order to minimize the risk of having premature closure of the ductus arteriosus

C PREVENTION

Protection from Mosquito Bite

- Patients are advised to:
  - Avoid being bitten by mosquito especially on the first few days of illness (viremic phase) to prevent local transmission & other mosquitoes from being infected
  - Avoid going to mosquito-infested areas or in areas w/ known high transmission of Zika virus
  - Wear light-colored clothing, & long sleeves & pants to avoid skin exposure
  - Use nets (w/ or without treated insecticide) & insect repellents when outdoors (eg DEET, IR3535 or Icaridin)
  - Use air conditioning when indoors & keep windows & door screens closed
  - Seek consultation if symptoms of dengue, chickungunya & Zika virus have been recognized or developed

Prevention from Sexual Transmission

- It should be noted that even if the sexual partner is asymptomatic, he or she can still transmit the infection to his or her partner
- The following measures are recommended to prevent sexual transmission of Zika virus:
  - Pregnant women are advised to abstain from sex for the remainder of her pregnancy
    - Avoid having unprotected sex for 6 months w/ their male partners who have traveled to a moderate- to high-risk area
  - Use condoms during sex, especially for those who have partners who lived in or have traveled to areas w/ active Zika virus transmission
  - Couples whose partner has been in an area w/ active Zika virus transmission are also advised to abstain from sex or use male or female condoms (to be used from start to finish, every time during vaginal, anal & oral sex) & use of dental dams (latex or polyurethane sheets)

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C PREVENTION (CONT'D)

Prevention from Sexual Transmission (Cont'd)

- All pregnant patients should be tested, especially those who have been exposed to Zika virus sexually & those who developed symptoms after having sexual exposure to a partner who is asymptomatic
- For pregnant women who have traveled in an area w/ active transmission & who developed or did not develop symptoms within 2 weeks of traveling, testing for Zika virus should be advised
  - Ultrasound every 3-4 weeks is recommended
- For pregnant women who lived in an area w/ active transmission, consultation w/ a healthcare professional is advised
  - Should be tested on the 1st prenatal visit & 2nd trimester of pregnancy
  - If pregnant women present w/ symptoms associated w/ Zika, they should be tested anytime during pregnancy

Prevention from Unintended Pregnancy

- Patients are advised to seek consultation before planning on having a baby, especially those couples living in areas w/ high-risk of Zika virus infection
  - Reproductive life plans, pregnancy intentions & timing of pregnancy must be discussed
- Women should have access to safe & effective contraceptive methods in case they want to delay or avoid pregnancy

Preventive Measures Among Pregnant Women & Their Partners

- Prevent mosquito bites
- Pregnant women should avoid traveling in areas known to have Zika virus transmission
  - If traveling cannot be delayed or prevented, consultation w/ a healthcare professional prior to travel is recommended
- Consider postponing non-essential travel to places w/ reports of Zika virus infection (eg local transmission or traveling in countries w/ adjacent borders that have limited information about Zika virus & its transmission)
- Advise preventive measures to avoid being infected w/ Zika virus
- For men & women who live in areas w/ active viral transmission & have developed symptoms, men are advised to wait for at least 6 months & at least 8 weeks for women from the onset of symptoms before they attempt conception

Caretakers, Family Members & Visitors of a Person w/ Zika Virus Infection

- Avoid touching body fluids, blood & contaminated surfaces, especially for those w/ exposed skin
- Wash hands w/ soap & water or use an alcohol-based hand rub immediately after providing care
- For clothes w/ soiled blood & body fluids, remove & wash the clothes w/ detergent immediately
  - Use of bleach is not necessary
- All devices must be reprocessed using a sterilant & disinfectant

Preventive Measures in Healthcare Setting & Among Healthcare Professionals

- Use standard precaution to protect all healthcare professionals from disease transmission
  - All body fluids, blood, secretions, excretions, mucous membranes & non-intact skin must be considered as infectious agents
    - Blood, semen & vaginal secretions are associated w/ the transmission of Zika virus
- Occupational exposure
  - Evaluation of blood, body fluids, secretions & excretions must be required in all healthcare personnel that have been exposed to Zika virus
  - If possible exposure has occurred, it should be reported immediately & personnel should be assessed for all the possible pathogens including ZIKA, HIV & hepatitis
  - Wounds that have been exposed to blood & body fluids should be washed w/ soap & water immediately
  - For exposed mucous membranes, flushing & cleansing w/ copious amounts of water must be done
- Labor & delivery setting
  - Presence of body fluids & other infectious materials should be assessed & based on:
    - Condition of the patient
    - Type of anticipated contact
    - Nature of the procedure or activity performed
    - Application of practices & personal protective equipment (PPE)
- Pregnant personnel
  - May care for patients infected w/ Zika virus; however, all facility managers & supervisors should be advised on the potential exposure of the personnel to needle stick or cut w/ a sharp object, chapped or abraded skin & mucous membranes
  - Advise the personnel to adhere to the standard precautions for all patients
- Healthcare professional w/ Zika virus infection
  - For asymptomatic healthcare personnel, no work restrictions are given
  - For symptomatic healthcare personnel, work restrictions may be given based on the presenting symptoms of the patient

C PREVENTION (CONT'D)

Preventive Measures in Healthcare Setting & Among Healthcare Professionals (Cont'd)

- Disinfection of patient's room
  - No special cleaning materials or practices are required in cleaning the rooms of patients who are suspected or known to have Zika virus
  - Daily cleaning of the surfaces & floors is advised & a hospital disinfectant should be used after cleaning
  - Bed linens, towels & wash cloths should be managed using the standard precaution for workers handling the soiled textiles
- Reprocessing of equipments & devices
  - Instruments & devices should be cleaned, dried, sterilized & packed properly
  - All devices must be reprocessed using a sterilant & disinfectant
- Prevention of exposure in dentistry setting
  - Protect the eyes from splashes
  - Only sterilized & disinfected devices should be used

HIV & Zika Virus Infection

- HIV-infected adults coinfected w/ Zika & have severe immunosuppression should be closely monitored for all infections

Community Control Measures

- Schools, government & health organizations, healthcare facilities, tourism & social development agencies should collaborate & participate in reducing the vector density & preventing further transmission

Vaccination

- At present, several vaccines are being developed worldwide for the prevention of Zika virus infection
  - A DNA-based Zika vaccine being developed by the National Institute of Allergy & Infectious Diseases' Vaccine Research Center is undergoing phase II clinical trial
  - A purified inactivated vaccine called ZPIC developed by the Walter Reed Army Institute of Research, & several mRNA-based Zika vaccines are being evaluated in different phase I clinical trials
  - A live-attenuated Zika vaccine being developed by the US National Institutes of Health & the Butantan Institute is in phase I

Dosage Guidelines

ANALGESIC & ANTIPYRETIC

Drug	Dosage	Remarks
Paracetamol (Acetaminophen)	**Adults:** 0.5-1 g PO 4-6 hrly **Max adult dose:** 4 g/day **Childn:** **6-12 yr:** Up to 500 mg PO 6-8 hrly **1-5 yr:** 120-250 mg PO 6-8 hrly **3 mth-1 yr:** 60-120 mg PO 6-8 hrly **<3 mth:** 10 mg/kg body wt PO 6-8 hrly **Max childn dose:** 4 doses/day **Oral Susp:** **6-12 yr:** 250-500 mg PO 4-6 hrly **1-5 yr:** 120-250 mg PO 4-6 hrly	**Adverse Reactions** • Occasional hypersensitivity reactions (urticaria, dyspnea, hypotension in adults & angioedema in childn); rare & usually mild hematological reactions (thrombocytopenia, leukopenia, pancytopenia, neutropenia & agranulocytosis) **Special Instructions** • Use w/ caution in patients w/ known hepatic or renal impairment, CV or hematological disorders & alcohol dependency • Monitor patients if fever persists for >3 days or if pain continues for >5 days

All dosage recommendations are for non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.