MINISTRY OF HEALTH
24-26 GRENADA CRESCENT, KINGSTON 5, JAMAICA
EMERGENCY, DISASTER MANAGEMENT AND SPECIAL SERVICES BRANCH
TELEPHONE NOS. 1876-633-7922 CUG-1876-317-9980 Email: melodyennis5@gmail.com

ZIKA VIRUS INFECTION
CLINICAL MANAGEMENT PROTOCOL - PAEDIATRICS

Zika virus (ZIKV) is an arbovirus of the genus Flavivirus (family *Flaviviridae*), phylogenetically very close to other viruses, such as the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. It is a mosquito-borne RNA virus, transmitted mainly by the genus *Aedes*.

CLINICAL PRESENTATION

The symptoms of the disease usually appear after an incubation period of three (3) to twelve (12) days, and are similar to those of other arboviral infections; they include rash, fever, conjunctivitis, myalgia, arthralgia, malaise, and headache, and tend to last four (4) to seven (7) days.

Zika virus infection is characterized by the sudden onset of rash, which is usually maculopapular. Often, this is accompanied by a low-grade fever (< 38.5 °C).

The rash spreads in a cephalocaudal manner (head, trunk, and upper and lower extremities, frequently affecting the palmar and plantar surfaces; in the convalescent stage, there may be laminar desquamation). A marked feature of the rash is that it is pruritic, and often inteferes with the patient's daily activities, even hindering sleep.

Non-purulent conjunctival hyperemia usually occurs. Adenopathy or lymphadenopathy is rare, and when it occurs, the retroauricular ganglia lymph nodes are affected. In some cases, joint impairment is observed, usually in the form of polyarthralgia with bilateral, symmetrical periarticular edema.

In contrast to Chikungunya infection, pain associated with Zika virus infection tends to be milder and is not debilitating.

On physical examination, there may be mild articular edema, without hyperemia or local heat. The joints of the hands and wrists are most frequently affected, followed by the knees and ankles. Other possible manifestations include: headache, myalgia, nausea, diarrhea, and vomiting. In Zika virus infections no

instances of severe haematological or hemodynamic impairment have been observed as is seen in severe dengue cases.

Neurological manifestations may appear during or after the acute phase of infection. Guillain-Barré syndrome (GBS) is the most frequent neurological complication, usually in its typical clinical form or in one of its variants (such as Miller Fisher syndrome). Although less frequent, other manifestations include encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis, inflammatory myelopathy, and cranial nerve disorders or impairments.

Table 1: Clinical Manifestations

Common	Less Common	Atypical Manifestations/Complications
▪ Fever ▪ Maculopapular skin rash ▪ Arthralgia ▪ Headache ▪ Non-purulent conjunctivitis	▪ Myalgia ▪ Retro-orbital pain ▪ Nausea ▪ Vomiting ▪ Diarrhoea ▪ Constipation ▪ Ankle oedema ▪ Lymphadenopathy	▪ Guillain-Barre syndrome ▪ Meningoencephalitis ▪ Myelitis ▪ Acute disseminated encephalomyelitis ▪ Cerebellitis ▪ Cranial nerve palsies ▪ Neuropathy ▪ Immune thrombocytopenia purpura

Differential Diagnosis

Zika virus infection may be indistinguishable from other disease entities with fever, skin rash and arthralgia / arthritis. Zika virus may also coexist with other infections such as Dengue.

Differential diagnoses include but are not limited to:

- Dengue
- Chikungunya
- Malaria

- Leptospirosis
- Measles
- Rubella
- Typhoid fever
- Epstein Barr Virus – Infectious Mononucleosis
- Rheumatic Fever
- Rheumatoid Arthritis
- Juvenile Rheumatoid Arthritis
- Drug reaction
- Other Flaviviral infections

ZIKA VIRUS AND DENGUE

- Zika virus infection may be confused with Dengue. It is important to distinguish between the two, as Dengue may be associated with a more severe and complicated clinical course
- In Zika virus infection, severe thrombocytopenia, haemorrhage and shock are rare. The onset is more acute and duration of fever is shorter in Zika fever
- The maculopapular rash and conjunctivitis are seen more frequently in Zika virus than Dengue
- It is also important to note that co-infections with Zika and Dengue have been reported

HOW IS ZIKA VIRUS TRANSMITTED?

Zika virus is transmitted to humans primarily through the bite of an infected *Aedes* species mosquito. *Aedes* mosquitoes are aggressive daytime biters and feed both indoors and outdoors. They can also bite at night.

Although Zika virus infection in pregnancy is typically a mild disease, an unusual increase in cases of congenital microcephaly and other neurological complications have been reported in areas where outbreaks have occurred. Rapidly accumulating evidence from the current outbreaks in Brazil and other South American countries supports a link between Zika virus infection and microcephaly and other serious brain abnormalities.

Zika virus can be transmitted from a pregnant mother to her foetus during:

- pregnancy (congenital transmission) or

- around the time of birth (perinatal transmission)

Congenital or intrauterine transmission of Zika virus occurs when a woman is infected with Zika virus during her pregnancy, but before delivery, and the virus passes to the foetus.

Perinatal transmission of Zika virus occurs when a woman is infected with the Zika virus within approximately two (2) weeks of delivery, and the virus passes to the infant at or around the time of delivery. When an infant acquires Zika virus infection perinatally, the infant may develop symptoms such as maculopapular rash, conjunctivitis, arthralgia, and fever.

CLINICAL DESCRIPTION OF THE CONGENITAL SYNDROME ASSOCIATED WITH ZIKA VIRUS INFECTION

The syndrome is currently described as the presence of microcephaly with other signs such as facial or other cranial-facial disproportion and other anthropometric disproportions, such as redundant scalp with roughness, hypertonia or spasticity, irritability, and epileptic seizures.

In some cases, there have been reports of the following findings:

- Cerebral hypoplasia, hypoplasia or agenesis of the corpus callosum
- Cerebral calcifications (mainly cortical and subcortical) is characteristic
- Alterations in the cerebral ventricles
- Anomalies of the posterior fossa
- Lissencephaly
- Central hearing loss
- Visual abnormalities - focal retinal pigment epithelium changes, chorioretinal atrophy, and optic nerve hypoplasia
- Arthropathy – clubfoot or severe malformations of the hands and feet (arthrogryposis)

MICROCEPHALY

Microcephaly is a clinical sign and not a disease. It is defined as a head circumference (HC) < 2 standard deviations from the reference population average as standardized for age and sex OR less than the third percentile based on standard growth charts. Babies born with microcephaly are at risk of developmental delay and intellectual disability. They may also develop seizures, physical disabilities including hearing and vision impairment. Some of these infants will have normal neurological development.

The International Fetal and Newborn Growth Consortium for the 21st Century (Intergrowth-21st) include standards that provide a greater precision for the evaluation of microcephaly in premature newborns. Its

correct use requires having reliable data on gestational age (from first-trimester ultrasound or date of last menstrual period).

In full-term newborns for which reliable information on gestational age at birth is unavailable, it is recommended to use the standards from the WHO Multicentre Growth Reference Study.

CASE DEFINITIONS

SUSPECTED CASE

A Suspected case of congenital syndrome associated with Zika virus infection is a:

- live newborn who presents with microcephaly: head circumference below 2 standard deviations measured at 24 hours after birth according to the standardized guidelines for gestational age and sex; OR
- other congenital malformation of the central nervous system;

AND whose mother during pregnancy:

- resided in or travelled to an area with the presence of Zika virus transmission

OR

- had unprotected sex with a partner who resided in, or travelled to, an area with the presence of Zika virus transmission

PROBABLE CASE

A Probable case of congenital syndrome associated with Zika virus infection is a:

- live newborn who meets the criteria for a suspected case of congenital syndrome associated with Zika virus
  AND
- who has intracranial morphological alterations diagnosed by any imaging method, and excluding other known possible causes; OR
- whose mother had a rash during pregnancy

MICROCEPHALIC INFANTS

- Head circumference (HC) should be measured or confirmed within 24 hours of birth. If the child is discharged less than 24 hours after birth, measurement should be carried out before leaving the health facility. When measuring the head circumference, avoid rounding to centimetres, recording to one decimal point

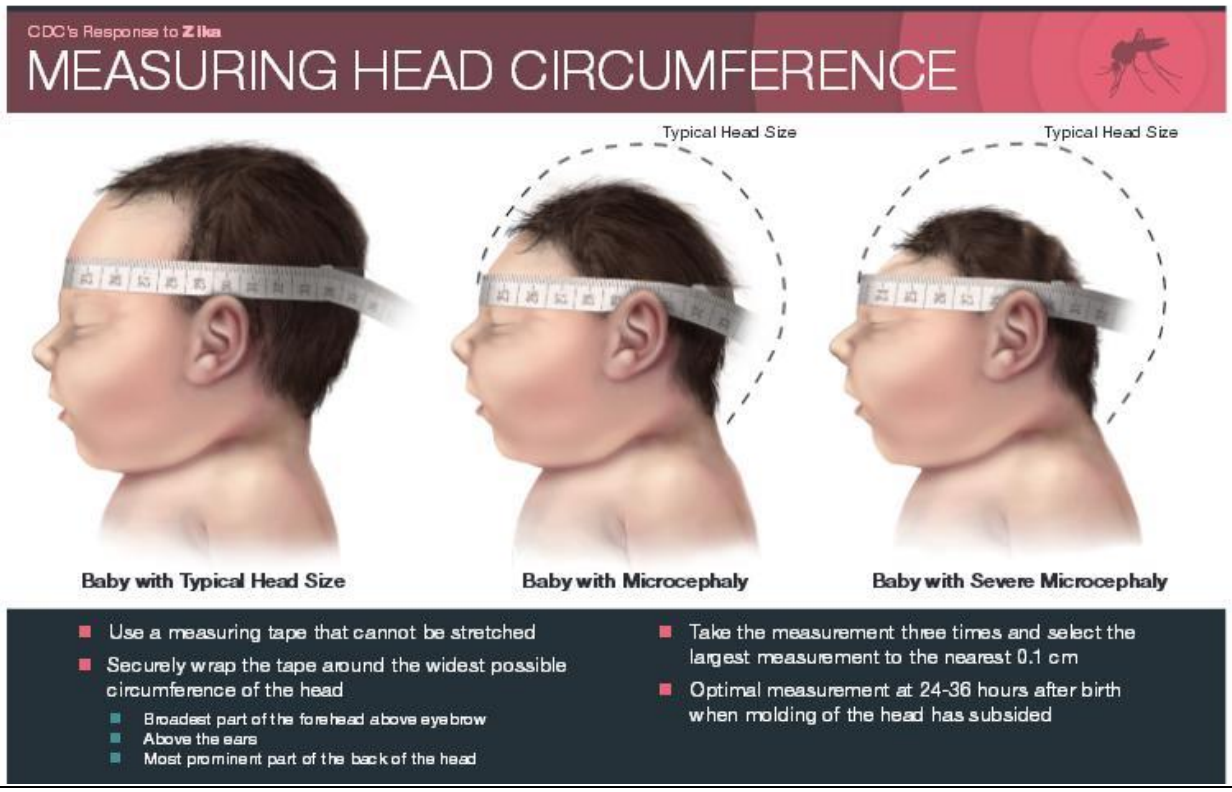
- Head circumference should be interpreted using SD scores specific for sex and gestational age
- WHO Growth Standards for term neonates and Intergrowth standards for preterm neonates should be used
- Neonates with a head circumference less than -2 SD i.e. more than 2 standard deviations below the mean should be considered to have microcephaly
- Neonates with a head circumference less than -3 SD i.e. more than 3 standard deviations below the mean should be considered to have severe microcephaly
- Neonates with a head circumference between -2 SD and -3 SD should have a clinical assessment and subsequent regular follow up during infancy including:

    - rate of head growth
    - pregnancy history and maternal and family history
    - developmental assessment
    - physical and neurological examinations for associated problems

Neonates with a head circumference less than -3 SD should have neuroimaging (CT scan or MRI; Ultrasound may perhaps be performed if the fontanelle is of a sufficient size) to detect structural brain malformations. In addition, they should also have a clinical assessment and subsequent regular follow-up during infancy including:

- clear and detailed pregnancy, maternal and family history
- rate of head growth
- developmental assessment
- physical and neurological examinations including hearing and ocular assessments for associated problems

Neonates with microcephaly and structural brain abnormalities diagnosed by neuroimaging, or neurological or developmental abnormalities should be considered to have microcephaly with a brain abnormality.


CDC's Response to Zika
MEASURING HEAD CIRCUMFERENCE
Typical Head Size
Typical Head Size
Baby with Typical Head Size
Baby with Microcephaly
Baby with Severe Microcephaly
Use a measuring tape that cannot be stretched
Securely wrap the tape around the widest possible circumference of the head
Broadest part of the forehead above eyebrow
Above the ears
Most prominent part of the back of the head
Take the measurement three times and select the largest measurement to the nearest 0.1 cm
Optimal measurement at 24-36 hours after birth when molding of the head has subsided

CDC 2016

CLINICAL MANAGEMENT

In some cases of microcephaly there are associated changes in the brain structure and neurological development impairment. Neonates with microcephaly or congenital abnormalities will require investigations and follow up. Patients who are ill should be referred to the nearest hospital with Paediatric facilities and specialist care. Stable patients should be referred to the nearest Paediatric Outpatient Department for appropriate investigations and management.

For infants born with microcephaly or intracranial calcifications secondary to congenital Zika virus infection, the following are recommended:

1. The infant should be tested for Zika virus infection
2. The mother should also be tested for a Zika virus infection, if this testing has not already been performed during pregnancy
3. Comprehensive physical examination, including careful measurement of the occipito-frontal circumference, length, weight, and assessment of gestational age
4. Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions
5. Rash, skin lesions, or dysmorphic features should be documented
6. Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, and herpes simplex virus infections
7. Complete blood count, platelet count, and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin
8. Cranial ultrasound
9. Hearing Evaluation within one (1) month of birth
10. Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within one (1) month of birth
11. Consultation with a Paediatric Neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram)

Infants with any positive findings for Zika virus infection an assessment for possible long-term sequelae must be conducted. This should include a repeat hearing screen at age six (6) months, even if the initial hearing screening test was normal, because of the potential for delayed hearing loss as has been described with other congenital viral infections.

The healthcare providers should evaluate for other possible etiologies and treat as indicated infants with microcephaly or intracranial calcifications who have negative results.

FOLLOW UP OF INFANTS WITH POSITIVE FINDINGS FOR ZIKA

The infant should be followed to assess for possible long-term sequelae. Follow-up should include:

- Cranial ultrasound
- Ophthalmologic examination
- Repeat hearing screen
- Developmental monitoring and screening during the first year of life is recommended for all children with congenital Zika virus infection

MANAGEMENT AND PREVENTION OF CONGENITAL ZIKA VIRUS INFECTIONS

- There is no specific antiviral treatment available for Zika virus infections
- There is no vaccine available against the Zika virus
- Treatment of congenital Zika virus infection is supportive and should address specific medical and neurodevelopmental issues for the infant's particular needs
- Psychosocial support for families of affected infants is recommended

BREAST FEEDING

Current WHO breastfeeding recommendations remain valid in the current context of Zika virus transmission.

a. Mothers with suspected, probable or confirmed Zika virus infection, during pregnancy or postnatally, should receive skilled support from healthcare workers to initiate and sustain breastfeeding, like all other mothers
b. Mothers and families of infants born with congenital anomalies (e.g. microcephaly) should be supported to breastfeed their infants in line with WHO recommendations. Feeding support by skilled breastfeeding counsellors should be provided, if required

In light of the current available evidence, the benefits of breastfeeding for the infant and mother outweigh any potential risk of Zika virus transmission through breast milk.

GUILLAIN-BARRÉ SYNDROME & NEUROLOGICAL SYNDROME

Complications of Zika virus infection include Guillain-Barré syndrome (GBS) meningoencephalitis, myelitis, neuropathies, immune thrombocytopenia purpura and congenital anomalies. See management of GBS.

MANAGEMENT OF ZIKA VIRUS INFECTION IN CHILDREN

Clinical presentation is typically asymptomatic, with rash and low grade fever being the prominent features. The history, physical examination and investigations (where indicated) should assist the clinician in determining severity of the infection and whether there are atypical manifestations or complications and the need for hospital admission.

AMBULATORY PATIENTS

Patients who are sent home should be alert, able to tolerate oral fluids, urinate at least once every 6 hours, and not have atypical manifestations.

Care givers should be instructed to take the patient to hospital immediately, if there is deterioration, persistent vomiting, severe abdominal pain, cold and clammy extremities, lethargy or restlessness, bleeding, oliguria, weakness of extremities, paralysis, diplopia, dysphagia, dysarthria and other neurological deficits.

IN-PATIENT MANAGEMENT

Patients with atypical manifestations, neurological syndromes, co-existing conditions such as cardiovascular disease, haematological disorders, haemoglobinopathies (Sickle Cell Disease), rheumatological disorders (Systemic Lupus Erythematosus) and Diabetes Mellitus that are complicated by the viral syndrome should be admitted to hospital.

TREATMENT

Treatment of Zika is supportive and involves fluids, rest, antipyretic and analgesic agents. The antipyretic and analgesic agent that is recommended is acetaminophen or paracetamol.

Non-steroidal anti-inflammatory agents (NSAIDS) such as ibuprofen, diclofenac and naproxen should not be used due to a risk of bleeding complications from thrombocytopenia, a missed diagnosis of Dengue or possible co-infection with Dengue which has been associated with haemorrhagic complications. The use of aspirin is not advised due to the risk of Reye's syndrome and bleeding complications in children.

Antihistamines such as diphenhydramine and chlorpheniramine may be used to relieve the symptoms of pruritus associated with the maculopapular skin rash. Topical antihistamine lotion may also be used to relieve itching.

PREVENTION OF TRANSMISSION

Zika virus infected individuals should avoid being bitten by mosquitoes during the first week of symptoms (viraemic phase) so as to reduce possible transmission to unaffected individuals. Use of insect repellents such as DEET (N, N-diethyl-3-methylbenzamide), Icaridin or IR3535 and bed nets (insecticide treated or not) is advised.

The repellents recommended by the health authorities offer the highest safety levels during pregnancy and breastfeeding. They should be applied on exposed body areas, and even over clothes, whenever indicated, and re-applied as suggested by the manufacturer on the product label. The repellent will have no protective effect unless it is used following the manufacturers' recommendations.

For newborns and children under three (3) months of age, repellents are not recommended; instead, bed nets should be used. All persons should protect themselves from mosquito bites using insect repellents and other protective measures such as wearing long sleeve tops and pants (preferrably light-coloured) that covers as much of the body as possible. Physical barriers such as screens, closed doors and windows and sleeping under mosquito nets are also recommended.

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