ZEN Colombia Study

Zika in Pregnant Women and Children in Colombia

Supporting Statement: Part B

Submitted : September 26, 2016

Cheryl Broussard, PhD
Telephone: 404-498-3949
Fax: 404-498-3550
E-mail: CBroussard@cdc.gov
Pregnancy and Birth Defects Task Force
CDC Zika Virus Response Team
Centers for Disease Control and Prevention
Atlanta, Georgia 30341

Table of Contents

B. Collections of Information Employing Statistical Methods

B. Collections of Information Employing Statistical Methods

B.1. Respondent Universe and Sampling Methods

The target for the ZEN Colombia study enrollment is 5,000 pregnant women, up to 1,250 male partners, 5,000 fetuses, and 4,500 newborns. This assumes a 25% participation rate among male partners and that 90% of infants are live born.

Participating pregnant women will be screened for eligibility and enrolled until a sample size of 5,000 is achieved. A sample size of 5,000 corresponds to 80% power to detect an odds ratio of 50 for the association between ZIKV infection in pregnancy and microcephaly, assuming an infection rate of 10% in the cohort and a baseline risk of microcephaly of 2 per 10,000 births.

Sample size calculations for different infection rates, odds ratios, and baseline prevalence of outcomes are shown in Table B1. Sample size calculations for nested case-control studies with 1:1, 1:2, and 1:3 case-control matching are also included in Table B2.

Table B1. Estimated total sample sizes required for 3 outcomes by ZIKV infection rate in the cohort and minimum detectable odds ratios.

		2/10,000 Prevalence			3/1,000 Prevalence			1/10 Prevalence		
ZIKV [a]	OR[b]	N[c]	ZIKV Exp.[d]	Cases[e]	N[c]	ZIKV Exp.[d]	Cases[e]	N[c]	ZIKV Exp.[d]	Cases[e]
1%	1.5							48,100	481	4,833
	2							15,300	153	1,544
	5				55,700	557	173	2,300	23	238
	10				20,100	201	65	1,000	10	109
	20				8,500	85	30	600	6	71
	50	44,000	440	12	3,200	32	13	300	3	44
	100	21,200	212	8	1,700	17	10	300	3	59
5%	1.5							9,980	499	1,022
	2				89,360	4,468	280	3,160	158	331
	5				11,460	573	40	480	24	57
	10	60,540	3,027	17	4,120	206	17	200	10	29
	20	25,320	1,266	9	1,760	88	10	120	6	23
	50	9,000	450	5	660	33	5	80	4	27
	100	4,320	216	4	340	17	5	60	3	35
10%	1.5							5,250	525	550

	2				46,720	4,672	154	1,660	166	182
	5	88,21	8,821		5,940	594		250	25	
		0		23			24			34
	10	31,29	3,129		2,130	213		110	11	
		0		11			11			20
	20	13,06	1,306		900	90		60	6	
		0		7			7			17
	50	4,640	464	4	340	34	5	40	4	23
	100	2,230	223	4	170	17	5	30	3	32
20%	1.5				84,765	16,95		2,925	585	
						3	279			321
	2				25,775	5,155	91	920	184	109
	5	47,85	9,570		3,225	645		135	27	
		0		16			16			23
	10	16,84	3,368		1,145	229		60	12	
		0		8			8			16
	20	6,990	1,398	6	485	97	6	35	7	16
	50	2,475	495	4	180	36	5	20	4	21
	100	1,185	237	4	95	19	5	15	3	31

Gray shaded boxed indicate total sample sizes >100,000.

[a] Proportion of study cohort with incident ZIKV infection.

[b] Minimum detectable odds ratio.

[c] Sample size required to detect the minimum detectable odds ratio at the given ZIKV infection rate.

[d] Expected number of women exposed to ZIKV in pregnancy.

[e] Expected number of cases occurring among women exposed and unexposed to ZIKV.

Table B2. Estimated sample size required by ZIKV infection in pregnancy among mothers without adverse outcomes, proportion of cases: controls, and minimum detectable odds ratio.

% Controls Infected	Odds Ratio	Sample Size					
		1:1 Match		1:2 Match		1:3 Match	
		Total	# Cases	Total	# Cases	Total	# Cases
1%	1.5	15,826	7,913	18,189	6,063	21,780	5,445
	2	4,710	2,355	5,490	1,830	6,616	1,654
	5	564	282	681	227	832	208
	10	200	100	246	82	300	75
	20	86	43	108	36	132	33
	50	36	18	45	15	56	14
	100	22	11	27	9	32	8
5%	1.5	3,362	1,681	3,855	1,285	4,612	1,153
	2	1,018	509	1,182	394	1,424	356

	5	134	67	159	53	192	48
	10	54	27	63	21	80	20
	20	28	14	33	11	40	10
	50	16	8	18	6	24	6
	100	12	6	15	5	16	4
10%	1.5	1,816	908	2,079	693	2,484	621
	2	562	281	648	216	780	195
	5	80	40	96	32	116	29
	10	36	18	42	14	52	13
	20	20	10	24	8	28	7
	50	14	7	15	5	20	5
	100	12	6	12	4	16	4
20%	1.5	1,070	535	1,218	406	1,452	363
	2	344	172	393	131	472	118
	5	58	29	66	22	80	20
	10	30	15	33	11	40	10
	20	20	10	21	7	24	6
	50	14	7	15	5	20	5
	100	12	6	12	4	16	4

B.2. Procedures for the Collection of Information

Pregnant women will be recruited in the first trimester of pregnancy at participating clinics in Colombia's private and public health care systems and followed through their pregnancy, delivery, and immediate post-partum period. The Pregnant Woman Eligibility Screener Form (Att B.1), administered to potential participants by trained ZEN research staff, will be used to confirm participant eligibility prior to consent. At the enrollment visit, pregnant women will be given the Pregnant Woman Enrollment Questionnaire (Att B.2) which includes information on demographics, risk factors for Zika virus exposure, pregnancy and medical history, and risk factors for ZIKV exposure and an Adult Symptoms Questionnaire (Att B.5). All pregnant women will attend monthly study visits that coincide with their prenatal care visits through the end of pregnancy and will be given the Maternal Follow-Up (Att B.3) and Adult Symptoms Questionnaires (Att B.5). Pregnant women will be monitored for incident ZIKV infection by collection of urine, about two weeks after visits to the clinic, until the middle of the third trimester (approximately 32 weeks gestation). If a woman is confirmed to have ZIKV, she will complete an Adult Symptoms Questionnaire (Att B.5) every 2 weeks until she is negative for 2 consecutive samples. If a woman chooses to terminate a pregnancy or has a spontaneous fetal demise, an Adult Symptoms Questionnaire (Att B.5) will be administered at that time. At delivery or within 72 hours postpartum, the mother will be administered the Infant Symptoms (Att B.6), Adult Symptoms (Att B.5), and Maternal Follow-Up (Att B.3) Questionnaires.

Infants of mothers participating in the study will be followed from birth to 6 months of age to detect health outcomes that might not have been detectable at birth. Study visits will correspond

to regular well-baby visits at 1, 2, 3 and 6 months of age. Study staff will conduct developmental assessments, physical examination, and hearing and eye exams. Mothers will be administered the Infant Symptoms Questionnaire (Att B.6) at each visit. Urine samples will be collected every 2 weeks to monitor for incident ZIKV infection in infancy. If an infant is confirmed to have ZIKV, the mother will administered the Infant Symptoms Questionnaire (Att B.6).

In addition to administered questionnaires, ZEN Colombia study staff will abstract medical records from mothers' prenatal care, sick visits, and delivery to capture relevant medical information. Mothers' medical record abstraction will be conducted up to 6 months after delivery to collect information on post-partum medical issues. Staff will also abstract medical records from children enrolled in the study to obtain information on diagnoses, test results, medical procedures, and hospitalizations up to the 6 month birthday.

Male partners will be recruited via their pregnant partners around the time of their partners' enrollment into the study. The Male Partner Eligibility Screener Form (Att B.8), administered to potential participants by trained ZEN research staff, will be used to confirm participant eligibility prior to consent. At enrollment, men will provide a blood sample and complete the Male Enrollment Questionnaire (Att B.4) and Adult Symptoms Questionnaire (Att B.5). Men will provide urine samples monthly through the second trimester of their partner's pregnancy (about 27 weeks of gestation) to monitor for incident ZIKV infection. Men will complete the Adult Symptoms Questionnaire (Att B.5) at the time of each specimen collection. If the male partner is confirmed to have ZIKV, semen collection kits will be provided to the participants with instructions for home collection. Semen will be collected every 2 weeks until semen is negative for ZIKV for two consecutive samples or until the partner's pregnancy ends. Semen samples will be picked-up by study staff when they are conducting their home visits. If a man does not want to provide semen samples, follow-up will be discontinued.

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

Efforts are made to maximize the response rate. Participants are encouraged to complete the study throughout the pregnancy and 6 months following the infant delivery, with the exception of pregnancies that end in fetal loss. Participating and completing the study is imperative to better understand the effect of ZIKV infection during pregnancy.

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. Additionally, pregnant women would be identified to facilitate referral to receive the increased level of prenatal care recommended for ZIKV-affected pregnancies, both the woman and her male partner will benefit from receiving information and counseling on the health effects they might expect for their infant, and the infant will benefit from being eligible to take part in services and screening recommended for children born to ZIKV-positive mothers. 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 motive their willingness to continue with the study.

To appreciate participants for the costs associated with travel to the clinic for study visits, pregnant women and men will receive 20,000 Colombian pesos (about 7 USD) for travel costs. If the time spent at the study visit extends through lunch, then the participant may be provided costs to cover a meal, 10,000-12,000 Colombian pesos (about 3 USD). These may be given to the participants in the form of cash or transportation tickets to appreciate for their participation.

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. In collaboration with the Instituto Nacional de Salud (INS), CDC plans to pilot test all data collection instruments, including data entry, data editing, and data management for ZEN Colombia study. Results from the pilot test will provide opportunity to refine and revise questions to minimize burden and improve efficacy.

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; Denise Jamieson, MD; Diana Valencia, MS, MS; Carol Rao, ScD; Elizabeth Ailes, PhD; Sherry Farr, PhD; Suzanne Gilboa, PhD; Candice Johnson, PhD; Jennita Reefhuis, PhD; Christina Renquist, MPH; Andrea Sharma, PhD; Van Tong, MPH; Sarah Tinker, PhD; Julie Villanueva, PhD), Emory University (Lisa Haddad, MD) and Colombia INS (Martha Lucia Ospina Martínez, MD; Jorge Martin Rodriguez, MD, MSc; Yamileth Ortiz Gomez, Bg, MSc; Marcela Mercado, Bact, MSc; Maritza Gonzalez, MD, MSc; May Bibiana Osorio Merchan, MSc).

ZEN Colombia Study designed by:

Pregnancy and Birth Defects Task Force
CDC Zika Virus Response Team
U.S. Centers for Disease Control and Prevention
Centers for Disease Control and Prevention
1600 Clifton Rd., NE
Atlanta, GA 30303
Tel: 770-488-7100
Project Officer: Margaret Honein
E-mail: mrh7@cdc.gov

Instituto Nacional de Salud (INS)
Av. Calle 26 No. 51-20
Bogota, D.C., Colombia
Commutador: (1) 220-7700 Ext. 1703-1704
Fax: (1) 220-7700 Ext. 1283-1269
Directora General: Martha Lucia Ospina Martínez
E-mail: mospina@ins.gov.co

Data collected from 2016-2017 by:

Vysnova Partners, Inc.
1901 Research Blcd. Suite 502
Rockville, MD 20850

Pregnancy and Birth Defects Task Force
CDC Zika Virus Response Team
U.S. Centers for Disease Control and Prevention
Centers for Disease Control and Prevention
1600 Clifton Rd., NE
Atlanta, GA 30303
Tel: 770-488-7100
Project Officer: Margaret Honein
E-mail: mrh7@cdc.gov

Instituto Nacional de Salud (INS)
Av. Calle 26 No. 51-20
Bogota, D.C., Colombia
Commutador: (1) 220-7700 Ext. 1703-1704
Fax: (1) 220-7700 Ext. 1283-1269
Directora General: Martha Lucia Ospina Martínez
E-mail: mospina@ins.gov.co

Data analyzed by:

Pregnancy and Birth Defects Task Force
CDC Zika Virus Response Team
U.S. Centers for Disease Control and Prevention
Centers for Disease Control and Prevention
1600 Clifton Rd., NE

Atlanta, GA 30303
Tel: 770-488-7100
Project Officer: Margaret Honein
E-mail: mrh7@cdc.gov

Instituto Nacional de Salud (INS)
Av. Calle 26 No. 51-20
Bogota, D.C., Colombia
Commutador: (1) 220-7700 Ext. 1703-1704
Fax: (1) 220-7700 Ext. 1283-1269
Directora General: Martha Lucia Ospina Martínez
E-mail: mospina@ins.gov.co