Zika Virus: The Pediatric Perspective

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Pediatric Infectious Diseases
Pediatric Specialists of Virginia
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Objectives

1. Understand congenital Zika virus and why evaluating for congenital Zika virus is important

2. Who?, what?, when?, where? of Zika testing in babies

3. Be aware of your responsibility to communicate with health department about possible Zika virus

4. Know how to complete Zika Infant Registry forms at birth, 2, 6, 12 months of age

5. Be aware of late manifestations of congenital Zika virus
   a. Late Microcephaly
   b. Developmental Delays in all realms
   c. Seizure risk including infantile spasms
   d. Spasticity, MR, CP, feeding disorders, speech disorders, hearing and visual defects
Congenital Zika Virus Infection
Congenital Zika Virus

Zika Virus and Birth Defects — Reviewing the Evidence for Causality
Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H., Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities
Fetal Brain Disruption Sequence

- First described in 1984 but noted in earlier literature
- Brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae and neurologic impairment
- Images below from 1990 series; phenotype appears to be present in some affected babies in Brazil (2015—present)

Moore et al., J Peds, 1990
Adverse outcomes in Zika infected babies to date

- Eye abnormalities
- Hearing impairment
- Seizures
- Swallowing impairment
- Hypertonicity and posturing
- Contractures including club foot and arthrogryposis
- Severe irritability
- Developmental Delay
- Growth abnormalities including IUGR and disproportionate growth
Congenital Zika Syndrome

1. Severe microcephaly with partially collapsed skull
2. Thin cerebral cortices with subcortical calcifications
3. Macular scarring and focal pigmentary retinal mottling
4. Congenital contractures
5. Marked early hypertonia and symptoms of extrapyramidal involvement
Term infant born to mother who spent first 4 months of pregnancy in Latin America

• Family did not admit travel until microcephaly diagnosed

• Mother denied Zika symptoms

Had prenatal US near term that showed all growth parameters were “low”
Multiple parenchymal calcifications on HCT and HUS
Polymicrogyria, primarily bi-frontal
Septation in frontal horn
Multiple punctate calcifications, mostly at grey/white matter junction
Normally formed corpus callosum
At 2 weeks, 2mo, 4 months

Baby A had overt hypertonia and microcephaly by 2 weeks life

Worsening spasticity over time, fisted hands
No hearing defects, ?astigmatism in future
Lost to follow up
Which Infants to Test?

1. Test Every Baby Born to Mother with Positive or Equivocal Tests

2. Test Every Baby with concerns for Congenital Zika Virus Syndrome at birth:
   - Microcephaly (<3%ile) for age
   - Intracranial Calcifications at birth
   - Structural Brain or Eye Abnormalities
   - Other congenital CNS related abnormalities

REGARDLESS of Mom’s Test Results

Test within 2 days of life
Case definition of microcephaly

- Head circumference (HC) at birth is less than the 3rd percentile for gestational age and sex.
- If HC at birth is not available, HC less than the 3rd percentile for age and sex within the first 6 weeks of life.
Measuring head circumference

- 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 within 24 hours after birth.

» Commonly-used birth head circumference reference charts by age and sex based on measurements taken before 24 hours of age.

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

Outpatient management and follow-up

Infant negative for congenital Zika virus infection

Routine care
Specialist Evaluation of Congenital Zika

**Peds Neurologist** - determination of appropriate neuroimaging and evaluation

**Peds Infectious disease specialist** - diagnostic evaluation of other congenital infections

**Peds Ophthalmologist** - comprehensive eye exam and evaluation for possible cortical visual impairment prior to discharge from hospital or within 1 month of birth

**Peds Endocrinologist** - evaluation for hypothalamic or pituitary dysfunction

**Clinical Geneticist** - evaluate for other causes of microcephaly or other anomalies if present

May need: Pediatric Ortho, PM&R, PT, OT, Speech, Pulmonary, ENT, GI, nutritionist
<table>
<thead>
<tr>
<th>Infant with abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection</th>
<th>2 weeks</th>
<th>1 mo.</th>
<th>2 mo.</th>
<th>3 mo.</th>
<th>4-6 mo.</th>
<th>9 mo.</th>
<th>12 mo.</th>
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<td>Repeat audiology evaluation (ABR)</td>
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- Routine preventive health care including monitoring of feeding, growth, and development
- Routine and congenital infection-specific anticipatory guidance
- Referral to specialists as needed
- Referral to early intervention services

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<thead>
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<th>Infant with abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection</th>
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<th>1 mo.</th>
<th>2 mo.</th>
<th>3 mo.</th>
<th>4-6 mo.</th>
<th>9 mo.</th>
<th>12 mo.</th>
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</table>
| ☐ Evaluate for other causes of congenital anomalies
| ☐ Further management as clinically indicated

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<th>9 mo.</th>
<th>12 mo.</th>
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| ☐ Ophthalmology exam
| ☐ ABR
| Consider repeat ABR
| ☐ Developmental screening
| ☐ Behavioral audiology evaluation if ABR was not done at 4-6 mo |
| ☐ Monitoring of growth parameters (Head circumference, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits

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| ☐ Monitoring of growth parameters (Head circumference, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits

INITIAL EVALUATION AND OUTPATIENT MANAGEMENT
DURING THE FIRST 12 MONTHS OF LIFE FOR INFANTS WITH POSSIBLE CONGENITAL ZIKA VIRUS INFECTION

Follow management and follow-up recommendations indicated in Outpatient Management Checklist

CDC's Response to Zika

Download at:
**TABLE 1**

<table>
<thead>
<tr>
<th>Infant test results*</th>
<th>Interpretation</th>
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<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>
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<td>Negative</td>
<td>Negative</td>
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</tbody>
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**Interpretation of results of laboratory testing of infant’s blood, urine and/or cerebrospinal fluid for evidence of congenital Zika virus infection**

**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).

**CHECKLIST 1**

Initial clinical evaluation & management of infants with laboratory evidence of Zika virus infection and abnormalities consistent with congenital Zika syndrome*

**Consultation with:**
- Neurologist for determination of appropriate neuroimaging and additional evaluation.
- Infectious disease specialist for diagnostic evaluation of other congenital infections (e.g., syphilis, toxoplasmosis, rubella, cytomegalovirus infection, syphilitic congenital infection, and herpes simplex virus infection).
- Ophthalmologist for comprehensive eye exam and evaluation for possible cortical visual impairment prior to discharge from hospital or within 1 month of birth.
- Endocrinologist for evaluation for hypothalamic or pituitary dysfunction.
- Geneticist to evaluate for other causes of microcephaly or other anomalies if present.

**Consider consultation with:**
- Orthopedist, physical therapist, and physical therapist for the management of hypertonia, club foot or arthrogryposis-like conditions.
- Pulmonologist or otorhinolaryngologist for concerns about aspiration.
- Lactation specialist, nutritionist, dietitian, or speech or occupational therapist for the management of feeding issues.
- Perform ABR to assess hearing.
- Perform complete blood count and metabolic panel, including liver function tests.
- Provide family and supportive services.

**CHECKLIST 2**

Outpatient management of infants with laboratory evidence of Zika virus infection and abnormalities consistent with congenital Zika syndrome*

- A medical home should be established, and visits with primary care provider should occur monthly for at least the first 6 months of life.
- Fellow growth parameters, monitor development, encourage parents and other caregivers to monitor child’s development, provide routine immunizations and anticipatory guidance, psychosocial support, and to ensure infants receive necessary testing and consultations.
- Neurologic examination by the primary care provider at 1 and 2 months of age. Refer to neurology for any abnormalities, or for any parental or provider concerns.
- Refer to developmental specialist and early intervention services.
- Repeat a comprehensive ophthalmologic exam at 6 months of age, and refer to ophthalmology for any abnormal findings, or for any parental or provider concerns.
- Repeat ABR testing at 4-6 months of age, and follow up on any abnormal findings, or for any parental or provider concerns.
- Repeat testing for hypothyroidism (i.e., TSH, total T4 and estimated free T4) at 2 weeks and 3 months of age, even if the initial testing was normal. Refer to endocrinology for any abnormal findings.
- Provide family and supportive services.

**CHECKLIST 3**

Outpatient management of infants with laboratory evidence of Zika virus infection, but without abnormalities consistent with congenital Zika syndrome*

- A medical home should be established.
- I f follow growth parameters, perform developmental monitoring at each well-child visit and encourage parents and other caregivers to monitor child’s development.
- Emphasize anticipatory guidance for families regarding developmental milestones, feeding and growth, sleep and irritability, and abnormal movements.
- Use a standardized, validated developmental screening tool at 9 months as currently recommended, or earlier for any parental or provider concerns.
- Referral to ophthalmology for comprehensive eye exam within one month of birth. Perform visual screening and assess visual acuity at every well child visit, and refer to ophthalmology for any abnormal findings, or for any parental or provider concerns.
- Perform ABR within one month of birth. Perform behavioral diagnostic testing at 9 months of age, or consider repeat ABR at 4-6 months. Refer to audiology for any abnormal findings, or for any parental or provider concerns.
- Provide family and supportive services.
Infant’s State/Territory ID ______________________ Registry ID ____________
Mother’s State/Territory ID ______________________

U.S. Zika Pregnancy Registry
Infant Follow-Up Form

These data are considered confidential and will be stored in a secure database at the Centers for Disease Control and Prevention.

Please return completed form via SAMS or secure FTP—request access from ZIKApregnancy@cdc.gov
The form can also be sent by encrypted email to this address or by secure fax to 404-718-1013 or 404-718-2200

<table>
<thead>
<tr>
<th>Infant follow up:</th>
<th>2 months</th>
<th>6 months</th>
<th>12 months</th>
<th>____ months</th>
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<thead>
<tr>
<th>IFU.1. State/Territory reporting</th>
<th>Select State</th>
<th>IFU.2. Date of infant examination</th>
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<tbody>
<tr>
<td>[ ] No</td>
<td>[ ] Yes</td>
<td>________________</td>
<td>______</td>
</tr>
<tr>
<td>IFU.7. Infant Death:</td>
<td>IFU.8. If yes, cause of death:</td>
<td>IFU.9. If yes, Date [ ] or Age at death [ ]</td>
<td>Unknown</td>
</tr>
<tr>
<td>[ ] No</td>
<td>[ ] Yes</td>
<td>________________</td>
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</table>

IFU.10. Weight: _______ grams or ______ lbs ______ oz
IFU.11. Length: ______ cm or ______ in
IFU.12. Head circumference: ______ cm or ______ in
IFU.13. Infant findings for corrected age at examination: (For infants born preterm, please account for corrected age: chronological age minus weeks born before 40 weeks’ gestation)

Check all that apply
Estimated Rate of Birth Defects

• At least 10% of lab confirmed pregnancies resulted in birth defects in US

• Higher in first trimester but no trimester spared

• Late manifestations in babies with normal evaluations, HC at birth
Figure 2. Pregnancy and Infant Outcomes According to the Week of Gestation at the Time of ZIKV Infection.

Adverse outcomes included 9 cases of fetal death in 125 pregnancies (7.2%) and 49 abnormal clinical findings, imaging findings, or both during the newborn period in 117 infants (42%) born from 116 pregnancies. Adverse outcomes occurred in women who were infected during the period from 6 to 39 weeks of gestation. Abnormalities are detailed in Table S2 in the Supplementary Appendix.
Putting CDC and VDH Guidance into Action
Women’s healthcare needs are different than a man’s. Our collaborative interdisciplinary team includes board-certified specialists in the areas most important to women: primary care, obstetrics and gynecology, breast care and cardiology. Our woman-centric care means our physicians and staff are especially attuned to these areas of key health for the adult female. We offer women 18 and older a lifetime of access to state-of-the-art, high-quality clinical care.

Learn more about the Inova Women’s Comprehensive Health Center: [www.inova.org/healthwoman](http://www.inova.org/healthwoman)
Zika Virus

The Centers for Disease Control has confirmed test results showing Zika virus present in the blood of a "non-traveler" in the continental United States. The CDC confirmed this is the first U.S. Zika case in someone who had not traveled abroad in the current outbreak, and was likely transmitted sexually, rather than by a mosquito. Based on this information, the CDC will provide guidance on sexual transmission of the virus. Cases of Zika virus have been reported in returning travelers in other states, including Virginia. The number of Zika cases among travelers visiting or returning to the United States will likely increase, and these cases could result in the local spread of the virus in the U.S. Even though it is not mosquito season in Virginia, it is important to be aware of Zika virus, including its potential impact to pregnant women and their babies.

Algorithm for VDH Testing (updated 11.8.16)

WUSA-9 Interview: FDA Regulations for Screening Blood for Zika Virus (9/26/16) new!

Inova Zika Procedures

- Zika Virus Evaluation of Pregnant Women and Their Babies (updated 8.30.16) new!
- Screening Patients for Zika Virus in Physician Offices (updated 8.9.16)
- Long Term Evaluation of Babies Born to Mothers with Zika Virus (updated 8.30.16) new!

Zika Testing Procedures: Click here for steps necessary for sample submission through Inova facilities. (updated 8.22.16)

- Inova Patient Service Locations for Zika Specimen Collection
Prior to Delivery (OB Nurse and OB Physician To Perform)

1. Every pregnant woman should be screened for Zika virus by asking:

<table>
<thead>
<tr>
<th>Risk Factor Screening Questions</th>
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<tbody>
<tr>
<td>1) Have you traveled to a Zika-affected area within the past 12 weeks?</td>
</tr>
<tr>
<td>2) Have you had possible sexual exposure to Zika virus within the last 12 weeks?</td>
</tr>
<tr>
<td>3) Do you have ≥ 2 symptoms* of Zika and had mosquito bite(s) in the 2 weeks before symptom onset?</td>
</tr>
</tbody>
</table>

*Symptoms of Zika:
- Fever
- Rash
- Arthralgia (joint pain)
- Conjunctivitis
- Pregnancy complication (fetal loss, fetus or neonate with congenital microcephaly, intracranial calcifications, other structural brain or eye abnormality, or other congenital central nervous system related abnormality)
2. Any woman with any of the 3 above risk factors should have been tested by OB for Zika during pregnancy
   a. Has the woman had testing for Zika?
      i. Yes: what is the mother’s result?
         1. **Negative**: If baby has not been diagnosed with microcephaly, intracranial calcifications, brain or eye abnormality or other CNS-related abnormality (including by fetal ultrasound), then baby warrants only routine infant care
         2. **Positive, Presumptive Positive, Equivocal or “Possible Flavivirus Identified” Test Results**: Baby must be tested for Zika virus
         3. **I don’t know the results**: Call the Department of Health in county where testing sent for her results
         4. **Mother’s test results are pending**
            a. **Healthy Infant**: Obtain samples for Zika testing.
               i. High suspicion of Zika in mother – Forward specimens to DCLS for testing
               ii. Low suspicion of Zika in mother – Forward specimens to DCLS.
                  (Note: Specimens will be held pending the results from the mother.)
      ii. **No**: Mother was not tested for Zika but SHOULD have been tested
         1. Request/Discuss Zika testing for the mother via the health department
         2. Evaluate baby as outlined in #4 (Mother’s test results are pending) above
      iii. **No**: Mother was not tested for Zika and doesn’t fit any category for risk or testing
          1. Standard care for infant and mother
3. Any infant with signs of congenital Zika infection should be tested for Zika.
   a. Signs of congenital Zika infection include:
      1. Microcephaly (<3rd percentile for sex and gestational age, optimally measured 24-36 hours after birth)
      2. Intracranial calcifications
      3. Structural brain or eye abnormality
      4. Other congenital central nervous system related abnormality
For babies AT RISK FOR Zika Virus who require testing for Zika virus, 4 samples are required and should be collected at birth.

1. Blood for Zika RT-PCR and IgM ELISA
   a. At least 1 gold top tube filled to top (2ml) whole blood from blood in serum separator tube (tiger top or gold top) spun down and separated to collect serum

2. Urine for Zika RT-PCR
   a. 5-10mL collected in urine specimen container
   b. Urine specimen may be bagged specimen

3. Fixed (Formalin) Placenta Tissue and Fetal Membranes (for histopath and placenta Zika PCR)
   a. At least three (3) full thickness (0.5-1.0 cm x 3-4cm in depth) pieces from middle third of placental disk
   b. One (1) piece from the placental disk margin
   c. One (1) 5x12 cm strip of fetal membranes
   d. Include samples of pathogenic lesions when possible

4. Umbilical Cord
   a. At least four (4) 2.5cm segments of cord

Additionally, if baby requires testing of CSF for other clinical purposes then a CSF sample is requested by CDC for Zika Virus testing

1. Zika Virus RT-PCR (from CSF)
   a. At least 1.0 mL of CSF in a sterile tube

See [DCLS/VA department of health website for laboratory specimen requirements](https://www.dchd.virginia.gov/laboratorystandards/)
See [CDC guidance for fetal tissue specimen requirements](https://www.cdc.gov/zika/health-care-providers/lab-testing.html)
OB clinician must complete pathology requisition for placental testing
Zika Virus

Public health guidance on Zika virus is updated as more information becomes known.

Zika is mainly spread through the bite of an infected Aedes mosquito. Zika also can be spread from a pregnant woman to her fetus, through sexual contact and possibly through blood transfusion.

Take steps to prevent mosquito bites to lower your chance of infection. If you think you may have Zika, contact your health care provider.

Outreach Materials
Fairfax businesses can request printed materials for employees and customers.

Clinical Testing for Zika
Health care providers, complete the Zika testing request form.

Zika Virus Disease and Prevention Presentation Slides

Zika Pregnancy Registry
- About the Zika Pregnancy Registry
- Maternal Health History Form
- Neonate Assessment at Delivery Form
- Infant Follow-Up Form

*Contact the Communicable Disease/Epidemiology Unit for the VA Zika ID.
Fairfax County Health Dept. Zika Testing Request

- Complete and submit the Zika Testing Request. Please fill in all required fields.
- The Communicable Disease/Epidemiology Unit will respond to your request regarding testing eligibility determination and next steps by close of the next business day. Please know that this is a request for testing and that testing eligibility will have to be determined. Approval by the Fairfax County Health Department’s Communicable Disease Epidemiology Unit must be obtained for Zika Virus testing. Any specimens submitted to the Health Department without prior approval or necessary paperwork will not be tested.
- If you experience any problems requesting Zika testing or have additional questions, please call the Communicable Disease/Epidemiology Unit at 703-246-2433.

Provider Information

Provider Last Name: [ ]
Provider First Name: [ ]
Address: [ ]
Email: [ ]
Phone: [ ]
Fax: [ ]

Patient Information

Last Name: [ ]
First Name: [ ]
Patient Address: [ ]
Street: [ ]
City: [ ]
State: [VA]
Zip code: [ ]
Phone: [ ]
Alt Phone: [ ]
Date of Birth: [ ]
Male: [ ]
Female: [ ]
EPIC communicable disease screening

Went LIVE August 2016

Updated travel notice areas:
Miami, Fl and Brownsville, TX

Zika screening for all pregnant women at registration/intake (inpatient and outpatient)
OB Grease Board
ORDER SETS for L&D and for Post-partum Baby Care
Late Manifestations
Late Microcephaly with Congenital Zika

- Reports of babies born to mothers with positive or equivocal testing for Zika who have normal exams at birth
- Months later…Baby B
  - Microcephaly
  - Developmental delays
  - Hypertonicity
Right cerebral hemisphere volume loss
Decreased sulcation/lissencephaly in right frontal and parietal lobes
Normal corpus callosum
No abnormal calcifications
Twin Differences
Twin studies are showing differential effects in babies born to Zika infected mothers.
Maternal Test Refusal

• Zika Virus is no longer making the headlines
• Risk of Male to Pregnant Female Transmission
• Testing issues, no lab test provides evidence of past infection
• Pregnancy Counseling vs. Birth Counseling
Zika Vaccine and Treatment

• In Phase 1/2 clinical trials now
• No therapeutics
• No treatment to reverse brain damage in these babies
Completed pregnancies with or without birth defects

1,471

Includes aggregated data reported to the US Zika Pregnancy Registry*

Liveborn infants with birth defects*

64

Includes aggregated data reported to the US Zika Pregnancy Registry*

Pregnancy losses with birth defects**

8

Includes aggregated data reported to the US Zika Pregnancy Registry*

Zika Virus - Protecting Pregnant Women and Babies

44 states reported cases of pregnant women with evidence of Zika in 2016. Most were travel-associated.

About 1 in 10 pregnant women with confirmed Zika had a fetus or baby with birth defects.

Only 1 in 4 babies with possible congenital Zika were reported to have received brain imaging after birth.
Summary

- Zika Virus Causes Birth Defects including Late Effects and Possible Twin Differences
- Testing Pregnant Women at Risk is Important
  - Provide Risk Counseling
- Evaluating and Testing Babies is Imperative
  - Families don’t understand “Equivocal”
- Long-term Monitoring of Babies and Maximizing Neurodevelopmental Outcomes
- Prevention, Protection, possibly Therapeutics