

# A Prospective, Longitudinal Assessment of Infants of Mothers with Zika Infection in Pregnancy

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# Purpose

- Congenital Zika Syndrome (CZS) is a constellation of disorders including infant microcephaly, retinal lesions, hearing loss, and musculoskeletal abnormalities.
- Vertically transmitted infection may be apparent at birth or may manifest later with decelerating infant head growth, delays in neurodevelopment and special sensory function.
- It is vitally important to understand the spectrum of acute and long-term health effects of gestational Zika virus infection or exposure during critical phases of development of the brain, sensory organs, and other end organs.

# Study Design

- Prospective, longitudinal follow-up study of infants born to mothers with evidence of Zika virus infection in pregnancy.
- Retrospective enrollment of infants born to previously missed mothers with evidence of prenatal Zika infection, especially after our 2016 South Florida outbreak of mosquito-borne Zika infection.
- Comprehensive assessments of brain and somatic growth, neurobehavior, neurodevelopment, and ophthalmologic outcomes in infants and toddlers with prenatal Zika virus infection or exposure.
- Comparison of methods of detection of Zika virus by qRT-PCR assays in maternal and infant blood, urine, and saliva and in breast milk.



# Study Population

- 150 Zika-positive pregnant and postpartum women and their Zika-infected or Zika-exposed infants
- 150 control Zika-negative mothers and their infants
- Full-term or preterm infants (<37 wks gestational age)
- Matched on gestational age, maternal age, race-ethnicity, and infant sex
- Informed consent in English, Spanish, or Haitian-Creole
- Exclusion criteria:
  - Mother unwilling or unable to provide informed consent
  - Maternal uncontrolled major psychiatric disorder
  - Maternal HIV/AIDS, toxoplasmosis, CMV, syphilis, rubella, HCV, HBV
  - Maternal active neoplastic disease or treatment in last 3 years



# Neurodevelopmental Component

## Specific Aims:

- To compare infant birth growth measures (head circumference, birth weight, length) and growth trajectory through age 24 months.
- To compare neonatal neurobehavior in the 1<sup>st</sup> week and at 4-6 weeks postnatal age and the trajectory of change over time.
- To compare infant and toddler neurodevelopment at ages 6, 12, 18, and 24 months and the trajectory of change over time.



# The NICU Network Neurobehavioral Scale (NNNS)

The **NNNS** is a 20- to 30-minute standardized infant assessment performed by a trained certified examiner:

- Physical maturity
- Active and passive tone
- Primitive reflexes
- Social and behavioral functions:
  - Visual and auditory tracking
  - Cuddling and soothability
- Checklist of stress signs by organ systems
- Research measure used in multi-site NIH studies
- Therapeutic measure to enhance maternal-infant interaction

Consultant: J Hofheimer, University of North Carolina



# NNNS Assessment in NICU



# Bayley Scales of Infant and Toddler Development 3<sup>rd</sup> Edition (Bayley-III)

- Well-standardized measure for research and clinical use
- Cognitive, language, motor, socioemotional and adaptive functioning
- 50- to 90-minute exam, depending on age.
- Protocol study visits at 6, 12, 18, and 24 months (age-adjusted for prematurity).
- Florida's *Early Steps Program* uses the Bayley-III in high-risk infants to identify possible developmental delays qualifying for enhanced services.





# Additional Health and Psychosocial Measures

- Gross Motor Function Classification System
- Test of Infant Motor Performance
- The Child Behavior Checklist Modified
- Checklist for Autism in Toddlers
- Edinburgh Postnatal Depression Scale
- Brief Symptom Index
- Parenting Stress Index, 4<sup>th</sup> Ed
- Social Factors Inventory



# Ophthalmology Component

## Specific Aims

- To determine the prevalence of primary ophthalmologic findings in infants exposed to Zika virus in pregnancy.
- To characterize the type and location of the eye findings.
- To determine the long-term effects of Zika virus on vision development.
- To assess the predisposition to secondary ocular disease such as cataract formation, glaucoma, and retinal detachment.

Study Protocol for infants with gestational Zika-infection or exposure:  
Birth - 1 month, 6, 12, 18, and 24 months, and as clinically indicated.



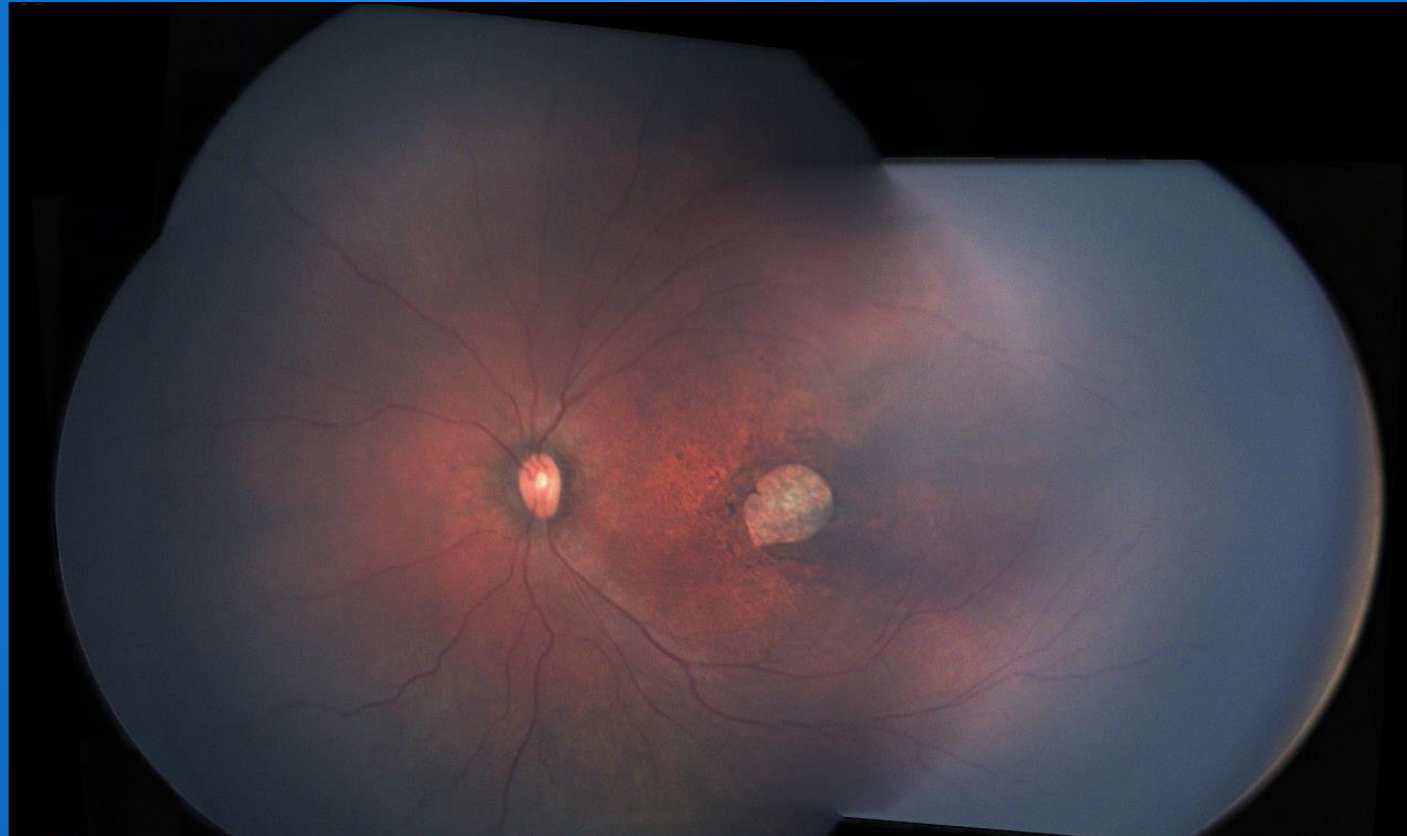
# Infant Fundoscopy in the NICU



# RetCam Digital Photography in the NICU



# Retinal Lesions in Infant with Congenital Zika Syndrome



# Advanced Ophthalmologic Techniques

JMH-Holtz NICU or Bascom Palmer Eye Institute Clinic

- Retcam Digital Photography
- Fluorescein Angiography (FA) detects peripheral avascularity
- Spectral-domain optical coherence tomography (SD-OCT) measures retinal nerve fiber layer thickness (RNFL)

# Virology Component

- To determine the relationship of viral load in mothers with Zika infection in pregnancy and the health and developmental outcomes of their infected and exposed infants.
- For prenatal participants, samples of blood, urine and saliva are collected for qRT-PCR at enrollment and weekly, if positive, until all samples are negative.
- Samples of blood, urine, and saliva are obtained in the mother-infant dyads during birth hospitalization or postnatal enrollment. If any sample is qRT-PCR positive, samples will be repeated serially until negative.
- Breast milk is also tested by qRT-PCR for viral shedding.
- Several qRT-PCR methods will be used for comparison purposes.
- Florida Gulf Coast University collaborators: S Michael and S Isern.



# Other Infant-Toddler Assessments supported by UM FDOH Zika Research Awards

- Inflammatory and immunologic responses, and end organ outcomes (Gonzalez, Andreansky)
  - Ocular ultrasonography (Berrocal)
  - Neurology, Electroencephalography (Pensirikul)
  - Cardiology, Echocardiography (Hunter)
  - Nephrology, Renal Ultrasounds (Katsoufis)
- Audiology, speech and language, suck and swallow, and craniofacial dysmorphism (Younis, Liu, and Fifer)
- Enhanced Brain Magnetic Resonance Imaging (Saigal, Govind)



# Progress to Date

- Formed the University of Miami Pediatric Zika Research Consortium to enhance collaboration and networking.
- Addressed research administration and regulatory issues and staff recruitment, hiring, and training.
- Obtained IRB approval for the Pediatric Zika protocols and recruitment of mothers and their infants with informed consent in English, Spanish, or Haitian-Creole.
- Collaboratively recruited, enrolled, and implemented the schedule of assessments of 10 mother-infant dyads to date.



# Impact on Floridians

- This *Florida Department of Health Zika Research Initiative* sponsors an unprecedented research endeavor to confront the threat of Zika virus infection.
- Our investigators are poised to have significant impact in our state, nation, and the global scientific community with respect to detecting and diagnosing the spectrum of adverse outcomes in offspring of mothers with Zika virus infection in pregnancy.
- This investigation is anticipated to yield valuable information for preventing, ameliorating, and ultimately treating this potentially devastating infection in our most vulnerable citizens.

***Our Children Are Our Future!***



# Acknowledgements

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- Participating mothers and their infants
- Jackson Health Systems
- Jackson Memorial Holtz Children's Hospital
- Bascom Palmer Eye Institute
- Batchelor Children's Research Institute
- Mailman Center for Child Development
- Florida Early Steps Program
- Healthy Start Coalition of Miami-Dade County

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