Neurodevelopmental assessment of infants exposed to Zika Virus

Background

Zika virus (ZIKV) is a mosquito-born flavivirus that was first identified in Uganda's Zika forest in 1947. ZIKV is closely related to other flaviviruses such as Dengue and West Nile and outbreaks were rare before May 2015 (Paixao, Barreto, Teixeira Mda, Costa Mda, & Rodrigues, 2016)and (Krauer et al., 2017). Since, the geographical range of the Zika virus has expanded rapidly with reports of autochtonous transmission in 67 countries throughout the world (Krauer et al., 2017). The magnitude and severity of the epidemic prompted the World Health Organization (WHO) to declare Zika infection as a *Public Health Emergency of International Concern* on February 1, 2016 (Heymann et al., 2016).

Zika infections are often asymptomatic in approximately 80% of patients, with 20% having mild self-limiting symptoms including fever, maculopapular rash, arthralgia, and non-purulent conjunctivitis. A small subset of Zika-infected adults develop Guillain-Barre syndrome, meningoencephalitis, or myelitis. During pregnancy Zika virus can be transplacentally transmitted and cause a spectrum of abnormalities, a condition known as congenital Zika virus syndrome (CZVS). These abnormalities may include fetal demise, limb contractions, hearing, sight and brain abnormalities, fetal growth restriction, congenital birth defects, seizures, congenital microcephaly, and associated brain damage (Krauer et al., 2017; Mlakar et al., 2016; Rasmussen, Jamieson, Honein, & Petersen, 2016) a condition known as Zika virus congenital syndrome. Importantly, several babies who had normal head circumference at birth, did manifest an acquired microcephaly when examined at 12 months of age (McCarthy, 2016).

Given the timeline of developments in this field, little research has been performed on secondary outcomes and complications of Zika exposure and treatment. As there is evidence that birth defects and underlying neurodevelopmental issues predict attachment disorganization and parental relationship problems (Wolke, Eryigit-Madzwamuse, & Gutbrod, 2014), there is significant need for assessment of these outcomes in this ZIKV population.

As of March 30 2017, the Centers for Disease Control and Prevention (CDC) reported 1,016 laboratory- confirmed symptomatic Zika virus disease cases in New York, representing 20% of all U.S. cases (CDC 2017). Given the concentration of residents in Washington Heights of Caribbean origin, Columbia University Medical Center (CUMC) has many patients who frequently visit the

Dominican Republic (D.R.) and other countries and provinces deemed to be at "Very High Risk" for ZIKV infection. Currently at CUMC, eighty pregnant women exposed to ZIKV are followed in the High Risk Obstetrics Clinic. Testing for Zika virus exposure has been validated using IgM, IgG and PCR analysis (Wong et al., 2017).

Infection in the fetal environment is known to be associated with neurological impairment. Previous research has suggested that infants exposed to chorioamnionitis with inflammatory response show a significantly different cortisol response at 18 months compared to infants without prenatal inflammation (Gover et al., 2013). Early ZIKV exposure may lead to a similar effect.

In light of the severity of these neurological symptoms, the need for assessment of both cortisol and maternal relationship in this population, and the unique position of our interdisciplinary research team, our proposal seeks to recruit all mothers and babies exposed to Zika virus born at CUMC for a longitudinal cohort study. We will assess if: 1. Babies exposed to ZIKV (Maternal IgM+ and/or PCR+) are more likely to have (a) neurological deficits on examination and (b) developmental delays. Abnormal neurological findings would include microcephaly or focal neurological examination findings. Developmental delays include cognitive impairment or statistically significant delays on standard developmental testing. 2. Babies exposed to ZIKV (Maternal IgM+ and/or PCR+) with abnormalities (defined as abnormal head ultrasound, presence of neurological deficits or developmental delays) are more likely to differ in their maternal caregiver relationship compared with those that do not have neurological atypicalities or delays. The relations between developmental status and maternal mood and bonding will be assessed via standardized neuropsychological testing and parent report measures. 3. Babies exposed to ZIKV with either IgG+ or elevated serum cortisol at 18 months of age are more likely to have neurological atypicalities, developmental delays or deficient parent bonding than those who are IgG- or with normal cortisol levels.

Study Design:

We seek to recruit up to eighty pregnant women exposed to Zika virus (Maternal ZIKV IgM and/or PCR+) receiving care at CUMC's High Risk OB clinic. As part of their standard obstetric care at CUMC, expectant mothers at risk for Zika are assessed for clinical symptoms consistent with the ZIKV infection and ZIKV-specific IgM and PCR assays. Pregnant women with possible exposure to Zika virus are followed with serial ultrasounds to assess fetal growth as well as a detailed fetal anatomical survey to assess for congenital anomalies. Babies also have ultrasound and Zika panel testing (serum IgM and PCR) in the nursery as a

standard of care. Maternal informed consent will be taken at time of enrollment.

This study proposes additional clinical evaluations to compliment, validate, and expand the standard of care evaluations for pregnant women and their infants who may have been exposed to Zika during gestation. Babies will be evaluated at birth and every six months after delivery.

Serum testing: This study will complement existing care – assessment for ZIKV using IgM assay and clinical symptoms, growth parameters, and general exam are all standard in this patient population. The study will collect data from these visits and further evaluate the neurological status of these children and their maternal relationship. Serum will be obtained at the 18 month visit for both the mother and the child. Labs to be obtained include serum IgG and cortisol (both mother and child cortisol). Serum IgG being evaluated by NYS Wadsworth Laboratory and cortisol evaluated by the Irving Institute for Clinical and Translational Research's Biomarkers Core Laboratory.

Examinations: The general examination will be performed at every visit inclusive of growth parameters. The neurological exam will consist of a mental status examination, assessment of cranial nerves, motor examination, sensory examination, reflex examination, and gait and coordination assessment as applicable. These are all standard of care measures.

Neurodevelopmental testing: the Bayley Scales of Infant and Toddler Development - 3rd Edition (Bayley, 2006) is a reliable and valid measure of cognitive and motor development for children ages 0 – 42 months. The Bayley-III provides individual measures of early problem solving, receptive and expressive language, and fine and gross motor skills, and it will be used to capture growth in these domains at 6 month intervals. Measures of adaptive and socioemotional functioning are also included.

Gross motor maturation: the Alberta Infant Motor Scale (AIMS), a 58 item observational assessment scale validated and reliable in assessing infants ranging from 0 to 18 months or until independent walking is achieved, will be used at each visit. The AIMS examines four positions: prone, supine, sitting and standing. Each item describes three aspects of quality of movement: weight distribution, posture and antigravity movements. The AIMS is a norm-referenced discriminative measure differentiating infants' motor development as normal, at

risk or abnormal.

Parent Questionnaire Battery: A standardized battery of neuropsychological testing will be implemented to study the relations between developmental status and maternal mood and bonding. The classic Piagetian A-not-B/delayed response and delayed alternation tasks (Diamond, 1991) will be used to capture foundational executive skills including working memory, inhibitory control, and shifting. If the child is able to pass A-not-B, Delayed Alternation will also be administered. The Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) is a reliable and valid measure commonly used to assess mood in new mothers that has also been demonstrated as an appropriate screener for women past the initial postpartum period (Cox et al., 1996). The Mother and Infant Bonding Scale (MIBS; Taylor et al., 2005) is a brief screening measure in which the mother rates 8 adjectives on a likert scale. It shows adequate reliability and validity as well as strong correlations with maternal affect (Taylor et al., 2005; Wittkowski et al., 2007). Higher scores on these measures are indicative of mood and bonding difficulties.

STATISTICAL PROCEDURES

This is a two-year prospective longitudinal cohort study of new mothers and their infants, with follow up until 18 months after delivery. We seek to recruit up to eighty pregnant women exposed to Zika virus (Maternal ZIKV IgM and/or PCR+) receiving care at CUMC's High Risk OB clinic. Once enrolled, infants will be evaluated every six months, as detailed above. At each time point neurodevelopmental assessment scores will be calculated for each participant. Mean scores and standard deviations will be calculated for each time point using data from all the participants, and these will be compared to scores of age-matched infants of mothers not exposed to the Zika virus. Difference between the mean will be analyzed by unpaired student t-test. Based on power calculations using the standardized scores of Bayley assessments (mean = 100 and SD = 15), using an N=80 for both study and control groups, we estimate that we can distinguish a difference of 6.7 Bayley score between the two groups. Neuropsychological testing scores measuring the relations between developmental status and maternal mood and bonding will be analyzed in a similar fashion.

REFERENCES

Besnard, M., Lastere, S., Teissier, A., Cao-Lormeau, V., and Musso, D. (2014).

Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill. *19*.

Besnard, M., Dub, T., and Gérardin, P. (2017). Outcomes for 2 Children after Peripartum Acquisition of Zika Virus Infection, French Polynesia, 2013-2014. Emerging Infect. Dis. *23*, 1421–1423.

Besnard, M., Eyrolle-Guignot, D., Guillemette-Artur, P., Lastère, S., Bost-Bezeaud, F., Marcelis, L., Abadie, V., Garel, C., Moutard, M.-L., Jouannic, J.-M., et al. (2016). Congenital cerebral malformations and dysfunction in fetuses and newborns following the 2013 to 2014 Zika virus epidemic in French Polynesia. Euro Surveill. *21*.

Faye, O., Freire, C.C.M., Iamarino, A., Faye, O., de Oliveira, J.V.C., Diallo, M., Zanotto, P.M.A., and Sall, A.A. (2014). Molecular evolution of Zika virus during its emergence in the 20(th) century. PLoS Negl Trop Dis *8*, e2636.

Gover, A., Chau, V., Miller, S.P., Brant, R., McFadden, D.E., Poskitt, K.J., Synnes, A., Weinberg, J., and Grunau, R.E. (2013). Prenatal and postnatal inflammation in relation to cortisol levels in preterm infants at 18 months corrected age. J Perinatol *33*, 647–651.

Haddow, A.D., Schuh, A.J., Yasuda, C.Y., Kasper, M.R., Heang, V., Huy, R., Guzman, H., Tesh, R.B., and Weaver, S.C. (2012). Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. PLoS Negl Trop Dis *6*, e1477.

Honein, M.A., Dawson, A.L., Petersen, E.E., Jones, A.M., Lee, E.H., Yazdy, M.M., Ahmad, N., Macdonald, J., Evert, N., Bingham, A., et al. (2017). Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. Jama *317*, 59–68.

Moura da Silva, A.A., Ganz, J.S.S., Sousa, P.D.S., Doriqui, M.J.R., Ribeiro, M.R.C., Branco, M.D.R.F.C., Queiroz, R.C. de S., Pacheco, M. de J.T., Vieira da Costa, F.R., Silva, F. de S., et al. (2016). Early Growth and Neurologic Outcomes of Infants with Probable Congenital Zika Virus Syndrome. Emerging Infect. Dis. *22*, 1953–1956.

Olson, J.G., Ksiazek, T.G., Suhandiman, and Triwibowo (1981). Zika virus, a cause of fever in Central Java, Indonesia. Trans. R. Soc. Trop. Med. Hyg. *75*, 389–393.

Roth, A., Mercier, A., Lepers, C., Hoy, D., Duituturaga, S., Benyon, E., Guillaumot, L., and Souares, Y. (2014). Concurrent outbreaks of dengue, chikungunya and Zika virus infections - an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. Euro Surveill. *19*.

Taylor, A., Atkins, R., Kumar, R., Adams, D., and Glover, V. (2005). A new

Mother-to-Infant Bonding Scale: links with early maternal mood. Arch Womens Ment Health *8*, 45–51.

van der Linden, V., Pessoa, A., Dobyns, W., Barkovich, A.J., Júnior, H.V.D.L., Filho, E.L.R., Ribeiro, E.M., Leal, M. de C., Coimbra, P.P. de A., Aragão, M. de F.V.V., et al. (2016). Description of 13 Infants Born During October 2015-January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth - Brazil. MMWR Morb. Mortal. Wkly. Rep. *65*, 1343–1348.

Ventura, C.V., Maia, M., Dias, N., Ventura, L.O., and Belfort, R. (2016). Zika: neurological and ocular findings in infant without microcephaly. Lancet *387*, 2502.