Zika Update: Clinical Laboratory Testing and Care of Infants with Congenital Zika Virus Infection

Clinician Outreach and Communication Activity (COCA) Call

August 23, 2016

Office of Public Health Preparedness and Response
Division of Emergency Operations

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Objectives

At the conclusion of this session, the participant will be able to:

- **Interpret revised testing guidance for newborns with possible congenital Zika virus infection.**
- **Discuss clinical evaluation of infants born to mothers with laboratory evidence of Zika virus infection.**
- **Outline outpatient management of infants with laboratory evidence of congenital Zika virus infection with and without abnormalities consistent with congenital Zika syndrome.**

TODAY'S PRESENTER

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TODAY'S PRESENTER

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Zika Virus

Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016

Sara Oliver, MD, MSPH
Medical Officer

Kate Russell, MD, MPH
Medical Officer

August 23, 2016

Topics to be covered

- **Background on the effects of Zika virus during pregnancy on the infant**
- **Updated recommendations for initial testing of infants born to mothers with laboratory evidence of Zika virus infection**
  - Infant diagnostic testing and interpretation
- **Clinical Evaluation**
  - Initial evaluation of all infants born to mothers with lab evidence of Zika
  - Outpatient management and follow up of infants with lab evidence of Zika

Background

Zika Virus Infection in Pregnant Women

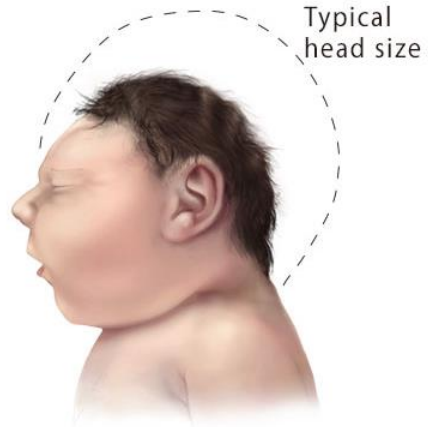
- Pregnant women can be infected:
  - Through the bite of an infected *Ae. aegypti* or *Ae. albopictus* mosquito
  - Through sex with an infected partner
- If infected around conception
  - Zika might present risk to fetus
- If infected during pregnancy
  - Zika can be passed to the fetus during pregnancy or around the time of birth

Brain Abnormalities Associated with Congenital Zika Virus Infection

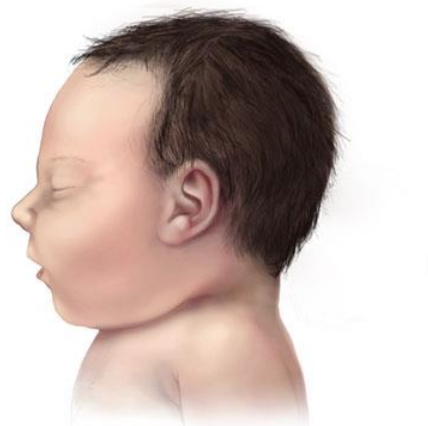
- Microcephaly
- Intracranial calcifications
- Hydrocephalus ex-vacuo
- Hydranencephaly
- Pachygyria, lissencephaly
- Agyria
- Brain atrophy and asymmetry
- Enlargement of posterior fossa
- Ventriculomegaly
- Restricted middle cerebral artery flow
- Abnormally formed or absent structures
  - Corpus callosum
  - Thalami
  - Cerebellar vermis
  - Brainstem

Karwowski MP, Nelson JM, Staples JE, et al. Zika Virus Disease: A CDC Update for Pediatric Health Care Providers. Pediatrics. 2016;137(5):e20160621

Infants with Microcephaly*

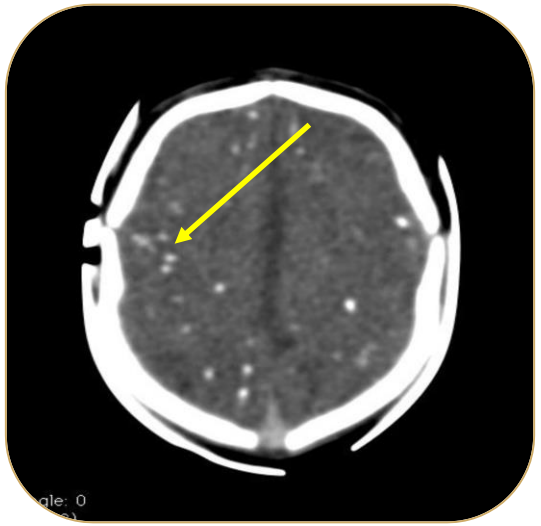


Baby with
Severe Microcephaly

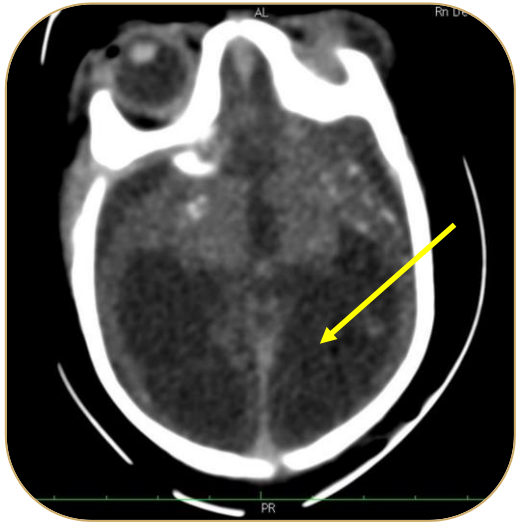


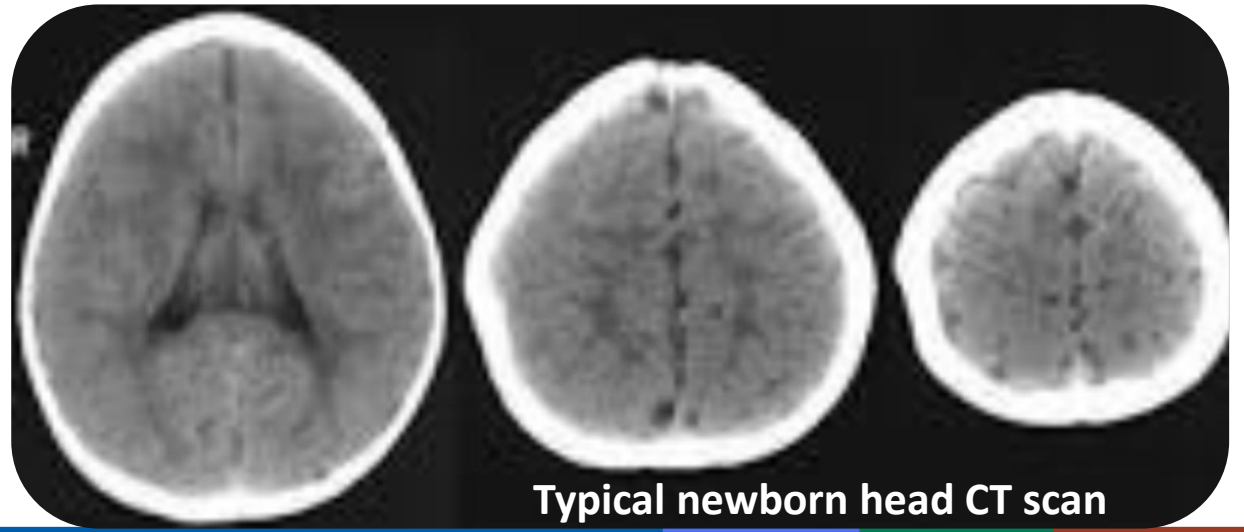
Baby with Typical Head Size

Note scattered intracranial calcifications



Note large ventricles and volume loss





Typical newborn head CT scan

***CT scan images courtesy of Dr. Erin Staples, Division of Vector-Borne Diseases, CDC**

***Not for reproduction or dissemination**

Adverse Outcomes and Zika Virus

- Linked to spontaneous abortion and stillbirth
  - Evidence insufficient to confirm Zika virus as cause
- Other infant outcomes:
  - Eye abnormalities
  - Hearing impairment and loss
  - Limb abnormalities (arthrogryposis, club foot, congenital hip dysplasia)
  - Seizures
  - Swallowing impairment
  - Severe irritability
  - Developmental delay
  - Growth abnormalities

Karwowski MP, Nelson JM, Staples JE, et al. Zika Virus Disease: A CDC Update for Pediatric Health Care Providers. Pediatrics. 2016;137(5):e20160621

What CDC is Doing to Learn More

Collecting data for action

US Zika Pregnancy Registry

Zika Active Pregnancy Surveillance System (Puerto Rico)

Proyecto Vigilancia de Embarazadas con Zika (Colombia)

US Zika Pregnancy Registry (USZPR)

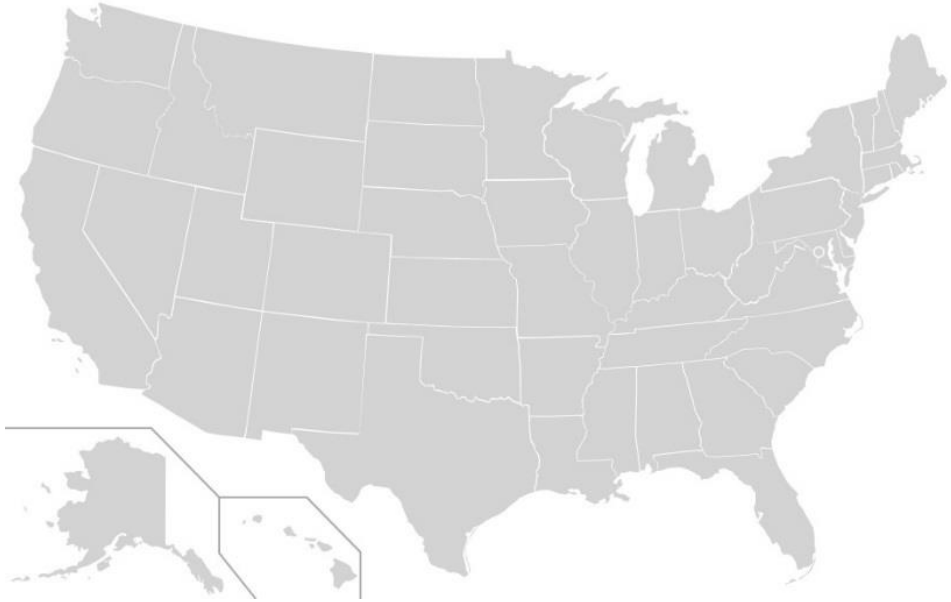
- Involves collection of information on Zika-affected pregnancies and congenitally exposed infants up to 1 year of age
- Allows monitoring for any adverse pregnancy and fetal/neonatal outcomes (e.g., microcephaly)

Zika Active Pregnancy Surveillance System (ZAPSS)

- Similar to USZPR
  - Conducted in Puerto Rico
  - Data collection of congenitally exposed infants extended to 3 years of age

Number of Pregnant Women Who May Be Affected

- Currently there are over 1,000 pregnant women with laboratory evidence of possible Zika virus infection in the United States and U.S. territories



Infant Diagnostic Testing and Interpretation

Challenges with Diagnosis of Congenital Zika Infection

- **Real time reverse–transcription polymerase chain reaction (rRT-PCR):**
  - Positive can confirm congenital Zika virus infection
  - Negative does not exclude infection- little is known about duration of viral shedding in congenital Zika virus infection
- **Immunoglobulin M (IgM)** results difficult to interpret because of false-positive and false-negative results
- **Antibody neutralization testing** cannot distinguish maternal from infant antibodies

Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

- **Testing is recommended for:**
  - Infants born to mothers with laboratory evidence of Zika virus infection*

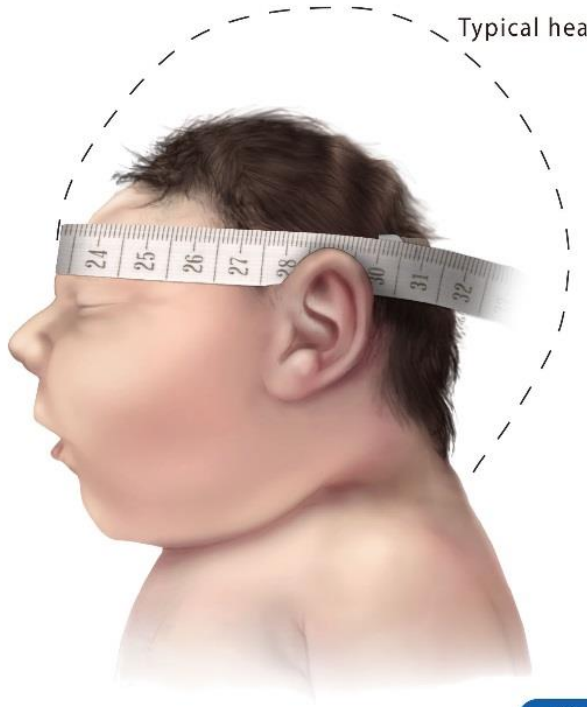
    *Lab evidence of maternal Zika virus infection includes: Zika virus RNA detected by rRT-PCR OR positive Zika virus IgM with confirmatory neutralizing antibody titer

  - Infants with abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link† suggesting possible transmission, regardless of maternal testing results

    † Epidemiologic link includes: Travel to/residence in an area of Zika virus transmission, OR sex with a partner who traveled to/resided in such area

Congenital Zika Syndrome

- Congenital Zika syndrome is a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes:
  - Microcephaly
  - Intracranial calcifications
  - Other brain anomalies
  - Eye anomalies
  - Other findings



Baby with Severe Microcephaly

Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

- Zika virus rRT-PCR should be performed on infant **serum** and **urine**
- Zika virus IgM antibody testing should be performed on infant serum
- If cerebrospinal fluid (CSF) is obtained for other purposes, rRT-PCR testing for Zika virus RNA and Zika virus IgM should be performed
- Lab testing of cord blood specimens is no longer recommended
- Testing should be performed within 2 days after birth
  - If testing is performed later, distinguishing between congenital, perinatal and postnatal infection will be difficult

Interpretation of Infant Zika Virus Testing

Infant test results*		Interpretation
rRT-PCR	IgM	
Positive	Positive or Negative	Confirmed congenital Zika virus infection
Negative	Positive	Probable congenital Zika virus infection[+]
Negative	Negative	Negative for congenital Zika virus infection[+]

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

*Infant serum, urine or cerebrospinal fluid

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

Plaque Reduction Neutralization Test (PRNT)

- PRNT measures virus-specific neutralizing antibodies
  - Used to confirm specificity of IgM antibodies against Zika virus
- PRNT cannot distinguish between maternal and infant antibodies

Infant Plaque Reduction Neutralization Test (PRNT)

Infant initial sample PCR positive

→ No need for additional PRNTs, congenital Zika virus infection confirmed

Infant initial sample PCR negative IgM positive

→ If PRNT not performed on maternal sample, PRNT should be performed on infant sample

→ PRNT should be performed when child is aged 18 months or older to confirm congenital infection

Infant initial sample PCR negative IgM negative

→ PRNT can be performed on child aged 18 months or older if clinical concerns remain

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↓

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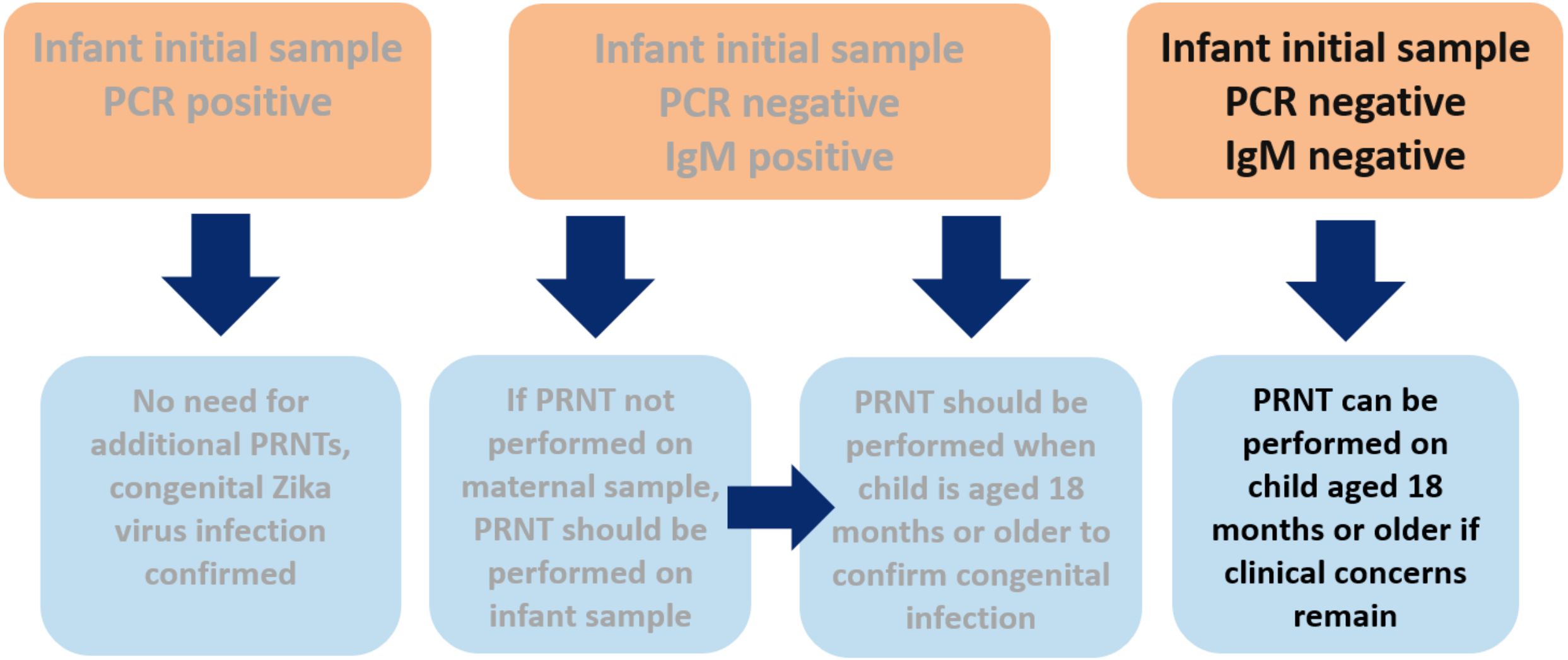
Infant Plaque Reduction Neutralization Test (PRNT)



Plaque Reduction Neutralization Test (PRNT)

- **If PRNT results at 18 months are negative:**
  - Child considered to not have congenital Zika virus infection

- **If PRNT results at 18 months are positive:**
  - Congenital Zika virus infection is presumed
    - Postnatal infection cannot be excluded

Zika Virus Testing of the Placenta

- **Detection of Zika virus RNA in the placenta can confirm maternal infection**
  - Cannot distinguish between maternal and congenital infection
- **Placental testing can be helpful to confirm maternal infection when maternal testing:**
  - Not previously performed
  - Performed beyond 12 weeks after exposure
  - Not definitive (e.g., Flavivirus Not Otherwise Specified)
- **Clinical implications for infant with Zika virus RNA detected in the placenta are unknown, especially if infant testing is negative**

Maternal Testing Not Yet Performed

- **For infants born to mothers with risk factors for Zika virus infection during pregnancy, but maternal testing not performed:**
  - Perform maternal diagnostic testing
  - Consider placental rRT-PCR testing
  - Perform infant testing if abnormalities consistent with congenital Zika syndrome are present
- **If an infant appears clinically well, infant lab testing for Zika virus infection can be deferred until maternal tests are available**
  - If concerns about infant follow-up, testing should be performed before hospital discharge

Evaluation and Management of Infants with Congenital Zika Virus Infection

CDC and AAP Collaboration

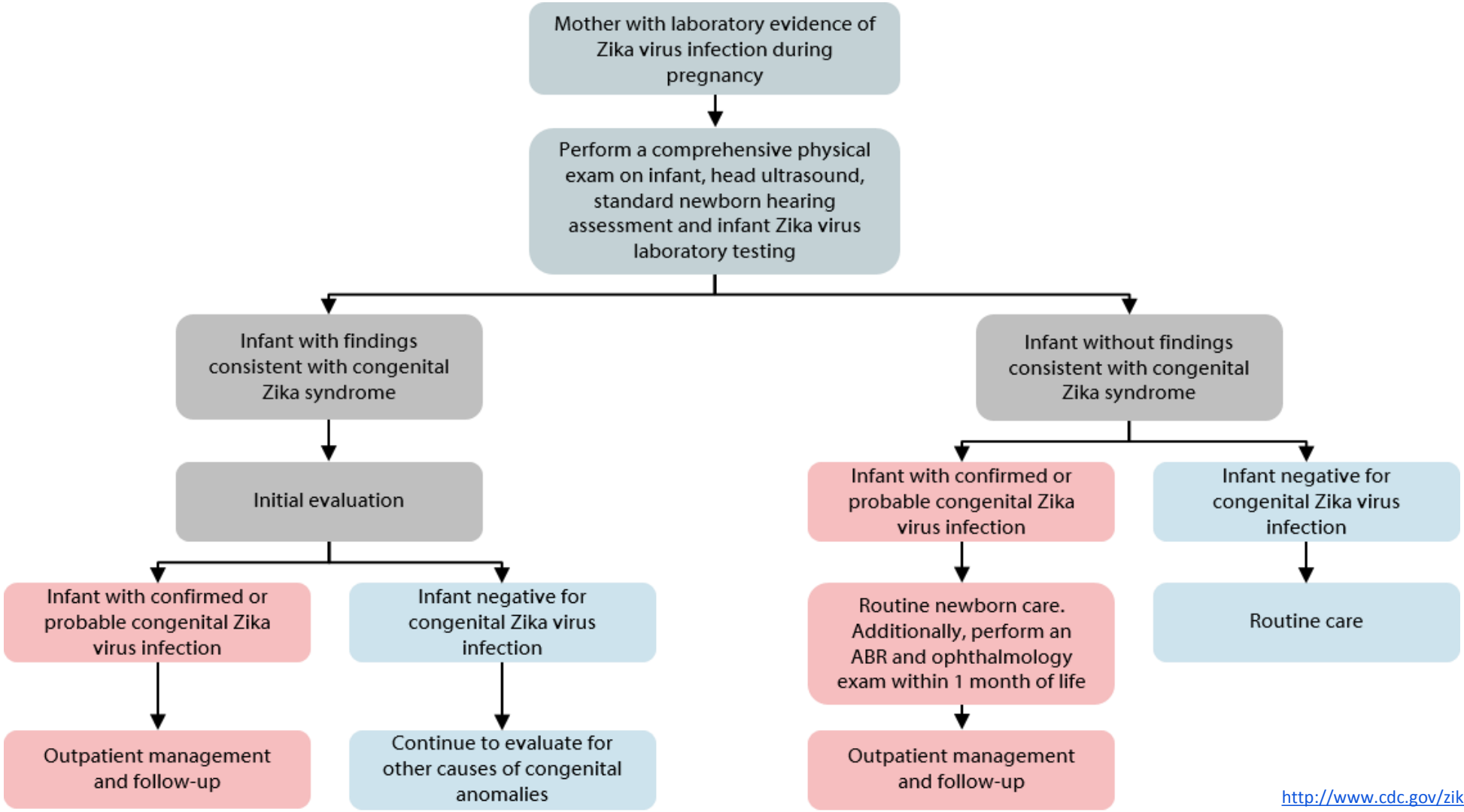
- On July 21–22, CDC sponsored a meeting in collaboration with American Academy of Pediatrics (AAP), entitled "**Clinical Evaluation and Management of Infants with Congenital Zika Virus Infection**" involving:
  - Specialties
    - Audiology, clinical genetics, critical care, developmental and behavioral pediatrics, endocrinology, hospitalist medicine, infectious disease, lactation and infant feeding, maternal-fetal medicine, neonatology, neurology, nutrition, ophthalmology, orthopedics, pediatrics, physical medicine and rehabilitation
  - Principal partners
    - AAP, AAP Puerto Rico chapter, American Academy of Family Physicians, American Congress of Obstetricians and Gynecologists, Association of Maternal and Child Health Programs, Family Voices, March of Dimes, Parent to Parent, and the National Association of Pediatric Nurse Practitioners
  - Other federal agencies
    - Administration for Children and Families, Office of the Assistant Secretary for Preparedness and Response, Maternal & Child Health Bureau of the Health Resources and Services Administration, and National Institute of Child Health and Human Development, National Institutes of Health

Three Areas of Focus

1. Initial evaluation and testing of infants born to mothers with laboratory evidence of possible Zika virus infection during pregnancy
2. Outpatient management and follow-up of infants with laboratory evidence and with findings consistent with congenital Zika syndrome
3. Outpatient management and follow-up of infants with laboratory evidence of congenital Zika virus infection, but without findings consistent with congenital Zika syndrome

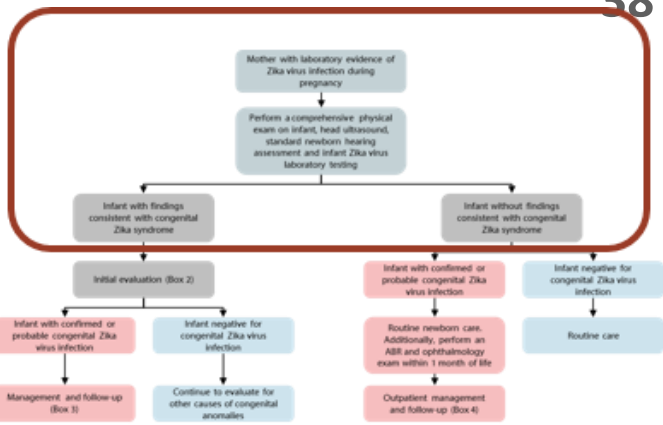
Initial Evaluation

Interim Guidance for Evaluation and Testing: Infants with Possible Congenital Zika Virus Infection



http://www.cdc.gov/zika/pdfs/zika_peds.pdf

Interim Guidance for Evaluation and Testing: 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

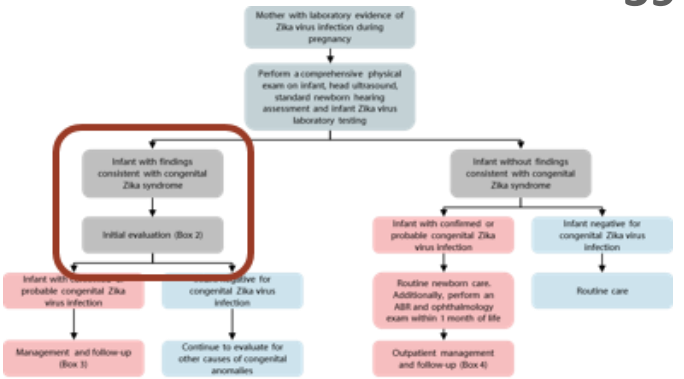
↓

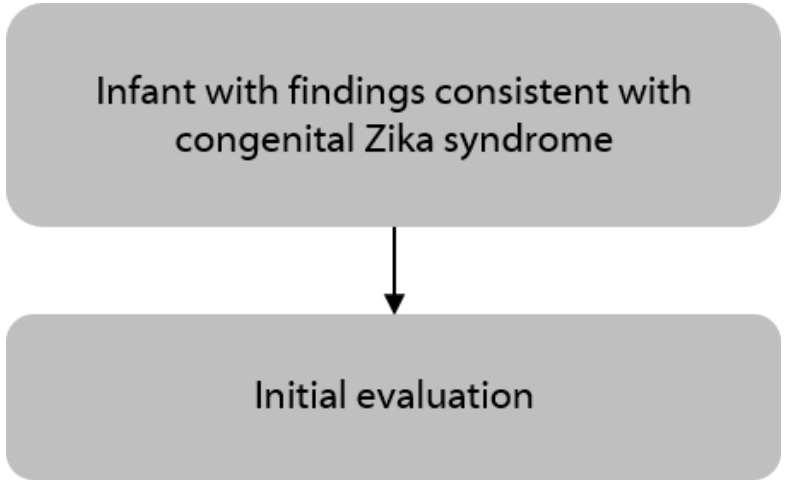
Infant with findings consistent with congenital Zika syndrome

Infant without findings consistent with congenital Zika syndrome

*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 IgM with confirmatory neutralizing antibody titers. Mothers should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or by 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.

Infants with Findings Consistent with Congenital Zika Syndrome

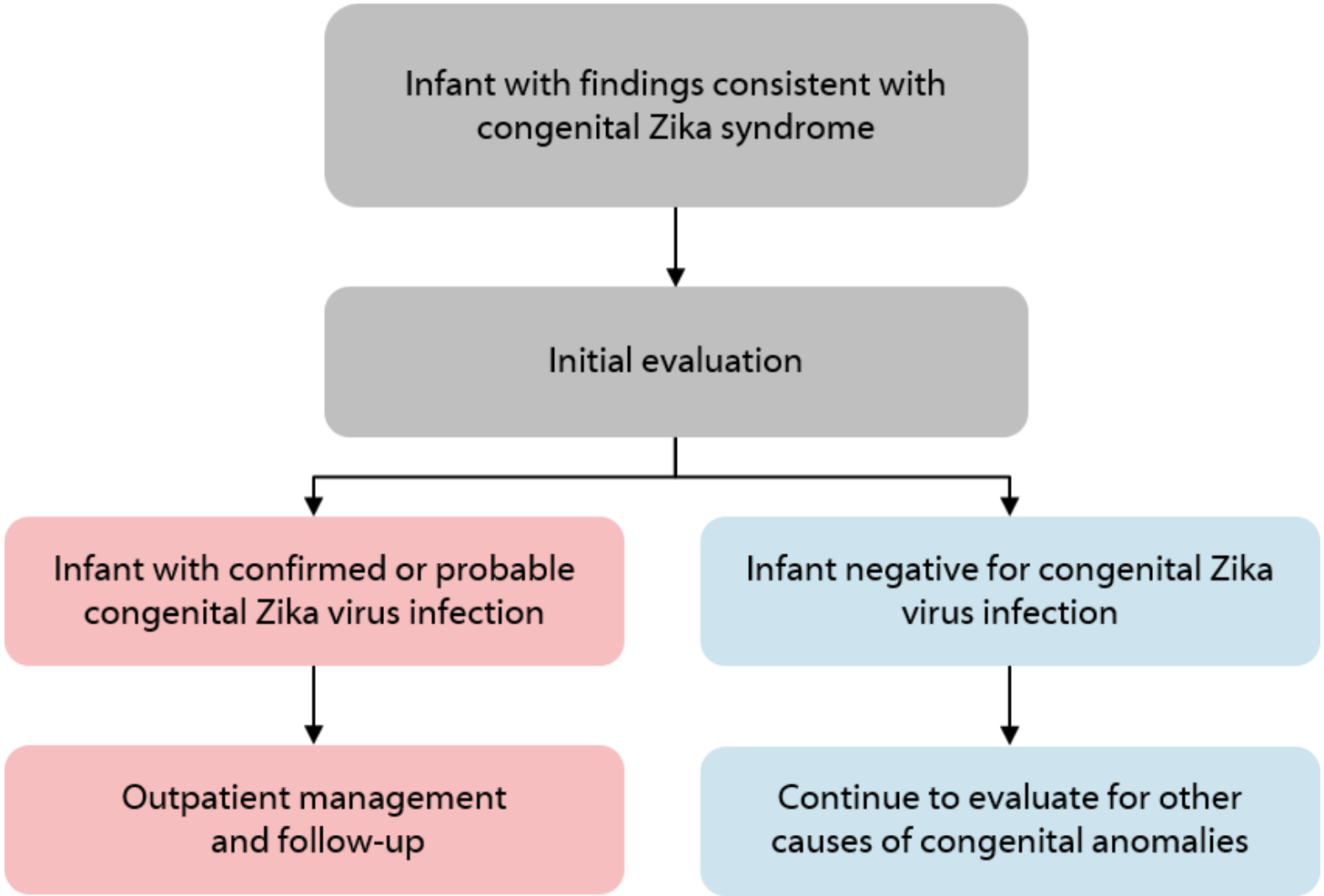




Initial Evaluation

- Consultation with: Neurologist, infectious disease specialist, ophthalmologist, endocrinologist, clinical geneticist
- Consider consultation with: Orthopedist, physiatrist and/or physical therapist, pulmonologist and/or otolaryngologist, lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist
- Perform ABR to assess hearing
- Perform complete blood count and metabolic panel, including liver function tests
- Provide family and supportive services

Infants with Findings Consistent with Congenital Zika Syndrome



Infants without Findings Consistent with Congenital Zika Syndrome

Infant without findings consistent with congenital Zika syndrome

Infant with confirmed or probable congenital Zika virus infection

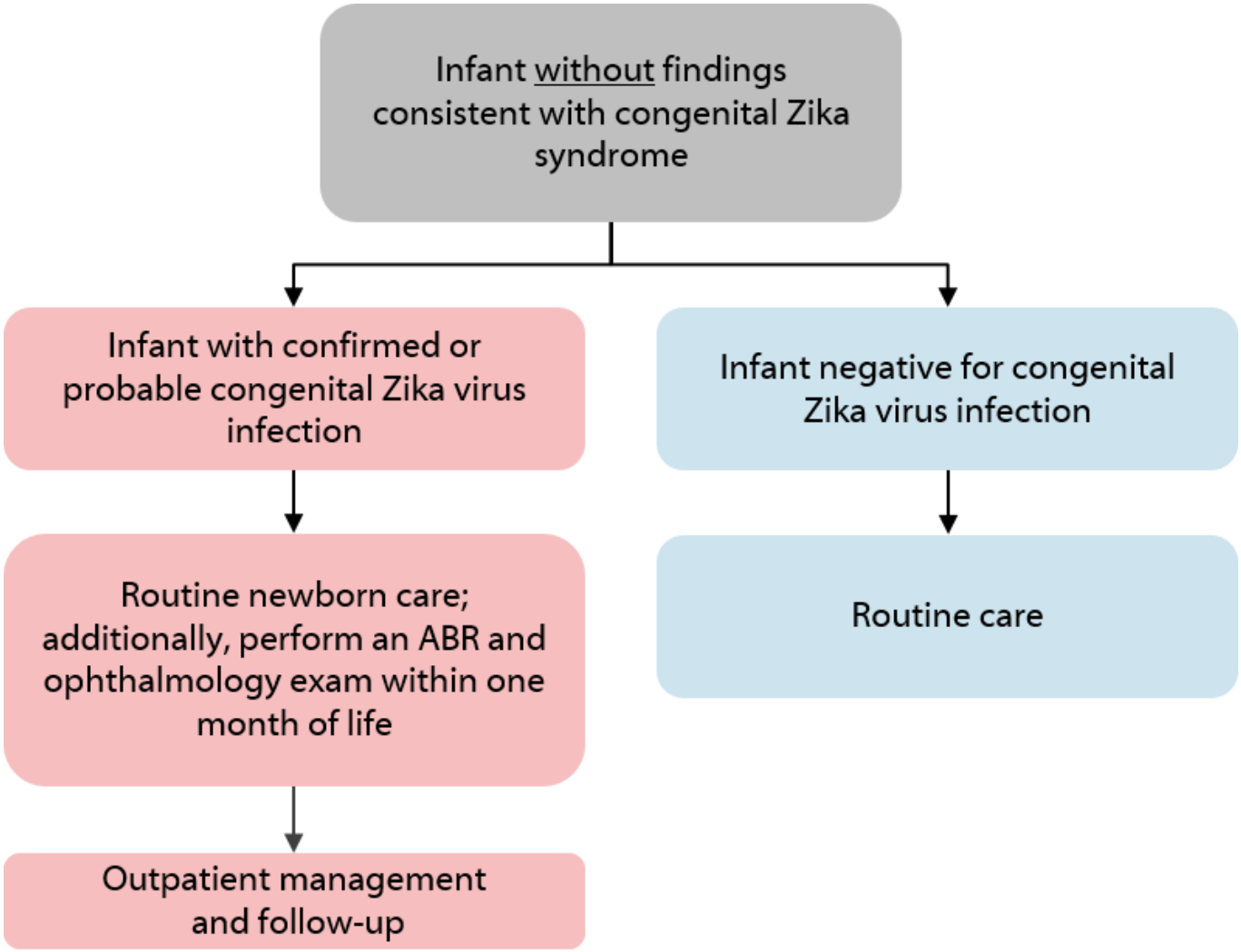
Routine newborn care; additionally, perform an ABR and ophthalmology exam within one month of life

Outpatient management and follow-up

Infant negative for congenital Zika virus infection

Routine care

Infants without Findings Consistent with Congenital Zika Syndrome



Reminder: Information on all pregnant women with laboratory evidence of Zika virus infection and their infants, regardless of infant test results, should be reported to USZPR or ZAPSS

Outpatient Management

Outpatient Management Checklist

	2 weeks	1 mo.	2 mo.	3 mo.	4-6 mo.	9 mo.	12 mo.
Infant with abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection	❑ Thyroid screen (TSH & free T4)	❑ Neuro exam	❑ Neuro exam	❑ Thyroid screen (TSH & free T4) ❑ Ophthalmology exam	❑ Repeat audiology evaluation (ABR)	❑ Developmental screening	
	❑ 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						
Infant with abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection	❑ Evaluate for other causes of congenital anomalies ❑ Further management as clinically indicated						
Infant with no abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection	❑ 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.						
Infant with no abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection	❑ 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.						

http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf

Outpatient Management Checklist

	2 weeks	1 mo.	2 mo.	3 mo.	4-6 mo.	9 mo.	12 mo
Infant <u>with</u> abnormalities consistent with congenital Zika syndrome and <u>laboratory evidence</u> of Zika virus infection	❑ Thyroid screen (TSH & free T4)	❑ Neuro exam	❑ Neuro exam	❑ Thyroid screen (TSH & free T4) ❑ Ophthalmology exam	❑ Repeat audiology evaluation (ABR)	❑ Developmental screening	
	❑ 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						

Outpatient Management Checklist							
	2 weeks	1 mo.	2 mo.	3 mo.	4-6 mo.	9 mo.	12 mo.
Infant <u>with</u> abnormalities consistent with congenital Zika syndrome and <u>negative</u> for Zika virus infection	❑ Evaluate for other causes of congenital anomalies ❑ Further management as clinically indicated						

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	2 weeks	1 mo.	2 mo.	3 mo.	4-6 mo.	9 mo.	12 mo.
Infant <u>without</u> abnormalities consistent with congenital Zika syndrome and <u>laboratory evidence</u> of Zika virus infection	❑ Ophthalmology exam ❑ ABR				❑ Consider repeat ABR	❑ Developmental screening ❑ Behavioral audiology evaluation if ABR was not done at 4-6 mo	
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Outpatient Management Checklist							
	2 weeks	1 mo.	2 mo.	3 mo.	4-6 mo.	9 mo.	12 mo.
Infant <u>without</u> abnormalities consistent with congenital Zika syndrome and <u>negative</u> for Zika virus infection	❑ 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.						

Family and Psychosocial Support

- Families and caregivers of infants with congenital Zika virus infection will require ongoing psychosocial support
- Health care providers should work closely with parents to ensure that the care plan is consistent with the infant's needs and the family's wishes
- Disproportionate burden of Zika virus infection might affect families with already limited access to medical care
  - Language, cultural, and financial barriers to care
- Barriers to care for all affected infants and their families should be addressed through linkage to national, state and local health programs

Resources for Clinicians

- Health care providers should work closely with the state, local, or territorial health department to ensure that all appropriate testing will be performed.
- CDC maintains a 24/7 Zika consultation service for health officials and healthcare providers caring for infants born to pregnant women to assist with test interpretation and questions about clinical management
  - To contact the service, call 770-488-7100 and ask for the Zika Pregnancy Hotline or email ZIKAMCH@cdc.gov

Additional Resources

- Pocket guide
  - http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf
- Resources for Zika webpages

  For healthcare providers:
  - http://www.cdc.gov/zika/hc-providers/infants-children/resources-hc-providers-for-infants.html

  For families:
  - http://www.cdc.gov/zika/parents/families-of-newborns-affected-zika.html
- Webcast of CDC meeting in collaboration with AAP
  - http://www.cdc.gov/zika/hc-providers/webcast-clinicalevalution.html

Thanks to our many collaborators and partners!

For clinical questions, please contact

ZikaMCH@cdc.gov

For U.S. Zika Pregnancy Registry questions, please contact

ZikaPregnancy@cdc.gov

For more information, contact CDC
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