# Understanding the Neurodevelopmental Impact of Congenital Zika Virus Exposure

## Research Led by Windward Islands Research and Education Foundation

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## Goal

The Maternal and Child Survival Program (MCSP) provided targeted technical assistance to countries in the eastern and southern Caribbean, with the goal of improving care and support for Zika-affected children and their families. MCSP collaborated with national ministries of health (MOHs), local universities, and professional associations to address gaps in health system and provider capacity to care for women, newborns, children, and families affected by Zika virus (ZIKV) infection. In Grenada, MCSP partnered with the Windward Islands Research and Education Foundation (WINDREF) at St. George's University to characterize the impact of in utero ZIKV exposure on neurocognitive development. WINDREF measured multiple neurodevelopmental outcomes in a well-characterized cohort of children with and without prenatal ZIKV exposure in Grenada using sensitive measures of cognition, language, fine and gross motor skills, behavior, attention, and social-emotional reactivity. Data collection is ongoing, but preliminary results provide a snapshot of the neuropsychological impact of ZIKV exposure in human infants in their first 2 years of life.[1]

A research team member uses the OX-NDA tool to measure neurodevelopmental outcomes of a Zika-affected child in Grenada. Photo by Michelle Fernandes, National Institute for Health Research

## Background

The Caribbean island nation of Grenada experienced a ZIKV outbreak from April 2016 through March 2017, with peak transmission from May through October 2016. During this period, WINDREF recruited 383 pregnant women from local health clinics across all six parishes and collected serum samples during their antenatal and/or postnatal period. All pregnant women who presented at local health clinics for antenatal and postnatal appointments were eligible to enroll in the study. WINDREF has been conducting neurodevelopmental assessments of children born to these mothers (388 children, five twin births) as they turn 1 year of age (12 $\pm$ 2 months) using the Oxford Neurodevelopment Assessment (OX-NDA), an internationally validated tool for the measurement of multiple neurodevelopment outcomes (cognition, language, motor skills, behavior, attention problems, and socialemotional reactivity), since May 2018. WINDREF continues to follow these children as they age to characterize their neurodevelopmental functioning at 22–26 months of age using

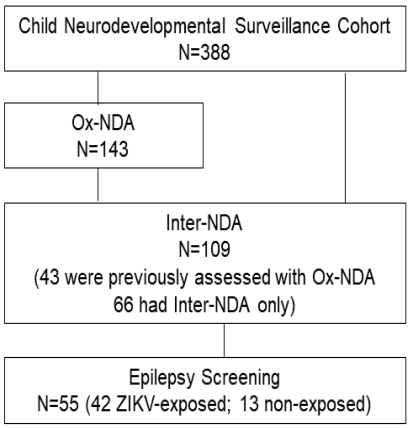
[1] Santos IS, Bassani DC, Matijasevich A, et al. 2016. Infant sleep hygiene counseling (sleep trial): protocol of a randomized controlled trial. *BMC Psychiatry*/ 16(1):307. doi: 10.1186/s12888-016-1016-1.

the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA),[2, 3] an internationally validated, comprehensive measure of cognition, fine and gross motor skills, expressive and receptive language, behavior, attention problems, and social-emotional reactivity. Children are also screened for epilepsy using a parent questionnaire and electroencephalography (EEG), which are interpreted by board-certified pediatric neurologists in the United States via a telemedicine platform. The primary goal of this research is to ensure that children with in utero ZIKV exposure reach their full developmental potential at 1 and 2 years of age by identifying and addressing developmental challenges as early as possible.

## Program Approaches

- **Training and capacity-building in early child developmental assessments in Grenada.** WINDREF built expertise and capacity in neuropsychological assessment by training eight Caribbean people to perform the neurodevelopmental assessments. Michelle Fernandes, developer of OX-NDA and INTER-NDA, traveled to Grenada for 7 days in June 2018 to provide in-person training on both OX-NDA and INTER-NDA for the assessment team.
- **Neuropsychological data.** WINDREF collected data from 209 infants of women who were enrolled in the study and had serum tested for ZIKV infection during the antenatal/postnatal period. The OX-NDA was administered to 143 1-year-olds, and the INTER-NDA was administered to 109 2-year-olds (43 of whom previously completed the OX-NDA; see Figure 2). These ongoing assessments will identify children who are falling behind their peers in the development of language, problem-solving, and motor skills so that interventions can target these domains for remediation.

**Figure 1. Flow diagram shows how many children have completed each assessment procedure to date.**




## Key Results and Findings

### Results

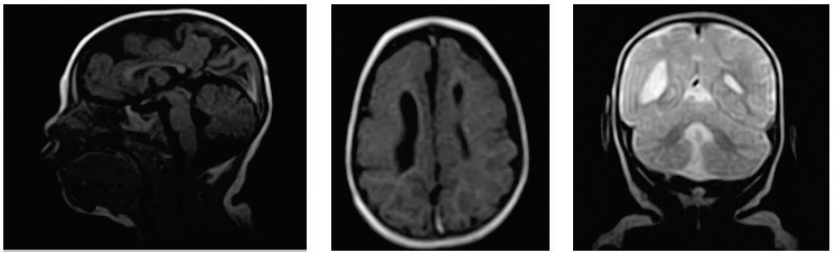
- **Impact of ZIKV on neurodevelopment.** WINDREF investigators aimed to determine whether Zika-exposed children showed signs of developmental delays in cognition and behavior at 1 and 2 years of age. Of the 143 1-year-olds assessed to date, maternal antenatal ZIKV status was confirmed in 49 children (12 non-exposed children and 37 Zika-exposed children). Preliminary group comparisons did not reveal any differences in cognition or behavior between non-exposed and Zika-exposed children at 1 year of age, but small sample sizes warrant caution in interpreting these results. INTER-NDA assessments are ongoing as children turn two years of age. Those who fall below the 10th percentile using international normative standards will be referred for early intervention with GRENCASE's Roving Caregivers, a local organization that provides home-based service delivery to vulnerable populations across Grenada. GRENCASE's Roving Caregivers were trained in MCSP's Therapeutic Early Stimulation Package and Conscious Discipline, a neurodevelopmentally focused method that emphasizes safety, attachment, and self-regulation.[4]
- **Epilepsy monitoring.** A total of 55 1- and 2-year-old children (13 non-exposed and 42 Zika-exposed) were screened for seizures with a pediatric epilepsy screening tool and EEG. Thus far, "probable epilepsy" was detected in two Zika-exposed children and "suspect epilepsy" in one Zika-exposed child. Within the non-exposed children, all were classified as "no epilepsy," with the exception of one child, who showed subclinical focal epileptiform activity on the EEG. Children who screened positive for epilepsy were referred to a local pediatrician for an evaluation if treatment had not already been initiated.

[2] Fernandes M, Stein A, Newton CR, et al. 2014. The INTERGROWTH-21st Project Neurodevelopment Package: a novel method for the multi-dimensional assessment of neurodevelopment in pre-school age children. *PLoS One*. 9(11): e113360. doi: 10.1371/journal.pone.0113360.
[3] Villar J, Fernandes M, Purwar M, et al. 2019. Neurodevelopmental milestones and associated behaviours are similar among healthy children across diverse geographical locations. *Nat Commun*. 10(1): 511. doi: 10.1038/s41467-018-07983-4.
[4] Bailey BA. 2015. *Conscious Discipline*. Oviedo, Florida: Loving Guidance Inc.

## Findings and Lessons Learned

- **Case study.** One study participant was born with microcephaly; serum analysis from a prenatal and postnatal blood draw in the mother were positive for ZIKV. On examination, the child showed signs of severe developmental delays, as well as hypertonia and hyperreflexia, more pronounced in the left upper and lower extremities. The child screened positive for epilepsy and was taking epilepsy medications at the time of the EEG scan. Clinical review of this child's EEG by a board-certified epileptologist revealed focal epileptiform discharges and moderate slowing in the right frontal region. Neuropsychological assessment revealed severe developmental delays across language, motor, and cognitive domains. This child, who is receiving follow-up medical care, is currently being followed by GRENCASE's Roving Caregivers, who are administering MCSP's Therapeutic Early Stimulation Package. Subtle gains in motor skills and communicative behavior are being observed across repeated assessments.

**Figure 2. T1-weighted MRI from 15-month-old child born with microcephaly and positive ZIKV serum analyses.**



A) Sagittal FSE T1: Intact corpus callosum; low supratentorial brain volume consistent with microcephaly

B) Sagittal FSE T1: Ventriculomegaly more pronounced in right hemisphere

C) Coronal FSE T1: Ventriculomegaly and white/gray matter volume loss more pronounced in right hemisphere

- **Human capacity development.** Standardized neurodevelopmental assessment of infants and toddlers using internationally validated assessment tools is not currently available outside of a research context in Grenada. Research assistants were trained in the administration of two internationally standardized neuropsychological/neurodevelopmental tests, strenthening the capacity for early neurodevelopmental assessment in Grenada and the early identification of potential developmental delays. Training and mentoring of local research assistants will continue throughout the extension of the WINDREF project, which is being supported by the National Institute of Child Health and Human Development R21 grant Rescuing Neurodevelopment in Zika-exposed Children.
- **Community and health systems strengthening.** Study implementation involved the MOH, various health facilities and frontline providers, research assistants, and participating families. All parties contributed to the success of this study and to public health awareness of ZIKV and its impact in Grenada. Both MCSP subawardees—WINDREF and GRENCASE's Roving Caregiver Programme—collaborated to bring their two streams of work together to benefit Grenadians affected by the Zika outbreak. The Roving Caregivers have been trained in MCSP's Therapeutic Early Stimulation Package and Conscious Discipline, which they will incorporate into their home-based care approach. Parents in the WINDREF study will have the opportunity to learn skills from GRENCASE's Roving Caregivers to connect and communicate more effectively with their children, which in turn will foster healthier neurodevelopment.

# Recommendations and Future Research

The neurodevelopmental impact of congenital Zika virus exposure poses many challenges for countries impacted by the outbreak, including the fact that effects may be variable, have delayed onset, require complex specialty care, and/or may be invisible to the naked eye. As such, the following are recommended strategies for countries in the region:

- Increased local capacity across a broad range of areas, including the following:

- Screening for normal developmental milestone attainment in pediatric care settings
- Multisectoral collaboration and engagement in provision of services for children at risk for not reaching their neurodevelopmental potential (e.g., health, education, social welfare)
- Referral and management of potential neurodevelopmental delay
- Frequent adaptation of and evidence-based updates to pre-service and in-service educational curricula for those cadres who contribute to prevention and management of the potential negative neurodevelopmental impacts of congenital Zika infection
- Public health communication strategies that reach all families and cut across both the public and private sectors
- Surveillance mechanisms that contribute data efficiently to pregnancy registries
- Promotion of the role of community workers in health and social welfare systems
- Facilitation of community voices to impact the way that support and care are provided to families with children exposed to congenital Zika infection

A GRENCASE Roving Caregiver and caretaker provide early stimulation therapies to a young Grenadian during a home-based care session using local, easy-to-find materials. Photo: Thecla Richards/

- Prevention of unintended pregnancy through voluntary family planning programs helps to prevent Zika-affected pregnancies. Enabling couples and individuals to determine whether, when, and how often to have children is vital to safe motherhood, healthy families, and prosperous communities, whether or not they are impacted by infectious disease outbreak. When a woman bears children too closely together, too early or too late in life, the health of the mother and baby are at risk. Ensuring that clients are offered, either directly or through referral, a broad range of family planning methods and services will help to prevent these health risks.
- Public health human subjects research in Grenada is still a novel concept for many Grenadian nationals, and it can be difficult to disseminate the goals and outcomes of research to local stakeholders. Improving clinical research literacy in communities may encourage greater public understanding of future research projects and their potential value to public health in the region and beyond.
- After completion of data collection in 2-year-old participants, dissemination of findings to the MOH and local health care providers should occur to inform family planning and other prevention and response measures in the event of a future ZIKV or similar outbreak.
- In an extension of this study, enabled through additional funding from the National Institutes of Health (R21HD93551; Rescuing Neurodevelopment in Zika-Exposed Children), WINDREF is carrying out ongoing assessments of the same children who were screened as part of the US Agency for International Development-funded study described above. This study extension will investigate the efficacy of a community-based psychosocial intervention on neurodevelopment and the mitigation of the impact of adverse neurodevelopmental disturbances on the participating children and their families. This intervention leverages MCSP training provided to GRENCASE's Roving Caregivers Programme in Grenada, uses MCSP's Therapeutic Early Stimulation Package, and uses training in Conscious Discipline, a neurodevelopmentally focused "brain smart" method that emphasizes safety, attachment, and self-regulation in addition to stimulation.[5] Roving Caregivers will continue to work with WINDREF participant caregiver-child dyads weekly and will assess maturational gains in cognition and behavior.

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[5] Bailey BA. 2015. *Conscious Discipline*. Oviedo, Florida: Loving Guidance Inc.