

ZEN Colombia Study
Zika in Pregnant Women and Children in Colombia

Supporting Statement: Part A

OMB # 0920-17ABB

May 19, 2017

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Goal of the study: The goal of the ZEN Colombia study is to better understand modifiable factors affecting the acquisition of Zika infection among pregnant women in Colombia, and the link between Zika infection during pregnancy and adverse outcomes. 3

Intended use: The data from the ZEN Colombia study will provide critical information leading to evidence-based strategies to prevent ZIKV infection in pregnancy; improved counseling of patients about risks to themselves, their pregnancies, and their children; and effective preparedness for agencies providing services to affected children and families.



Overview

A causal link has been established between Zika virus (ZIKV) infection in pregnancy and microcephaly and other severe fetal brain defects. CDC surveillance and research efforts are underway in the United States (U.S.) (including territories, particularly Puerto Rico), Brazil, and Colombia to understand the range of other adverse pregnancy and infant outcomes associated with Zika infection during pregnancy. However, there are key knowledge gaps that cannot be addressed using surveillance data or retrospective data, and thus there is an urgent need to prospectively study pregnant women in areas of high Zika virus transmission in order to contribute to understanding of:

- Risk factors for ZIKV infection in pregnant women and their infants, including behaviors such as use of mosquito-bite prevention measures or condoms to prevent sexual transmission, and factors associated with maternal-to-child transmission;
- Absolute and relative risk for adverse maternal, fetal, and infant outcomes associated with ZIKV infection; and
- Modifiers of the risk for adverse outcomes among pregnant women and their infants following ZIKV infection, including gestational age at infection, presence of ZIKV symptoms, extended viremia, mode of transmission, prior infections or immunizations, and co-infections.

In early February 2016, the Presidents of the U.S. and Colombia met and agreed that the countries would conduct joint epidemiologic investigations through Colombia's Instituto Nacional de Salud (INS) and the U.S. Centers for Disease Control and Prevention (CDC). These joint research efforts include estimating the prevalence of microcephaly in Colombia, assessing risk factors associated with Zika virus infections and microcephaly, and to better understand the (at that time) potential link between Zika infection and adverse birth outcomes. Please see: <https://www.whitehouse.gov/the-press-office/2016/02/04/fact-sheet-peace-colombia-new-era-partnership-between-united-states-and> for additional details. Following this meeting, CDC received a formal letter of invitation from the Vice Minister of Health of Colombia requesting technical assistance and collaboration regarding the Zika virus epidemic (available upon request). Multiple projects have been jointly developed between INS and CDC, including enhanced surveillance of pregnant women with symptomatic Zika virus disease. We now seek to implement a prospective cohort study in which we will follow women enrolled in the first trimester of pregnancy, their male partners, and their infants in several cities in Colombia in which ZIKV transmission is currently ongoing.

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

This Information Collection Request is submitted as a "New" Information Collection Request, **(an Emergency Collection Request, OMB # 0920-1142, was approved on November 1, 2016 and expires on May 31, 2017)**. The length of data collection request for Office of Management and Budget (OMB) approval is two years. The National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention

(CDC) is making this request as authorized by Section 301 of the Public Health Service Act (42 U.S.C. 241) (**Attachment A**).

ZIKV is a mosquito-borne flavivirus transmitted by *Aedes* species mosquitoes; sexual transmission, mother-to-child transmission, and laboratory-acquired infections have also been reported. Evidence of human ZIKV infection was observed sporadically in Africa and Asia prior to 2007, when an outbreak of ZIKV caused an estimated 5,000 infections in the State of Yap, Federated States of Micronesia. Since then, evidence of ZIKV has been found in 65 countries and territories, mostly in Central and South America. Common symptoms of ZIKV in humans include rash, fever, arthralgia, and nonpurulent conjunctivitis. The illness is usually mild and self-limited, with symptoms lasting for several days to a week; however, based on previous outbreaks, some infections are asymptomatic. The prevalence of asymptomatic infection in the current Central and South American epidemic is unknown.

Although the clinical presentation of ZIKV infection is typically mild, ZIKV infection in pregnancy can cause microcephaly and related brain abnormalities when fetuses are exposed *in utero*. Other adverse pregnancy outcomes related to ZIKV infection remain under study, and include pregnancy loss, other major birth defects, arthrogryposis, eye abnormalities, and neurologic abnormalities.

Colombia's Instituto Nacional de Salud (INS) began surveillance for ZIKV in 2015, reporting the first autochthonous transmission in October 2015 in the north of the country. As of October 2016, Colombia has reported over 105,000 suspected ZIKV cases, over 19,000 of them among pregnant women. The ZEN (Zika en Embarazadas y Niños en Colombia) Colombia study, this translates to Zika in Pregnant Women and Children in Colombia, is a prospective cohort study following pregnant women, their male partners, and their infants in Colombia. Given that the Zika virus may transition from outbreak levels to endemic level, it is critical to begin enrollment rapidly to ensure that a large number of pregnant women with Zika virus infection in the first trimester can be enrolled and followed up to assess outcomes. This study supports CDC's mission as authorized in section 301 of the Public Health Service Act (42 U.S.C. 241) (Att A).

Since receiving emergency OMB approval, the study protocol has been approved by the appropriate Colombian scientific and ethics committees. Training of study staff began on January 30, 2017, and the first pregnant women were enrolled on February 9, 2017, in the first city of Barranquilla. Bucaramanga started training on March 28, 2017 and began enrolling on May 15, 2017. Training in the third site, Tuluá began May 8, 2017 and implementation is planned for the week of May 22, 2017. As of May 19, 2017, 139 pregnant women and 29 male partners have been enrolled in the study. Enrollment is on-going. We are also in the process of obtaining IRB approval to include pregnant minors (16 -17 years); although this will not change our burden, it does broaden our population of interest.

During the Emergency Clearance period, the project team was able to quickly field the interview-administered questionnaires at study enrollment and follow-up visits for all participants. Since initial implementation, protocol changes were made to reflect site-specific

needs. These include changes to questionnaires, flyers, and other documents previously approved in the emergency OMB application. These changes were made to improve comprehension by study participants, reduce participant burden, and capture additional information later found to be necessary for conducting the study. In addition, there is a need to include questionnaires for the mothers to assess infant development during the 0-6 month follow-up.

A.2. Purpose and Use of Information Collection

CDC's goal in developing the ZEN Colombia study is to better understand the adverse pregnancy, maternal and infant health outcomes associated with ZIKV during pregnancy and/or early infancy. In addition, the ZEN Colombia study will assess the modifiable factors affecting the acquisition of Zika infection among pregnant women in Colombia. The data from the ZEN Colombia study will provide critical information supporting the evidence-based strategies to prevent ZIKV infection in pregnancy; improved counseling of pregnant women and their partners about risks to themselves, their pregnancies, and their children; and effective preparedness for agencies providing services to affected children and families.

The primary research questions we aim to address with the ZEN Colombia study are:

1. Evaluate associations between ZIKV in pregnancy and adverse pregnancy or maternal outcomes, such as preterm birth, preeclampsia, maternal death, postpartum hemorrhage, and intrapartum fetal demise, among others. Effect modification by gestational age of infection will also be explored.
2. Quantify the magnitude of the association between ZIKV infection in pregnancy and major birth defects, with specific focus on microcephaly and congenital Zika syndrome. The prospective design of the study will allow estimation of both absolute and relative risk for microcephaly for women with ZIKV infection during pregnancy.
3. Identify risk factors for symptomatic ZIKV infection in pregnancy among all women with laboratory-confirmed ZIKV in pregnancy. A spectrum of risk factors will be considered, including maternal demographics, ZIKV infection characteristics, and other potential risk factors such as smoking and medication use.
4. Identify risk factors for ZIKV infection in infancy. A spectrum of risk factors will be explored, including maternal infection factors and birth and pregnancy factors.
5. Identify risk factors for symptomatic ZIKV infection in infancy among infants with laboratory-confirmed ZIKV born to women enrolled in the study. A spectrum of risk factors will be considered, including maternal ZIKV infection in pregnancy factors, co-infections, sociodemographic characteristics and birth factors.
6. Investigate associations between ZIKV infection in utero or in infancy and hearing loss and other physical, neurologic, and neurodevelopmental outcomes at 6 months of age.
7. Estimate survival of infants born to ZIKV infected mothers.

Secondary research questions we aim to address with the ZEN Colombia study are:

1. Identify risk factors for ZIKV infection in pregnant women, partners and infants. A spectrum of risk factors will be explored, including mosquito bites and mosquito bite preventive measures, sexual transmission, sociodemographic characteristics, and medical

risk factors. The results of this analysis will provide information on the reduction in risk associated with adherence to recommended preventive measures and risk factors for infection in pregnant women.

2. Identify characteristics associated with taking preventive measures (mosquito bite prevention, sexual transmission) against contracting Zika virus among pregnant women and their partners. The results of this analysis will assist in targeting education or intervention to individuals at greatest risk for Zika infection.
3. Describe symptoms associated with ZIKV and estimate the positive predictive value of certain symptoms or constellations of symptoms in pregnant women, men, and infants to allow for refinement of clinical diagnosis of ZIKV infection in a setting in which testing and/or results might not be readily available.
4. Assess the duration of viremia following ZIKV infection and investigate risk factors (such as sociodemographics, comorbidities, and co-infections) associated with prolonged viremia among pregnant women, men, and infants with laboratory-confirmed ZIKV infection in blood.

This study is a part of an ongoing public health emergency response related to the Zika virus outbreak in Colombia. Results of this study will be used to guide INS's and CDC's recommendations for surrounding prevention of ZIKV infection in pregnancy and infancy both internationally and domestically; to improve counseling of patients about risks to themselves, their pregnancies, their partners, and their children; and for enhancing preparedness of agencies providing services to affected children and families.

During the Emergency Clearance period, data collection started in February 2017, and protocol changes were made to adjust to the local setting. The current request is to continue data collection beyond the expiration of the Emergency Clearance period (May 31, 2017). As of May 19, 2017, 139 pregnant women and 29 male partners have been enrolled in the study. Enrollment is on-going. The expected total enrollment will be 5000 pregnant women and 1,250 male partners.

Overview of the Data Collection System

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; C.1), administered to potential participants by trained ZEN research staff, will be used to confirm participant eligibility prior to consent or assent. At the enrollment visit, study staff will interview pregnant women using the Pregnant Woman Enrollment Questionnaire (Att B.2; C.2) and an Adult Symptoms Questionnaire (Att B.5; C.5). All pregnant women will attend monthly study clinic visits through the end of pregnancy and will be interviewed using the Maternal Follow-Up (Att B.3; C.3) and Adult Symptoms Questionnaires (Att B.5; C.5). Pregnant women will have interval visits (about two weeks after clinic visits) where they will be monitored for incident ZIKV infection by collection of urine and be interviewed using the Adult Symptoms Questionnaire (Att B.5; C.5), until the middle of the third trimester (approximately 32

weeks gestation). If a woman is confirmed to have ZIKV, she will be interviewed using the Adult Symptoms Questionnaire (Att B.5; C.5) every 2 weeks and Maternal Follow-Up Questionnaire every month (Att B.3; C.3) until she is negative for 2 consecutive blood samples. If a woman has a spontaneous fetal demise, she will be interviewed using an Adult Symptoms Questionnaire (Att B.5; C.5) if one has not been completed within 7 days prior to the event. At delivery or within 10 days postpartum, the mother will be interviewed using the Infant Symptoms (Att B.6; C.6), Adult Symptoms (Att B.5; C.5), and Maternal Follow-Up (Att B.3; C.3) Questionnaires. All Questionnaires will be conducted in-person (or via telephone if the participant prefers).

Infants of mothers participating in the study will be followed until 6 months of age to detect health outcomes that might not have been detectable at birth. Mothers will be interviewed using the Infant Symptoms Questionnaire (Att B.6; C.6) at each visit and the Ages and Stages Questionnaires (Att B.8; B.9, C.8, C.9) at the 2 and 6 month visit. If an infant is confirmed to have ZIKV, the mother will be interviewed using the Infant Symptoms Questionnaire (Att B.6; C.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 6 months of age.

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.7; C.7), administered in-person (or via telephone if the participant prefers) 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 will be interviewed using the Male Enrollment Questionnaire (Att B.4; C.4) and Adult Symptoms Questionnaire (Att B.5; C.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 and be interviewed using the Adult Symptoms Questionnaire (Att B.5; C.5) at the time of each specimen collection. If the male partner is confirmed to have ZIKV, semen will be collected every 2 weeks until semen is negative for ZIKV for two consecutive semen samples or until the partner's pregnancy ends and men will be interviewed using the Adult Symptom Questionnaire (Att B.5; C.5). Study staff will also abstract medical records for male partner's sick visits.

Description of Information to be Collected

Study staff will interview all study participants in either a face-to-face or phone format.

1. *Pregnant Woman Enrollment Questionnaire – Att B.2; C.2*

This questionnaire should be administered to pregnant women at the time of enrollment,

after consent or assent has been given. The purpose of this questionnaire is to gather demographic, environmental, and behavioral information; health insurance information; medical and pregnancy history; and current knowledge and perceptions about ZIKV.

2. *Maternal Follow-Up Questionnaire – Att B.3; C.3*

This questionnaire is administered to participating pregnant women at each monthly prenatal clinic visit and once during the postpartum period (within 10 days of delivery). The purpose of this questionnaire is to gather information about changes in health insurance, risk or protective factors for ZIKV infection or adverse pregnancy and infant outcomes that may change over the course of a woman’s pregnancy.

3. *Male Enrollment Questionnaire – Att B.4; C.4*

This questionnaire is administered to male partners of enrolled women at the time of enrollment, after consent has been given. The purpose of this questionnaire is to gather demographic, environmental, and behavioral information; health insurance information, medical history; and current knowledge and perceptions about ZIKV.

4. *Adult Symptoms Questionnaire – Att B.5; C.5*

This questionnaire is administered to pregnant women and their male partners at each clinic visit, interval visit, or any time he or she becomes ill with Zika-like symptoms in between regularly-scheduled visits. This questionnaire is also asked of the mother in the postpartum period (up to 10 days after delivery). The purpose of this questionnaire is to identify participants who have symptoms compatible with ZIKV, to refer symptomatic participants for ZIKV testing at a participating clinic, to identify healthcare-seeking behavior, and participation in other ZIKV studies.

5. *Infant Symptoms Questionnaire – Att B.6; C.6*

This questionnaire is administered to one of the parents to complete at the postpartum visit, at each clinic visit, interval visit, or any time the infant becomes ill with Zika-like symptoms in between regularly-scheduled visits. The purpose of this questionnaire is to obtain information on possible ZIKV symptoms among participating infants, breastfeeding practices and feeding difficulties among mothers of these infants, changes in health insurance, and participation in other ZIKV studies.

6. *Ages and Stages Questionnaires – Att B.8; B9; C.8; C9*

This screening tool is administered to one of the parents or guardians when the infant is approximately 2 and 6 months of age. The purpose of this questionnaire is to identify potential developmental delays in the child.

How Information Will Be Shared and for What Purpose

There are three main entities involved in the conduct of the ZEN Colombia study. Colombia’s Instituto Nacional de Salud (INS) is CDC’s scientific collaborator on this study. CDC employs a contractor, Vysnova Partners, Inc., to conduct the ZEN Colombia study in collaboration with

INS. All CDC and contractor personnel who have access to protected data are required to go through training on confidentiality protections and to sign a nondisclosure agreement (Atts F.1, F.2, F.3).

Patients' personally identifiable information (PII) will not be disclosed in any reports, statistical summaries, or shared or disclosed to public entities, external agencies, or other people or organizations outside the entities involved in the conduct of the ZEN Colombia study. We have engaged in discussions with researchers at the National Institute of Health who are launching the ZIP pregnancy cohort in several countries, including Colombia and the Center for Global Health at CDC who will be providing technical assistance to several smaller pregnancy cohorts in Guatemala, Kenya, Thailand and Haiti. Globally, there is growing interest in harmonization across these studies, to ultimately be able to conduct traditional aggregate data meta-analyses or individual participant data meta-analyses based on pooled de-identified data. If there is any possibility of sharing of de-identified data with selected researchers such as those noted here, we will certainly engage INS in any decision to do so. Currently, our plan is to share statistical summaries of de-identified data in peer-reviewed journals and conference presentations.

A.3. Uses of Improved Information Technology and Burden Reduction

The ZEN Colombia study questionnaires have been designed to collect the minimum amount of information necessary to meet the study's objectives. Questions about other factors with the potential to have mediating or moderating effects on primary outcomes have been considered and included. All questionnaire data will be obtained by trained interviewers via questionnaires administered to participants. All data will be entered and stored on the password-protected and secure web-based data collection system which will be housed on an INS server in Colombia.

A.4. Efforts to Identify Duplication and Use of Similar Information

While many experts agree that ZIKV causes microcephaly, more studies are needed to better understand the full spectrum of defects and other adverse pregnancy and infant outcomes caused by congenital ZIKV infection, to quantify the relative and absolute risks of these outcomes among infants who are born to women who were infected at different times during pregnancy, and to identify factors that modify the risk of an adverse pregnancy or birth outcomes (see Rasmussen et al., N Engl J Med 2016; 374:1981-1987). There is an urgent need to prospectively study pregnant women in areas of high Zika virus transmission because many of these key knowledge gaps cannot be addressed using surveillance data or retrospective data. Through its prospective design, the ZEN Colombia study is designed to systematically identify the timing of symptomatic and asymptomatic infections in pregnant women, the latter of which cannot be ascertained from surveillance data or retrospective studies. The prospective design also allows estimation of absolute risk of adverse outcomes, including less severe outcomes that may not yet have been identified, in addition to relative risk, because the base population is well-defined. The ZEN Colombia study is the only data source that collects comprehensive information of ZIKV

infection initiating in the first trimester and associated birth defects from multiple sites in Colombia.

As part of its Zika response efforts, CDC is collaborating with the National Institute of Health (INS) in Colombia, which has had the second-most cases of the mosquito-borne Zika virus after Brazil. The large number of cases and stage of the outbreak in Colombia provides an opportunity to collect actionable information on a shorter timeframe than is possible elsewhere. This collaboration is expected to provide critical scientific information to help the United States, Colombia, and other countries prepare for the unprecedented challenges posed by Zika. Participant enrollment is timed to coincide with the expected second wave of Zika virus cases in Colombia, the peak time for infection, and will provide CDC with the ability to rapidly obtain answers to questions about Zika that will help to shape the course of this public health emergency response.

Although the U.S. National Institutes of Health (NIH) developed an international effort to conduct a multi-country cohort study to evaluate risk of ZIKV infection among pregnant women and their fetus and infants, NIH does not collect symptom information or specimens from associated male partners. The ZEN Colombia study aims to assess the relative contribution of sexual transmission and mosquito-borne transmission to occurrence of infections in pregnancy. In addition, Zika outbreak dynamics may vary according to location. While the NIH study is an international collaboration, ZEN is an intensive, prospective data collection effort focused specifically on Colombia. ZEN will address questions specified by the Colombian government, which the US government has committed to helping INS address, as specified in the agreement between Presidents Obama and Santos, as described above.

Information collection as part of this study are not conducted elsewhere within CDC or within the Department of Health and Human Services.

In general, the ZEN project is the only prospective cohort study of pregnant women currently being undertaken by CDC. Although surveillance efforts focused on ZIKV in pregnancy are currently underway in the U.S. (including territories) and Colombia, the ZEN project is the only CDC-based project that will allow

- Study of both symptomatic and asymptomatic pregnant women with ZIKV infection; and
- Estimation of the absolute risk of microcephaly and other adverse outcomes among pregnant women infected with Zika virus during different gestational ages, which is not possible using a case-control design

Ongoing projects in the CDC Zika response and how the ZEN study fills gaps not addressed by these existing efforts

Project	Contribution added by ZEN
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Persistence of Zika virus in semen and urine of adult men in the United States with confirmed Zika virus infection (OMB Control No. 0920-1139)	Study population includes only adult men with Zika virus infection; one objective of ZEN includes examining persistent viremia specifically in pregnant women
Zika virus persistence in body fluids of patients with Zika virus infection in Puerto Rico (ZIPER Study) (0920-1140)	Study population includes all ages and sexes; one objective of ZEN includes examining persistent viremia specifically in pregnant women
The Effect of Community-Wide Vector Control Initiatives on Zika Virus Transmission in Puerto Rico, 2016 (0920-1137)	Not applicable – ZEN does not address community-wide vector control
Evaluation of In2Care Traps during the Zika Outbreak in Puerto Rico (0920-1071)	Not applicable – ZEN does not address community-wide vector control
Knowledge, Attitudes, and Practices related to a Domestic Readiness Initiative on Zika Virus Disease (0920-1136)	Not applicable – ZEN does not address a specific domestic readiness objective
Integrated Aedes aegypti Vector Control Intervention in Caguas City, Puerto Rico to Prevent and Control Zika Virus Infections (PRA N/A)	Not applicable – ZEN does not address community-wide vector control
Migrant Farm Workers Understanding and Use of Measures to Prevent Zika Transmission (0920-1126)	Not applicable – ZEN does not address migrant farm workers
US Zika Pregnancy Registry (0920-1101 0920-1143)	This project focuses on U.S. pregnant women with laboratory evidence of Zika virus infection; Voluntary reporting to the registry may result in ascertainment bias, while ZEN will prospectively identify pregnant women in early pregnancy. In addition, the ZEN study includes collection of data from maternal questionnaires.
Assessment of Interventions Intended to Protect Pregnant Women in Puerto Rico from Zika virus infections (0920-1118)	Not applicable – ZEN does not assess the effectiveness of specific interventions in preventing Zika virus infection
Assessment of Contraceptive Use and Needs, Puerto Rico, 2016 (0920-1114)	Not applicable – ZEN does not assess contraceptive use and needs
Enhanced Surveillance of Pregnancy and Infant Outcomes following with Zika Virus infection in Pregnancy, Colombia (PRA N/A)	ZEN will prospectively identify pregnant women in early pregnancy and collect data from maternal questionnaires, rather than relying solely on medical records, as is done in this surveillance effort; the surveillance data do not allow identification of absolute risk, because the base population is

	challenging to quantify. Further, because infections are identified retrospectively, exact timing of infection during pregnancy cannot be ascertained. Only symptomatic pregnant women are included in the surveillance project, while ZEN will allow identification of both symptomatic and asymptomatic pregnant women.
Characterization of Guillain-Barré Syndrome Cases in the Setting of Zika Virus Transmission— Colombia, 2016 (PRA N/A)	ZEN does not focus on Guillain-Barré Syndrome as an outcome
Formative Evaluation of Zika Prevention Kits for Pregnant Women in Puerto Rico (0920-1071)	ZEN does not propose evaluation of Zika Prevention Kits
Case-control microcephaly study in Brazil (0920-1011)	ZEN will start with a defined base population of pregnant women at risk for Zika infection in their first trimester of pregnancy and prospectively identify timing of infection in this cohort of pregnant women, which will allow estimation of the absolute risk of microcephaly and other adverse outcomes. Retrospective case identification is vulnerable to selection bias, particularly in relation to symptomatic infection. Further, a case-control study can only estimate relative risk.
Collection of serum and plasma from patients with antibodies reactive with Zika virus and other arboviruses (PRA N/A)	ZEN focuses specifically on pregnant women and their infants
Mosquito Surveillance Survey (0920-1101)	Not applicable – ZEN does not propose to assess mosquito populations
American Samoa Zika Surveillance (0920-1011)	ZEN will prospectively identify pregnant women in early pregnancy and collect data from maternal questionnaires, rather than relying solely on medical records, as is done in this surveillance effort; the surveillance data do not allow identification of absolute risk, because the base population is challenging to quantify. Further, because infections are identified retrospectively, exact timing of infection during pregnancy cannot be ascertained. ZEN will allow identification of both symptomatic and asymptomatic pregnant women.

Case-control GBS study in PR – Surveillance (0920-1106)	ZEN does not focus on Guillain-Barré Syndrome as an outcome
Case-control GBS study in PR - Records Abstraction (PRA N/A)	ZEN does not focus on Guillain-Barré Syndrome as an outcome
Formative evaluation among partners of pregnant women about Zika in PR (0920-0572)	Not applicable – ZEN does not include formative evaluation of any programs
Zika Postpartum Emergency Response Survey, Puerto Rico (0920-1127)	ZEN will ask mothers immediately postpartum information on Zika symptoms to go along with the specimen collected as well as a follow-up questionnaire to assess changes in risk and behavior since the last study visit. These questions build on each other, rather than being a point-in-time survey.
Monitoring & Evaluation for the Zika Contraception Access Network (0920-1164)	Not applicable – ZEN does not monitor and evaluate contraceptive use and needs
Zika Virus RNA Persistence in Pregnant Women and Congenitally Exposed Infants in Puerto Rico (PRN to be assigned)	ZEN will prospectively identify pregnant women in early pregnancy in addition to assessing prolonged viremia in pregnant women.

A.5. Impact on Small Businesses or Other Small Entities

Data will be collected from private and public health care systems in the study cities in Colombia, including some that may be small businesses. The study data collection elements are the absolute minimum required for the intended use of the data. The survey instruments will be presented in a clear and easy to complete format based on previous surveys and recommendations from survey methodology research.

A.6. Consequences of Collecting the Information Less Frequently

Each woman will participate starting in the first trimester of her pregnancy through the first 6 months of her baby’s life. Each male partner will participate, until about 27 weeks of gestation of his partner’s pregnancy or if ZIKV positive, until the end of his partner’s pregnancy. Infants will participate for the first 6 months of life. It is important to monitor health status for both mothers and infants throughout pregnancy and during early infancy with multiple visits, particularly for mothers with ZIKV infection. Male partners will be monitored for ZIKV infection. The data collection frequency is essential to answer questions about transmission of ZIKV, adverse maternal, fetal, and infant outcomes following ZIKV infection in pregnancy, and risk factors for infection and adverse outcomes. Collecting information less frequently may not permit this determination.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This information collection fully complies with all guidelines of 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A 60-Day Federal Registry Notice was published in the Federal Registry on November 17, 2016. Vol. 81, NO. 222, pp. 81144. One non-substantive public comment to the 60-day federal register notice was received. CDC's standard reply was sent in response.

CDC has consulted with other public health agencies, e.g., NIH, to ensure there are no duplication of similar efforts in the study location.

A.9. Explanation of Any Payment or Gift to Respondents

Participants may be provided a transportation cost that covers expenses incurred for travel and for meals that will be set in accordance with the local economy and recent research studies conducted with this population. The intent of the per diem is to minimize personal financial outlay of participants for their time and travel. This plan will be reviewed by a governmental ethics committee in each participating city in Colombia in accordance with Colombian research guidelines.

The actual amounts may be adjusted for each city based on what is appropriate for the local economy. These may be given to the participant in the form of cash, transportation tickets, or as determined by the cities as appropriate and within Colombian research guidelines. The cost value will range from 0 to 20,000 Colombian pesos (~0-7 USD) for any single trip and 0 to 12,000 pesos (~0-3 USD) for meals. If the local recommendation in a given study site is to not provide any cost coverage, then in that site, nothing will be provided.

A.10. Protection of Privacy and Confidentiality of Information Provided by Respondents

Data will be collected as information in identifiable form (IIF) therefore the Privacy Act does apply. Records are covered under CDC Privacy Act System of Records Notice (SORN) No. 0920-0136 "Epidemiologic Studies and Surveillance of Disease Problems" and SORN No. 09-20-0113, "Epidemic Investigation Case Records Systems Notice." The compilation of individual research results and responses into a study database for the ZEN Colombia study will be used only for research purposes. Investigators have completed certifications in Information Security and Privacy Awareness and will put systems in place to meet Privacy Act requirements. The sections below describe the protections in place to preserve privacy and confidentiality.

ZEN study site staff will protect the confidentiality of participant data and research records by assigning a unique study Participant Identification Number (PIN) to all study forms, specimens, and database. To ensure the anonymity of the research data, this PIN will be the only identifier associated with a subject's research data, such as their questionnaire responses, laboratory results, and abstracted medical information. An electronic crosswalk file that is separate from the research data will be kept to provide the link between the unique subject PIN and associated PII (e.g. names, dates of birth, contact information, etc.). Resulting reports or publications regarding this research are to be reported in aggregate and ensure individuals cannot be identified. A number of procedures and security measures are in place to protect patient privacy. At clinical sites, study forms will be stored in a locked file cabinet that only study staff can access. Study data will be stored on a password-protected database that only study staff can access. Patients' personally identifiable information (PII) will not be shared or disclosed to public entities, external agencies, or other people or organizations outside the entities conducting the ZEN Colombia study. CDC's Institutional Review Board oversees certain types of data analysis conducted with this information collection, and the confidentiality of information submitted by patients and clinics is protected by an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act. CDC has an Assurance of Confidentiality for this study (Appendix F.1). INS employees are not covered by this Assurance of Confidentiality.

During the administration of the informed consent or assent document, ZEN study staff will explain to respondents that participation is voluntary, they can end their participation at any time without negative consequences. An informed consent and assent for the collection of data has been approved (Atts D.1, D.2, D.3, and D.4).

The informed consent and assent documents (Att D.1, D.2, D.3, and D.4) clearly explain that the study findings will be compiled and only presented on a group level, with no individuals identified. Participants are also told that relevant test results will be shared with their doctors. In addition, within the informed consent or assent document, there is a separate item where the participant must check "Yes" or "No" regarding their approval to allow researchers store study samples and health information for future research.

Paper documentation, such as the questionnaires and documentation of informed consent or assent, will be stored in a designated and secured office area and similarly designated and locked filing cabinet within each study site. Research data will be stored in on online database and will be kept secure and confidential on the INS server, requiring user authentication and password protection. Administrator controls in place include regular backups, security training, completion of a security certification and accreditation (C&A), security plans, and policies. Access to ZEN Colombia study data is limited to CDC, INS, and contractor staff supporting the project. The contractor follows federal security requirements and adheres to all CDC security policies and regulations. Requirements for adherence to privacy provisions and policies, as well as instructions for destruction of study data and files when the contract ends, are specified in the contract language.

A.11. Institutional Review Board (IRB) and Justification for Sensitive Questions

The CDC Institutional Review Board (IRB) approved the study as Research (Att E.1). The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), Categories 2, 5, and 7. The IRB determined the study to be not greater than minimal risk to subjects. The IRB approved the inclusion of children under 45 CFR 46.404 and the inclusion of pregnant women under 45 CFR 46.204. A first CDC IRB amendment was approved on January 3, 2017, a second amendment on January 30, 2017, and a third amendment on March 06, 2017. As of May 19, 2017, a fourth amendment will be submitted for IRB review. INS approval was received on 12/12/16 (Att E.2). Vysnova reliance to CDC IRB was received 9/26/16 (Att E.3).

The participating IRBs will also conduct continuing reviews of routine annual data points as well as required review of any adverse events or protocol violations as needed. Some data to be collected for ZEN Colombia may be sensitive in nature to some respondents. To reduce the sensitivity of these questions, respondents will be completing questionnaires in private and will be reminded that they are not required to answer any questions to which they would prefer not to respond. Topics that may be perceived by subjects as sensitive are: 1) patient demographic information including social-economic status; 2) patient medical history including number of pregnancies lost; 3) Zika knowledge, symptom and diagnosis information; 4) sexual behavior and practice, and alcohol or drug use; 5) pregnancy outcome information; and 6) infant health information.

CDC developed the data collection requirements after extensive consultation with medical professionals and epidemiologists. There is consensus that the sensitive information collected is necessary to provide accurate information of the ZIKV infection in order to identify associated risk factors and adverse maternal, fetal, and infant adverse outcomes following ZIKV infection in pregnancy.

A.12. Estimates of Annualized Burden Hours and Costs

Burden Hours

Respondents are pregnant women and their male partners who agree to participate in the study.

ZEN Colombia study staff will use the Eligibility Screener Questionnaire to confirm eligibility of pregnant women. Because it is administered prior to initiation of the consent process, the burden estimate for administration of the ZEN Screener Questionnaire is based on a larger pool of pregnant women than that of women eligible and consented for the ZEN study. This assumes 25% of women screened will not meet eligibility criteria. The remainder of the burden estimate is based on completion of questionnaires by consented respondents: 5,000 pregnant women, 1,250 male partners, and 4,500 newborns. This assumes a 25% participation rate among male

partners and that 90% of infants are live born.

As exhibited in Table A.12-1, each study questionnaire instrument is considered one response. The annualized burden hours for each questionnaire was calculated by multiplying the number of respondents by the number of responses (estimated number of times each questionnaire would be completed) per respondent by the average burden per response.

The total estimated annualized burden for all information collection for ZEN is 20,541 hours. This includes adding two infant questionnaires. The Number of Respondents requested for the Emergency Clearance was based on the Number of Respondents that the Program estimated annually.

A. 12 – 1 Estimated Annualized Burden Hours

Respondents	Form Name	No. of Respondents	No. of Responses (Questionnaires) per Respondent	Average Burden per Response (in hours)	Total Burden Hours
Pregnant women	Pregnant women eligibility questionnaire	3,125	1	5/60	260
	Pregnant women enrollment questionnaire	2,500	1	35/60	1,458
	Adult symptoms questionnaire	2,500	15	10/60	6,250
	Pregnant women follow-up questionnaire	2,500	8	15/60	5,000
	Infant symptoms questionnaire	2,250	14	10/60	5,250
	Infant Ages and Stages Questionnaire: 2 Month	2,250	1	15/60	563
	Infant Ages and Stages Questionnaire: 6 Month	2,250	1	15/60	563
Male partners	Male partner eligibility questionnaire	2,500	1	5/60	208

	Male enrollment questionnaire	625	1	25/60	260
	Adult symptoms questionnaire	625	7	10/60	729
	Total				20,541

a) Estimated Annualized Cost to the Federal Government

Information for the ZEN Colombia study may be collected by nurses, social workers, data entry clerk, field study staff, lab technicians, and physicians.

A. 12 – 2 Annualized Cost to Respondents

Type of Respondents	Form Name	Number of Respondents	Number of Responses per Respondent	Average Burden Hours per Response	Total Burden Hours	Hourly Wage Rate	Total Costs
Pregnant women	Pregnant women eligibility questionnaire	3,125	1	5/60	261	\$2.50 USD*	\$652.50
	Pregnant women enrollment questionnaire	2,500	1	35/60	1,459	\$2.50 USD*	\$ 3,647.50
	Adult symptoms questionnaire	2,500	15	10/60	6,255	\$2.50 USD*	\$ 15,637.50
	Pregnant women follow-up questionnaire	2,500	8	15/60	5,000	\$2.50 USD*	\$12,500
	Infant symptoms questionnaire	2,250	14	10/60	5,250	\$2.50 USD*	\$ 13,125
	Infant Ages and Stages questionnaire: 2 months	2,250	1	15/60	562.50	\$2.50 USD*	\$1,406.25
	Infant Ages and Stages questionnaire: 6 months	2,250	1	15/60	562.50	\$2.50 USD*	\$1,406.25
Male partners	Male partner	2,500	1	5/60	208	\$2.50 USD*	\$520

	eligibility questionnaire						
	Male enrollment questionnaire	625	1	25/60	261	\$2.50 USD*	\$ 652.50
	Adult symptoms questionnaire	625	7	10/60	729	\$2.50 USD*	\$ 1,822.50
Total							\$51,370

*Source: UN International Labour Organization estimate of average monthly wage in Colombia (in 2015) divided by 160 hours/month (http://www.ilo.org/ilostat/faces/home/statisticaldata/ContryProfileId?_adf.ctrl-state=ydigxis12_154&_afLoop=691022007511742#!%40%40%3F_afLoop%3D691022007511742%26_adf.ctrl-state%3Dxcdb4823a_4)

A.13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no additional costs to respondents other than their time

A.14. Annualized Cost to the Federal Government

Estimates of annualized costs to the federal government are included in the following table.

A. 17 – 1 Annualized Cost to the Federal Government	
ZEN Colombia Study	
Contract	Annualized Cost
1. Total labor	\$1,842,321.00
2. Total other direct costs	\$1,224,408.00
3. Total overhead	\$11,203.50
4. General and administrative expense	\$279,177.00
5. Fee @ 8%	\$107,269.00
Subtotal	\$3,464,318.50
CDC FTEs	Salary
1. Epidemiologist, GS-601-14/15	\$228,500

2. Epidemiologist, GS-601-13	\$160,000
3. Health Scientist, GS-601-13	\$117,660
4. Statistician, GS-1529-13	\$67,500
5. Public Health Analyst, GS-1529-13	\$67,500
Subtotal	\$641,160
Total Federal Government Cost	\$4,105,478.50

The annualized cost to the federal government is \$4,105,478.50, which includes the contract with Vysnova and CDC staff time to oversee and collaborate on the study. The annual cost of the contract with Vysnova is \$3,464,318.50, which includes operational costs, contractor personnel, facilities, equipment, supplies, laboratory diagnostic tests, and materials necessary to assist CDC with the ZEN Colombia study. CDC staff members provide technical oversight and expertise, including analytic and scientific guidance, on ZEN and to the contract staff. CDC staff members participate in reviewing study protocol, implementation, and attend site visits. CDC staff also conducts scheduled calls to monitor the contractor’s performance and ensure that project standards are met and that the data are of high quality, thus ensuring accurate reporting and generation of valid success rates. CDC staff listed in table A.14-1 dedicates approximately 100% of their time to these activities.

A.15. Explanation for Program Changes or Adjustments

This is a new collection of information.

A.16. Plans for Tabulation and Publication and Project Time Schedule

A 2-year OMB clearance is requested to cover all data collection activities, including enrollment, follow-up and data analysis. Table A.16 below outlines the project time schedule after OMB approval. Analysis plans included conducting descriptive and modeling analyses. Results of the study will be disseminated to the scientific community through the published literature and presentation at meetings. In concert with dissemination to the scientific community, a roll-out plan will be created in collaboration with INS’s and CDC’s communications teams to release lay versions of the study results to the public, as warranted. Routes of communication include press releases, media interviews, INS or CDC websites, and social media.

Project Time Schedule

	Study Year 1				Study Year 2				Study Year 3			
	Jan-Mar	Apr - Jun	Jul - Sep	Oct-Dec	Jan-Mar	Apr - Jun	Jul - Sep	Oct-Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct-Dec
Pregnancy enrollment												
Pregnancy study visits												
Male enrollment												
Male study visits												
6 month infant follow up												
Data analysis, publications												

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate.

No exceptions from display of expiration date are requested.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exemptions to certification are sought.