ZIRP Puerto Rico Study

Zika Virus RNA Persistence in Pregnant Women and Congenitally Exposed Infants in Puerto Rico (ZIRP)

Supporting Statement: Part B

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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
EOC	Emergency Operations Center
IgM	Immunoglobulin M
IRB	Institutional Review Board
mL	Milliliter
MRI	Magnetic Resonance Imagining
OB	Obstetric
PRDH	Puerto Rico Department of Health
PI	Principal Investigator
POC	Point of Contact
PRDH	Puerto Rico Department of Health
RNA	Ribonucleic acid
rRT-PCR	Real-time reverse transcription–polymerase chain reaction
USZPR	US Zika Pregnancy Registry
ZAPSS	Zika Active Pregnancy Surveillance System
ZIKV	Zika Virus

B. Collections of Information Employing Statistical Methods

B.1. Respondent Universe and Sampling Methods

The objective of our study is to determine the prevalence and duration of persistent ZIKV RNA in pregnant women infected with ZIKV and their congenitally exposed infants. Our sampling frame will consist of all pregnant women and their congenitally exposed infants presenting to the study sites for routine pre-natal care. Pregnant women from the sampling frame testing positive for ZIKV by rRT-PCR will represent the final "pregnant woman" study cohort for analysis. Infants born from the "pregnant woman" cohort will represent the final "infant" study cohort for analysis In order to achieve this, using a hypothetical estimate of the prevalence of ZIKV RNA persistence of 5% after 12 months, and a two-sided 99% confidence interval width of 10% (or margin of error (ME) of ±5%), a sample size of 125 ZIKV positive pregnant women and congenitally-infected infants will be needed. Table B.1.1 shows different scenarios of potential sample sizes that were considered for the study.

Table B.1.1. Sample Size calculations for different proportions of pregnant women with prolonged detection of ZIKV RNA within a finite population in Puerto Rico, 2017

	Estimated Proportion of Pregnant Women with Persistent Detection of Zika Virus (ZIKV)RNA				
Confidence Level (%)	**3%**	**5%**	**15%**	**30%**	**45%**
95%	45	73	193	313	367
80%	20	32	84	137	161
90%	32	52	137	223	261
97%	55	89	235	381	446
99%	77	125	328	528	617
99,90%	125	202	524	834	969
99,99%	174	280	717	1129	1304

The sample size is tentatively estimated, given that there is little information on prevalence of ZIKV RNA persistence rates available in literature. The final sample size of 150 ZIKV positive pregnant women and their congenitally exposed infants is estimated for evaluation of the primary objective of the study which is the prevalence and duration of ZIKV RNA persistence in the 15 months in which the study will run.

B.2. Procedures for the Collection of Information

Pregnant women of any gestational age at the time of ZIKV diagnosis and their infants will be invited to participate. The Pregnant Women Screening Form (Att C.1) will be administered to potential participants by trained ZIRP research staff, and will be used to confirm participant eligibility prior to consent.

The pregnant woman will consent for her participation. Following consent, information will be collected at baseline regarding demographics and risk factors for ZIKV through the Pregnant Woman Enrollment Questionnaire (Att C.2) and a Pregnant Woman Symptom Questionnaire (Att C.3). Pregnant women will then be serially tested for ZIKV RNA in blood (7.5mL) and/or urine samples by rRT-PCR and ZIKV Immunoglobulin M (IgM) every two weeks . The blood samples will consist of one venous blood collection (via venipuncture) every two weeks and a one-time collection of capillary blood (via finger prick) at enrollment. If these visits do not coincide with a typical prenatal care visit, they will be asked to come in for a laboratory-only visit to obtain samples and to complete the Pregnant Woman Follow-up questionnaire (Att C.4).

Samples will be collected until blood and/or urine samples are all rRT-PCR-negative on two subsequent collection dates to confirm negative results. If a woman is still rRT-PCR positive at delivery, follow-up samples will be obtained every 2 weeks for up to three months post-delivery.

Infants born to women enrolled in the pregnancy cohort will be enrolled when the pregnant woman and the infant's father sign the infant informed consent form. At birth, the study staff will collect infant information on the Infant enrollment and delivery questionnaire (Att C.5), this information will be related to demographics, vital signs, delivery and abnormalities, laboratory sample collection and imaging. Blood and/or urine samples will be collected from these infants at birth and tested for the presence of ZIKV RNA by rRT-PCR. Infants who are rRT-PCR positive at birth will continue to be tested every month until samples confirm two negative test results or until they are 6 months of age. Infants who are born PCR-negative will have a confirmatory test at month 1 to ensure they continue to be negative and will complete the Infant follow-up questionnaire (Att C.6). If infant becomes PCR-positive, they will be tested every month after date of diagnosis of ZIKV infection until samples confirm two negative test results or until they are 6 months of age.

B.3. Methods to Maximize Response Rates and Deal with Non-response

Efforts will be made to maximize the response rate. Pregnant women will be encouraged to complete the study throughout the pregnancy up until 3 months post-delivery and their infants up to 6 months of age. To encourage study participation, after being provided with information about the study, potential participants will be given a phone number to call if they have questions about the study. In addition, once a participant is enrolled, study staff will follow-up with participants if a study visit is missed.

There are also a number of ancillary benefits to study participation that are expected to increase participation rates. As a part of this study, participants will have some tests and procedures performed that are not usually available in the standard prenatal care, including serial Zika testing, blood, and urine diagnostic testing. All of these tests and procedures will be paid for by the study as they are not part of the routine clinical care. Participants will also be given any new information gained during the course of the study that might increase their willingness to continue with the study.

Pregnant women and parent(s) may incur extra financial and other costs to participate, as the study will require time for extra clinic and laboratory visits, transportation costs, and the extra time needed to make these visits. To help cover these costs, we plan to offer a $25 gift card for each clinic visit and a $25 gift card for each laboratory visit. Participants will receive the gift card even if they give an incomplete collection of samples. Infants will receive a $25 gift card for each clinic visit. These may be given to the participants in the form of cash or transportation tickets to appreciate for their participation.

We anticipate being able to assess non-response bias by examining participation rates. In addition, some information on non-responders may be available from clinics so that we will be able to assess factors associated with non-response.

B.4. Tests of Procedures or Methods to be Undertaken

All data collection instruments were reviewed by medical personnel, laboratorians, epidemiologists, and subject matter experts for question working and appropriate and adequate response options.

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Data collection instruments were reviewed by medical personnel, laboratorians, epidemiologists and subject matter experts. These included individuals from the CDC Zika Virus Response Team, Pregnancy and Birth Defects Task Force (Margaret Honein, PhD; Sascha Ellington, MSPH; Cristina Valencia, MPH, MSc, EPIET; Abbey Jones, MPH; Carrie Shapiro, PhD, MPH; Dana Meaney-Delman, MD,MPH), CDC Dengue Branch, Puerto Rico (Jennifer Reed, MD; Jorge Munoz, MD; Janice Perez-Padilla, RN, MPH; Steve Waterman, PhD), University of Puerto Rico (Carmen Zorilla, MD; Alberto de la Vega, MD; Ines Garcia, MD; Juana Rivera, MD) and Puerto Rico Department of Health (Carmen Deseda, MD)

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