**ZEN Colombia Study**

**Zika in Pregnant Women and Children in Colombia**

**Supporting Statement: Part B**

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**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 | | |
| ZIKVa | ORb | Nc | ZIKV Exp.d | Casese | Nc | ZIKV Exp.d | Casese | Nc | ZIKV Exp.d | Casese |
| 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 | 88,210 | 8,821 | 23 | 5,940 | 594 | 24 | 250 | 25 | 34 |
|  | 10 | 31,290 | 3,129 | 11 | 2,130 | 213 | 11 | 110 | 11 | 20 |
|  | 20 | 13,060 | 1,306 | 7 | 900 | 90 | 7 | 60 | 6 | 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 | 16,953 | 279 | 2,925 | 585 | 321 |
|  | 2 |  |  |  | 25,775 | 5,155 | 91 | 920 | 184 | 109 |
|  | 5 | 47,850 | 9,570 | 16 | 3,225 | 645 | 16 | 135 | 27 | 23 |
|  | 10 | 16,840 | 3,368 | 8 | 1,145 | 229 | 8 | 60 | 12 | 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).

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