“...ambiguity is inevitable. It is not an anomaly; it is the norm. Accepting this allows us to re-calibrate our expectations, and move forward.”

John Keats, surgeon and poet, 1818
“In October 2015, the Brazil International Health Regulations National Focal Point notified the detection of an unusual increase in microcephaly cases in public and private healthcare facilities in Pernambuco state, Northeast Brazil.

As of epidemiological week 1 of 2016, there were 3,530 microcephaly cases recorded, including 46 deaths, in 20 states and the Federal District. Between 2010 and 2014, an average of 163 microcephaly cases (SD 19.6) was recorded nationwide per year.”

“In January 2016, ophthalmological findings were reported in 3 children with microcephaly and cerebral calcifications detected by CT scans and presumable intrauterine ZIKA infection. The 3 infants had findings involving the macular region, neuroretinal atrophy, loss of foveal reflex.”
Marilla Lima had Zika virus while pregnant. Her 2 1/2-month-old son, Arthur, has microcephaly — a birth defect characterized by a small head and severe brain damage.

Lourdes Garcia-Navarro
NPR NEWS
Tuesday, January 26, 2016
May 7, 2015. The Pan American Health Organization (PAHO) / World Health Organization (WHO) recommends its Member States establish and maintain the capacity for Zika virus infection detection, clinical management and an effective public communication strategy to reduce the presence of the mosquito that transmits this disease, particularly in areas where the vector is present.

The outbreak raised concerns regarding the safety of athletes and spectators at the 2016 Summer Olympics in Rio de Janeiro.

In Brazil, the Zika virus epidemic revealed structural problems of the health system, in particular in public health services and basic sanitation.

On February 1, 2016, WHO declared the outbreak a Public Health Emergency of International Concern as evidence grew that Zika can cause birth defects as well as neurological problems.
Rates of Microcephaly Over Time: the Americas and the Caribbean

Comparison of the rates of microcephaly in the Americas and Caribbean from 2010-2014 and 2015

Updated as of Epidemiological Week 52
(December 27, 2015 – January 2, 2016)

Microcephaly rates by state in Brazil
(cases per 1,000 live births)

- 0.1-1.0
- 1.1-15.0
- 15.1-30.0
- 30.1-45.0
- 45.1-88.6

Countries

Source:
What is Zika virus?

- Single-stranded RNA virus, closely related to dengue, yellow fever, Japanese encephalitis & WNV

- Primarily transmitted by the bite of Aedes aegypti (more efficient transmission) and Aedes albopictus
  - Aggressive daytime biters
  - Lay eggs in domestic water-holding containers
  - Live in and around households
  - Once a mosquito is infected with Zika virus, it remains infected for life. A mosquito lifespan is up to 30 days.

- Intrauterine and perinatal transmission
- Sexual transmission
- Laboratory exposure
- Blood transfusion
- No evidence of transmission in breast-milk
Zika Virus Epidemiology

First isolated from a monkey in the Zika forest of Uganda in 1947

Prior to 2007, only sporadic human disease cases reported from Africa and southeast Asia

In 2007, first outbreak reported on Yap Island, Federated States of Micronesia, 172 cases, 18% were symptomatic

In 2013–2014, >28,000 suspected cases reported from French Polynesia*

As of June 20, 2016, outbreaks of Zika were occurring in 48 countries

Zika Virus Incidence and Attack Rates

Infection rate: 73% (95%CI 68–77)

Symptomatic attack rate among infected: 18% (95%CI 10–27)

All age groups affected

Incubation period 3-14 days

Adults more likely to present for medical care

No severe disease, hospitalizations, or deaths in Yap Island outbreak

Reported Clinical Symptoms Among Confirmed Zika Virus Disease Cases with Symptoms (n=31 or 18% of total cases)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>90%</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
</tr>
</tbody>
</table>

### Clinical features: Zika virus compared with dengue and chikungunya

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Assessment & Treatment of Zika in the Normal Host

- Clinical illness is usually mild, no more severe with HIV co-infection
- Most common symptoms are: • Fever • Rash • Joint pain • Conjunctivitis
- Symptoms last several days to a week
- Severe disease is uncommon, fatalities are rare
- Once infected, a person is likely to be protected from future infections
- Treatment is supportive, but NSAIDS and aspirin should be avoided until dengue is ruled out, to reduce the risk of bleeding diathesis
- The differential diagnosis for Zika virus infection is broad: **dengue, chikungunya**, leptospirosis, rickettsia, rubella, measles, parvovirus, enterovirus, adenovirus, and alphavirus infections

Guillain-Barré syndrome reported in patients following suspected Zika virus infection (47% of 2016 GBS)

80% of patients with Zika infection have no symptoms at all.

Of those who do, fever, red eyes, headache, pruritic maculopapular rash, arthralgia and myalgia are common.

Period of viremia ranges 3-7 days.
• This series of 158 children with postnatally acquired Zika virus disease corroborates previously published reports suggesting that the clinical course of Zika virus disease is typically mild in children.

• In this case series, only two children were hospitalized, and no deaths occurred. Serious complications of Zika virus disease, such as Guillain-Barré syndrome, were not reported for any children in this analysis.

• Severe disease following Zika virus infection in children has rarely been reported. Two deaths possibly associated with postnatally acquired Zika virus disease have been reported among children, including a Brazilian girl aged 16 years with possible hemorrhage and a Colombian girl aged 15 years with sickle cell disease who developed SARS, hemothorax, and splenic sequestration.

• Guillain-Barré syndrome and meningoencephalitis also have been reported rarely among children during the recent outbreak in Brazil.
Evidence of perinatal transmission (during time of delivery) – Zika outbreak in French Polynesia 2013-2014

- Two pregnant women with signs and symptoms consistent with Zika infection around the time of delivery
- Both mothers tested positive for Zika virus RNA by RT-PCR
- Zika virus infection was confirmed in the neonates, 1-3 days after delivery
- Unlikely that neonates were exposed to mosquitoes
- Outcomes regarding microcephaly were not reported

Estimated range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2016*

*Aedes aegypti* mosquitoes are more likely to spread viruses like Zika, dengue, chikungunya than other types of mosquitoes such as *Aedes albopictus* mosquitoes.

- These maps show CDC’s best estimate of the potential range of *Aedes aegypti* and *Aedes albopictus* in the United States.
- These maps include areas where mosquitoes are or have been previously found.
- Shaded areas on the maps do not necessarily mean that there are infected mosquitoes in that area.

*Maps have been updated from a variety of sources. These maps represent CDC’s best estimate of the potential range of *Aedes aegypti* and *Aedes albopictus* in the United States. Maps are not meant to represent risk for spread of disease.*

Diagnostic testing for Zika virus

• Real time reverse transcriptase-polymerase chain reaction (rRT-PCR) for viral RNA in clinical specimens collected < 7 days (serum) or < 14 days (urine) after illness onset.

• Serology for IgM and neutralizing antibodies in serum collected up to 12 weeks after illness onset. (can react with other flavivirus, i.e. dengue and yellow fever)

• Plaque reduction neutralization test (PRNT) for presence of Zika virus-specific neutralizing antibodies in paired serum samples. Immuno-histochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues.
“On the basis of this review, we conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies.

Evidence that was used to support this causal relationship included Zika virus infection at times during prenatal development that were consistent with the defects observed; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with presumed or confirmed congenital Zika virus infection; and data that strongly support biologic plausibility, including the identification of Zika virus in the brain tissue of affected fetuses and infants.”
Pregnant women in any trimester should consider postponing travel to areas where Zika is present.
Zika Virus Disease Prevention: Pregnant Women

Avoid mosquito bites:
- Use EPA-registered insect repellent
  - EPA-registered repellents including DEET are considered safe to use in pregnant and lactating women
Wear long-sleeved shirts and long pants to cover exposed skin
- Wear Permethrin-treated clothes
- Stay and sleep in screened-in or air-conditioned rooms
Aedes mosquitoes that transmit Zika virus bite mostly during the daytime
- Practice mosquito prevention strategies throughout the entire day
Prevention of Mosquito Bites for women of child-bearing age who live in or travel to an area with Zika:

- Wear long-sleeved shirts and long pants
- Stay and sleep in places with air conditioning or that use window and door screens
- Use insect repellents with one of the following EPA-registered active ingredients: • DEET, picaridin, IR3535, oil of lemon eucalyptus, paramethane-diol, or 2-undecanone
- Once a week, empty and scrub, turn over, cover, or throw out items that hold water, such as trash containers, tires, buckets, toys, planters, flowerpots, birdbaths or pools
In December 2013, during a Zika virus (ZIKV) outbreak in French Polynesia, a patient in Tahiti sought treatment for hematospermia, and ZIKV was isolated from his semen.

ZIKV transmission by sexual intercourse has been previously suspected.

This observation supports the possibility that ZIKV could be transmitted sexually.
Basics of Zika Virus and Sex Transmission

- Zika can be passed through sex from a person who has Zika to his or her sex partners.
  - Sex includes vaginal, anal, oral sex, and the sharing of sex toys.
  - Sexual exposure includes sex without a condom with a person who traveled to or lives in an area with Zika.

- Zika can be passed through sex, even if the person does not have symptoms at the time. Viral shedding appears to be intermittent.
  - It can be passed from a person with Zika before their symptoms start, while they have symptoms, and after their symptoms end.
  - It may also be passed by a person who has been infected with the virus but never develops symptoms.

- Studies are underway to find out how long Zika stays in the semen and vaginal fluids of people who have Zika, and how long it can be passed to sex partners. Current research shows that Zika can remain in semen longer than in other body fluids, including vaginal fluids, urine, and blood.
Suggested timeframe to wait before trying to get pregnant

Jan 27, 2017 - UPDATE: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure

Possible exposure via recent travel or sex without a condom with a partner infected with Zika

Women: Wait at least 8 weeks after symptoms start or last possible exposure
Men: Wait at least 6 months after symptoms start or last possible exposure

People living in or frequently traveling to areas with Zika

Women: Positive Zika test: wait until at least 8 weeks after symptoms start
No testing performed or negative results: talk with your doctor

Men: Positive Zika test: Wait at least 6 months after symptoms start
No testing performed or negative results: talk with your doctor
### Interpretation of results of laboratory testing of infant’s blood, urine and/or cerebrospinal fluid for evidence of congenital Zika virus infection

<table>
<thead>
<tr>
<th>Infant test results*</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>rRT-PCR</td>
<td>IgM</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive or Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*Abbreviations: rRT-PCR = real-time reverse transcription-polymerase chain reaction; IgM = Immunoglobulin M

* Infant serum, urine or cerebrospinal fluid.

+ Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology results, clinical findings consistent with congenital Zika syndrome, and any confirmatory testing with plaque reduction neutralization testing (PRNT).

Congenital Zika Pathophysiology

Zika virus appears to primarily target neural progenitor cells resulting in cell death and disruption of neuronal proliferation, migration and differentiation, which slows brain growth and affects neural cell viability.

Some infants with presumed or confirmed congenital Zika virus infection have had a phenotype consistent with fetal brain disruption sequence, characterized by severe microcephaly, collapse of the skull, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and severe neurologic impairment.
Congenital Zika Syndrome

- Pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes
  - Severe microcephaly (small head size) resulting in a partially collapsed skull
  - Thin cerebral cortices with subcortical calcifications
  - Eye anomalies, including macular scarring and focal pigmentary retinal mottling
  - Congenital contractures or limited range of joint motion
  - Marked early hypertonia, or too much muscle tone, and symptoms of extrapyramidal involvement
- Infants with normal head circumference at birth may:
  - Have brain abnormalities consistent with congenital Zika syndrome
  - Develop microcephaly after birth
Figure 1. Cranial Morphology Supporting Fetal Brain Disruption Sequence Phenotype in Congenital Zika Syndrome

A  Lateral view of skull irregularities  
B  Excessive scalp with folds  
C  Lateral skull radiograph
A  Calcifications and shallow sulci  

B  Punctate calcifications and ventriculomegaly  

C  Calcifications and skull collapse  

D  Decreased cranial vault and small cerebellum  

E  Shallow sulci and calcifications  

F  Irregular cortex
Health problems associated with microcephaly include:

- Seizures
- Irritability
- Developmental delay: problems with speech, sitting, standing, and walking
- Intellectual disability, decreased ability to learn and function in daily life
- Problems with movement and balance, contractures
- Feeding problems, such as difficulty swallowing and aspiration
- Hearing loss
- Vision problems
All had brain anomalies consistent with congenital Zika syndrome. All infants showed a decrease in the rate of head circumference growth and postnatal microcephaly was diagnosed in 11 of 13 infants by the end of their first year.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Gestational Age (wks)</th>
<th>Birth Weight (gm)</th>
<th>Reported Prenatal Ultrasound Abnormalities*</th>
<th>Maternal Rash</th>
<th>Infant Zika Virus IgM Antibody by ELISA</th>
<th>Birth HC (cm) and (SD)</th>
<th>Age (mos) at Last Follow-up</th>
<th>Follow-up HC (cm) and (SD)</th>
<th>Ocular Findings‡</th>
<th>Craniofacial Disproportion at Birth‡</th>
<th>Arthrogryposis or Hip Dysplasia at Birth††</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>35</td>
<td>2,570</td>
<td>no</td>
<td>3 mo.</td>
<td>CSF, serum +</td>
<td>29.5 (-1.72)</td>
<td>11</td>
<td>39 (-3.86)</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>38</td>
<td>3,125</td>
<td>yes</td>
<td>2 mo.</td>
<td>CSF +</td>
<td>33.0 (-0.40)</td>
<td>10</td>
<td>41 (-3.33)</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>39</td>
<td>2,770</td>
<td>no</td>
<td>none</td>
<td>CSF, serum +</td>
<td>32.0 (-1.63)</td>
<td>11</td>
<td>43 (-2.11)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>37</td>
<td>2,785</td>
<td>yes</td>
<td>2 mo.</td>
<td>CSF +</td>
<td>31.0 (-1.65)</td>
<td>10</td>
<td>43 (-1.98)</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>37</td>
<td>2,465</td>
<td>yes</td>
<td>5 mo.</td>
<td>CSF +</td>
<td>31.0 (-1.39)</td>
<td>12</td>
<td>36 (-6.18)</td>
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<td>no</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>39</td>
<td>2,975</td>
<td>no</td>
<td>none</td>
<td>CSF +</td>
<td>33.0 (-0.78)</td>
<td>11</td>
<td>42 (-2.89)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>39</td>
<td>3,840</td>
<td>no</td>
<td>none</td>
<td>CSF +</td>
<td>33.0 (-0.78)</td>
<td>12</td>
<td>40 (-4.68)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>41</td>
<td>2,955</td>
<td>no</td>
<td>none</td>
<td>CSF +</td>
<td>32.0 (-1.95)</td>
<td>9</td>
<td>39.5 (-3.17)</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>39</td>
<td>3,155</td>
<td>no</td>
<td>3 mo.</td>
<td>CSF +</td>
<td>33.5 (-0.35)</td>
<td>11</td>
<td>42.5 (-2.50)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>40</td>
<td>3,100</td>
<td>no</td>
<td>none</td>
<td>CSF +</td>
<td>32.0 (-2.00)</td>
<td>10</td>
<td>40 (-4.27)</td>
<td>yes</td>
<td>yes</td>
<td>no data</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>38</td>
<td>2,965</td>
<td>no</td>
<td>none</td>
<td>CSF +</td>
<td>33.5 (0.02)</td>
<td>7</td>
<td>40 (-2.98)</td>
<td>no</td>
<td>no</td>
<td>no data</td>
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<tr>
<td>12</td>
<td>F</td>
<td>36</td>
<td>2,930</td>
<td>no</td>
<td>none</td>
<td>serum +</td>
<td>32.5 (0.30)</td>
<td>7</td>
<td>40.5 (-1.35)</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td>13</td>
<td>M</td>
<td>40</td>
<td>2,990</td>
<td>no</td>
<td>none</td>
<td>serum +</td>
<td>33.0 (-1.16)</td>
<td>5</td>
<td>40 (-2.12)</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Abbreviations: CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; F = female; HC = head circumference; IgM = immunoglobulin M; M = male; SD = standard deviation.

* Abnormalities include brain calcifications (patient 2), microcephaly (patient 4), and decreased brain volume with ventriculomegaly (patient 5).


§ Abnormalities include macular chorioretinal atrophic lesion in right eye (patient 2), discrete chorioretinal macular atrophy in left eye (patient 10), and macular atrophy in left eye (patient 13).

** Abnormalities include macular chorioretinal atrophic lesion (patient 2), hip dysplasia (patients 2, 7, 8), and diaphragmatic weakness (patient 2).
CDC Lab Confirms Zika In Fetal Tissues

- Zika virus has been shown to be present in fetal tissue
- Evidence of Zika virus has been detected in
  - Amniotic fluid
  - Placenta
  - Fetal brain tissue
  - Products of conception
- Zika virus has been found to continue to replicate in infants' brains after birth (Bhatnagar et al., 2017)

What is Microcephaly?

Clinical finding of a small head when compared to infants of same sex and age, usually defined as < 3%ile.

Measured by head circumference (HC) or occipitofrontal circumference (OFC).

Reliable assessment of intracranial brain volume.

Often leads to cognitive and/or neurologic issues:
- Primary due to abnormal development (often with a genetic etiology).
- Secondary due to arrest or destruction of normally-forming brain tissue (by infection, vascular disruption).

Difficult birth defect to monitor because of inconsistent definition and use of terminology.

SOURCE: THE CENTERS FOR DISEASE CONTROL AND PREVENTION
A Multiple contractures with knee dislocation

B Multiple contractures including right talipes equinovarus
CDC's Response to Zika
INTERIM GUIDANCE
Evaluation and testing of infants with possible congenital Zika virus infection

Mother with laboratory evidence of Zika virus infection during pregnancy*

Perform a comprehensive physical exam on infant, head ultrasound, standard newborn hearing assessment and infant Zika virus laboratory testing

Infant with findings consistent with congenital Zika virus syndrome

Initial evaluation

Infant with laboratory confirmed or probable congenital Zika virus infection

Outpatient management and follow-up

Infant negative for congenital Zika virus infection

Continue to evaluate for other causes of congenital anomalies

Infant without findings consistent with congenital Zika virus syndrome

Infant with laboratory confirmed or probable congenital Zika virus infection

Routine newborn care; additionally, perform an ABR and ophthalmology exam within one month of life

Routine care

Infant negative for congenital Zika virus infection

Outpatient management and follow-up

*Laboratory evidence of maternal Zika virus infection includes: (1) Zika virus RNA detected by real-time reverse transcription-polymerase chain reaction (rRT-PCR) in any clinical specimen; or (2) positive Zika virus immunoglobulin M (IgM) with confirmatory neutralizing antibody titers. Mother's should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or IgM within 2-12 weeks of exposure or symptom onset. Due to the decline in IgM antibody and viral RNA levels over time, negative maternal testing 12 weeks after exposure does not rule out maternal infection. Abbreviation: ABR = auditory brainstem response.

More information on the evaluation, management, and follow-up of infants with possible congenital Zika virus infection is available at www.cdc.gov/zika/hc-providers/infants-children.html.
Initial Evaluation
Infants with abnormalities consistent with congenital Zika syndrome born to a mother with lab evidence of Zika

• Before hospital discharge:
  ✓ Routine newborn care: physical exam, including occipitofrontal (head) circumference, weight, length, a neurologic exam, and universal hearing screen
  ✓ Head ultrasound
  ✓ Testing for congenital Zika virus infection
  ✓ Complete blood count, metabolic panel and liver enzyme testing
  ✓ Consult with multiple subspecialists
  ✓ Referral for comprehensive eye exam by an ophthalmologist
  ✓ Referral for auditory brainstem response (ABR) hearing evaluation
  ✓ Consider advanced cranial imaging (e.g., MRI)
  ✓ Consider transfer to hospital with specialty care

• Refer for a comprehensive ophthalmologic exam and evaluation of hearing by ABR testing before 1 month of age

https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
## Outpatient Management Checklist

**Row 1:**
- Infant with abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection:
  - 2 weeks: Thyroid screen (TSH & T4)
  - 1 month: Neuro exam
  - 2 months: Neuro exam
  - 3 months: Thyroid screen (TSH & T4) and Ophthalmology exam
  - 4-6 months: Repeat audiology evaluation (ABR)
  - 9 months: Repeat audiology evaluation (ABR)
  - 12 months: Repeat audiology evaluation (ABR)

  - Routine preventive health care including monitoring of feeding and growth
  - Routine and congenital infection-specific anticipatory guidance
  - Referral to specialists, including evaluation of other causes of congenital anomalies as needed
  - Referral to early intervention services
  - (See Page 3, Checklist 2)

**Row 2:**
- Infant with abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection:
  - 2 weeks: Ophthalmology exam
  - 1 month: ABR
  - 2 months: ABR
  - 3 months: ABR
  - 4-6 months: ABR
  - 9 months: ABR
  - 12 months: ABR

  - Continue to evaluate for other causes of congenital anomalies
  - Further management as clinically indicated

**Row 3:**
- Infant with no abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection:
  - 2 weeks: Monitoring of growth parameters (HC, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits (See Page 3, Checklist 3)
  - 1 month: Monitoring of growth parameters (HC, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits

**Row 4:**
- Infant with no abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection:
  - 2 weeks: Monitoring of growth parameters (HC, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits

**Abbreviations:**
- rRT-PCR = real-time reverse transcription-polymerase chain reaction; IgM = Immunoglobulin M; CBC = complete blood count; LFTs = liver function tests; PE = physical examination; US = ultrasound; ABR = auditory brainstem response; CT = computed tomography; MRI = magnetic resonance imaging; neuro = neurologic; HC = Head (acuplacement) circumference
- Laboratory evidence of Zika virus infection includes: (1) Zika virus RNA detected by real-time reverse transcription-polymerase chain reaction (rRT-PCR) in any clinical specimen; or (2) positive Zika virus IgM.
- Confirmatory neutralizing antibody titers are needed in addition to IgM for maternal Zika infection. Cord blood and testing of the placenta not recommended for infant testing for Zika virus.
- Outpatient management checklist for infants born to a woman with laboratory evidence of confirmed or possible Zika virus infection.
- Findings consistent with congenital Zika virus syndrome may include microcephaly, intracranial calcifications, or other brain or eye abnormalities.
- Mothers who traveled to or resided in an area of active Zika transmission or who had unprotected sex with a partner who had traveled to or resided in an area with active transmission should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or IgM within 2-12 weeks of exposure or symptom onset. Because of the decline in IgM antibody and viral RNA levels over time, negative maternal testing 12 weeks after exposure or symptom onset does not rule out maternal infection.
- Infant testing is recommended within the first two days after birth; if testing is performed later, it can be difficult to distinguish congenital infection from perinatally or postnatally acquired infection.
Outpatient Management

Infants with abnormalities consistent with congenital Zika syndrome and lab evidence of Zika

- Establish a medical home to facilitate coordination of care
- Provide routine preventive pediatric health care, including immunizations and monthly primary care visits for at least the first 6 months
- Conduct developmental monitoring at each routine visit
- Complete neurologic exam at age 1 and 2 months, then as needed
- Refer patients to developmental specialist and early intervention services
- Repeat ophthalmology exam with retinal assessment at 3 months
- Repeat ABR hearing assessment at age 4–6 months
- Conduct thyroid screening at age 2 weeks and age 3 months
- Provide family support services
- Provide appropriate referrals

Consult with Specialists

Infants with abnormalities consistent with congenital Zika syndrome and lab evidence of Zika

- **Neurologist** to determine appropriate neuroimaging and additional evaluation
- **Infectious disease specialist** to evaluate other congenital infections
- **Ophthalmologist** to examine the eye and evaluate for possible cortical visual impairment prior to discharge from hospital or within 1 month of birth
- **Endocrinologist** to evaluate for hypothalamic or pituitary dysfunction
- **Clinical geneticist** to evaluate for other causes of microcephaly or other anomalies if present
Consult with Specialists

Infants with abnormalities consistent with congenital Zika syndrome and lab evidence of Zika

Consultation with the following should also be considered:

- Orthopedist, physiatrist, and physical therapist to manage hypertonia, club foot, or arthrogrypotic-like conditions
- Pulmonologist or otolaryngologist to consult about aspiration
- Lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist to manage feeding issues
Initial Evaluation & Outpatient Management

Infants with lab evidence of Zika and without abnormalities consistent with congenital Zika syndrome

- Before hospital discharge infants should receive
  - Routine care including monitoring of occipitofrontal circumference, length, and weight
- Outpatient management includes routine follow up and
  - Establish medical home
  - Perform vision screening at every well child visit
  - Evaluate hearing: consider repeat ABR testing at 4–6 months or perform behavioral diagnostic testing at age 9 months if ABR is not done at 4-6 months
  - Provide referrals: Any children with identified or suspected delays should be referred to a developmental specialist or early intervention programs
  - Provide family support services, such as counseling, as needed

New Information

Out of 1297 completed pregnancies in US Zika Registry:

- Rate of brain anomalies increased 30x with maternal lab evidence of Zika
- Rate of brain anomalies 5% if mother’s infection unconfirmed by lab
- Rate of brain anomalies 10% if mother has lab confirmation of Zika
- Rate of brain anomalies 15% with first trimester Zika infection confirmed
- Limited reports that CSF PCR and or IgM was only positive specimen in some babies

- 84% of brain anomalies included microcephaly, calcifications, cortical volume loss
- 88% of infants with brain anomaly had macular retinal and optic nerve scarring, and 12% had congenital glaucoma

- [https://www.cdc.gov/mmwr/volumes/66/wr/mm6613e1.htm?s_cid=mm6613e1_e](https://www.cdc.gov/mmwr/volumes/66/wr/mm6613e1.htm?s_cid=mm6613e1_e)
January 1, 2015 – March 15, 2017

• **US States**
  • 5,139 Zika virus disease cases reported
    • 4,842 cases in travelers returning from affected areas
    • 222 cases acquired through presumed local mosquito-borne transmission in Florida (N=216) and Texas (N=6)
    • 75 cases acquired through other routes, including sexual transmission (N=45), congenital infection (N=28), laboratory transmission (N=1), and person-to-person through an unknown route (N=1)

• **US Territories**
  • 38,188 Zika virus disease cases reported
    • 147 cases in travelers returning from affected areas
    • 38,041 cases acquired through presumed local mosquito-borne transmission

• Completed pregnancies as of 2/22/17 in the US and District of Columbia: **1143**.
• Live-born infants with birth defects: **47**
• Fetal losses with birth defects: **5**
Zika, for further discussion:

1. why does the African lineage kill placental tissue and the Asian strain spare it to wreak neurological havoc?
2. why WHO insists that that the 90% of expected babies without CZS in Brazil for this year may have been misdiagnosed and had Chikunguna, whereas Yale is saying that previous infection with dengue sets up for more severe Zika, just like a second case of Dengue is more likely to be severe and hemorrhagic dengue.

3. Zika politics:
   1. need for Dengue control in Brazil documented >> 30 years ago, and not a single modification was made in that interval
   2. there was a lot of the PAHO and WHO understating this to try to spare the 2016 Olympics.
   3. February 2016 Argentina Physicians said that it was the insect spraying with pyriproxifene plus Zika making microcephaly, not Zika alone
   4. God bless Pope Francis for saying that contraception might be ok until the epidemic is over.
   5. control efforts with genetically modified mosquitoes and mosquitoes infected with Wolbachia bacteria, lethal to
   6. Erroneous Zika false positives with Labcorps
Clinical guidance and other resources:

US Zika pregnancy registry for mothers and babies: follows birth, 2m, 6m, 12m exams and ABR: https://www.cdc.gov/zika/reporting/registry.html

- Email: ZikaMCH@cdc.gov
- Zika Pregnancy Hotline: 770-488-7100, CDC-INFO: (800-232-4636)
- ArboNET Surveillance of Children with Postnatal Zika
- US Zika-Related Birth Defects Surveillance US Zika-Related Birth Defects Surveillance
- WHO: Psychosocial Support for Pregnant Women and for Families with Microcephaly and other Neurological Complications in the Context of Zika Virus - Interim Guidance for Health Care Providers
- aap.org: 10 tips for pediatricians, advice for families videos
Zika References:

• Moore CA, Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr 2016.
• Schuler-Faccini L, Possible association between Zika virus infection and microcephaly—Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59–62.
4) Updated Recommendations for Testing of Infant Specimens at Time of Birth

CDC has updated its website with more detailed instructions on the collection and submission of specimens from infants born to mothers who have tested positive for possible Zika or unspecified flavivirus exposure.

- Do not ship any specimens directly to CDC; all specimens should be sent to the DHMH Laboratories Administration.
- DHMH will obtain testing pre-approval from CDC for you.
- When submitting multiple tissue specimens, each individual specimen should be clearly labeled as to its source.
- Disregard the CDC guidance on the CDC website to transfer infant cord blood/serum to new containers; continue to submit these specimens in the original vacutainers in which they were collected and DHMH will process as appropriate.
Landscape

The drops pelting the puddle look like a million mosquitoes jumping up and down, but this is because they are on my mind and I was born with the luxury to think of them and the malaria they carry as but a metaphor or simile and not as something that could kill me.”