Assessment to Estimate the Effect of Community-Wide Vector Control Initiatives on Zika Virus Transmission in Puerto Rico, 2016

Request for OMB Approval of a New Emergency Information Collection

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Supporting Statement B

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1. Respondent Universe and Sampling Methods

The respondent universe includes all ~3.5 million residents of Puerto Rico.
On Monday of each week, a list will be generated of all laboratory-positive (i.e., by either RT-PCR or anti-ZIKV IgM ELISA) ZIKV cases identified to PRDH during the previous week. The Cluster Investigation Supervisor (CIS) will review the list and stratify cases by municipality of residence, and randomly select cases from intervention and non-intervention communities. Cluster Investigation Teams (CITs) assigned to either intervention or non-intervention communities will be provided with the case information for the randomly selected cases. Using the contact phone number provided during case reporting, the CIT leader will contact the case-patient or their parent/guardian by telephone, inform them of the investigation, and request a time when the team can visit their household (to administer a questionnaire to all members of the household and collect blood samples) in the next week when they will be present (potentially including nights or weekends). If the individual declines involvement in the investigation or an appointment cannot be made, the next most recent case from that health region will be contacted. This process will be repeated until a maximum of five appointments each have been made per week in the intervention and non-intervention communities.

On the same day as the interview of the residents of the case-patient's household, the same interviews will be conducted at all consenting households within a 100 meter radius of the case-patient's home. Households that are vacant/abandoned, unoccupied, or do not have an adult resident home will not be revisited or otherwise included in the investigation. Households that have outward signs of potential danger to investigation staff (e.g., threatening dog, suspected criminal activity) will not be offered participation. Field staff will document the number of homes in each cluster that appear to be abandoned or vacant.

We expect that by recruiting 500 participants we will be able to accomplish the goals of this investigation. Based on previous household cluster investigation, we expect to recruit, interview, and collect blood from about 32 houses in each cluster. We expect that on average 2–3 persons per home will participate. Therefore, we expect about 3 participants in the target household and an additional 62–93 interviews in the homes within the 100 meter radius of each cluster.

During the Chikungunya cluster investigation in Puerto Rico we found that only 8% of persons with symptomatic CHIKV infection sought healthcare and were identified as CHIKV+ through the surveillance system (this is related to Goal 1.d). Because Zika is a disease with less severe symptoms than Chikungunya, we expect this number to be even smaller. Therefore, we will need more people to be able to accurately estimate this number. We estimate that 500 participants would be sufficient to fulfill Goal 1.d. The exact number of participants will of course depend on exactly how many households per cluster and how many persons per household agree to participate).

Goal 1.e is to describe the clinical spectrum of illness due to ZIKV infection. During the Chikungunya cluster investigation we found that 30% of the participants had evidence of recent Chikungunya infection (5% positive by PCR and 25% positive by IgM ELISA). With 500 participants we would have approximately 150 Zika positive cases. We estimate that this will be sufficient to describe the clinical spectrum of illness by sex, age, and those that are symptomatic.

2. Procedures for the Collection of Information

Definitions

An intervention cluster will be defined as a 100-meter radius within a given community for which community-wide vector control activities (e.g., aerial spraying, mosquito fogging, use of mosquito traps) has been occurring for ≥4 weeks before the household visit. A non-intervention cluster will be defined as a 100-meter radius within a given community for which community-wide vector control activities (e.g., aerial spraying, mosquito fogging, use of mosquito traps) has not occurred for ≥4 weeks before the household visit.

Current ZIKV, DENV, or CHIKV infection will be defined by detection of ZIKV, DENV, or CHIKV nucleic acid in any specimen by RT-PCR. Recent ZIKV infection will be defined by detection of anti-ZIKV IgM antibody by ELISA in a serum specimen in the absence of anti-DENV IgM antibody. Recent flavivirus infection will be defined by detection of anti-ZIKV IgM and anti-DENV IgM antibody by ELISA in a serum specimen. Recent CHIKV infection will be defined by detection of anti-CHIKV IgM antibody by ELISA.

A ZIKV case will be defined as any individual reported to any surveillance system in Puerto Rico that:

i. had laboratory evidence of current or recent ZIKV infection;
ii. is a resident of Puerto Rico (defined by having a Puerto Rico driver's license and/or home address in Puerto Rico) during illness onset; and
iii. did not have a history of travel outside of Puerto Rico in the two weeks before illness onset or, if unavailable, specimen collection.

A dengue case will be defined as any individual reported to any surveillance system in Puerto Rico that: i) had laboratory evidence of current or recent DENV infection and criteria ii and iii above.

A chikungunya case will be defined as any individual reported to any surveillance system in Puerto Rico that: i) had laboratory evidence of current or recent CHIKV infection and criteria ii and iii above.

For household-based cluster investigations, participants will be defined as any member of a household invited to participate in the investigation that answer an individual questionnaire (Attachment H) and provide at least a serum specimen for diagnostic testing. Participants with ZIKV, DENV, or CHIKV infection will be defined by either acute or recent infection with ZIKV, DENV, or CHIKV, respectively.

Symptomatic infection will be defined by the criteria described above along with recent new-onset rash, fever, arthralgia, or conjunctivitis in the 3 months before and 14 days after specimen collection. Asymptomatic infection will be defined by the criteria described above along with absence of reported recent new-onset rash, fever, arthralgia, and conjunctivitis in the 3 months before and 14 days after specimen collection.

As per Puerto Rican law, adults will be defined as individuals ≥21 years of age or individuals ≥14 years of age that: a) live outside of their parents' home; b) have children; or c) are married. All individuals not meeting this criteria will be defined as minors.

Data collection

Passive surveillance data analysis

Suspected and laboratory-positive ZIKV cases reported to PADSS will be analyzed according to whether the case-patient resided in a municipality receiving community-wide vector control activities (e.g., aerial spraying) or not. Incidence rate ratios (IRRs) will be calculated for the periods of time both before and after initiation of vector control activities, as has been previously utilized to evaluate vector control activities during a West Nile virus outbreak in Texas[i]. Ratios-of-ratios (RoRs) will be calculated by comparing IRRs from intervention and non-intervention municipalities or health regions. Municipalities or health regions having successful vector control activities will be defined as those that produce statistically significant RoRs of at least 2.

Household-based cluster investigations

It is expected that a maximum of 10 cluster investigations will be conducted per week throughout the remainder of the ZIKV epidemic in Puerto Rico, or until the study investigators have determined that the investigations should be stopped (e.g., termination of vector control interventions, limited field resources).

At the agreed upon household visit date, the CIT will visit the household to offer participation to the head-of-household. If the head-of-household agrees to participate in the investigation, s/he will be requested to answer a questionnaire on household-specific characteristics (Attachment G), and all residents of the household that are present at the time of visit will be oriented to the investigation and read a consent (Attachments D and E) or assent (Attachment F) script. Individual questionnaires (Attachment H) will be administered and blood, saliva, and urine specimens will be collected from all household members that consent or assent to participate in the investigation. If any participants have reported acute illness at the time of the interview or test positive for ZIKV infection in any specimens by RT-PCR in the absence of symptoms (which could be indicative of either asymptomatic or pre-symptomatic viremia),

they will be contacted by telephone at least 14 days later to complete a follow-up interview to better characterize the individual's illness using the same questionnaire as was administered during the initial visit (Attachment H).

All collected blood, urine, and saliva specimens will be tested for evidence of current infection with ZIKV, DENV, or CHIKV by TrioPlex RT-PCR assay; serum specimens will be also be tested by IgM ELISA to detect evidence of recent ZIKV, DENV, or CHIKV infection. Participants will be informed that their diagnostic test results and appropriate counseling will be conveyed to them by email or telephone within 14 days of becoming available. If a pregnant women is identified as Zika positive then results will be provided to her physician. If participants report that they sought care for a recent acute illness, the patients' medical records may be obtained and reviewed to better describe the patient's illness, clinical diagnosis, and if they were reported as a suspected ZIKV disease case to any surveillance system in operation in Puerto Rico. In addition, any specimens remaining from the patient's medical visit may be collected for ZIKV disease diagnostic testing.

Questionnaires will be available to be administered in either Spanish or English. English version questionnaires will be translated to Spanish by a native Puerto Rican Spanish-speaker and back-translated to English to verify accuracy. Reading level of consent and assent forms will be estimated at Grade 8 and Grade 4 using Microsoft Word software.

Entomologic investigations will be conducted in all cluster investigations. Field staff will deploy up to 20 surveillance mosquito traps (either BG-Sentinel traps or Autocidal Gravid Ovitraps) around homes, and/or perform aspiration inside all participating homes, within the 100 meter radius to evaluate the species and density of mosquitoes. Collected mosquitoes species will be pooled (10 specimens/pool) and tested by RT-PCR to estimate the minimum ZIKV infection rate. It is expected that some 100 pools of mosquitoes (*Aedes aegypti*) will be collected per cluster (approximately 1,000 female mosquitoes).

All data will be entered into RedCap and will be analyzed by SAS, STATA, or R. All databases will be securely stored at CDC Dengue Branch (CDC-DB) and/or PRDH, and will be accessible only to study co-investigators. Rates of ZIKV infection by cluster will be compared between intervention and non-intervention communities to evaluate whether mosquito population densities are associated with rates of ZIKV infection. The rate of symptomatic ZIKV infection will be estimated by stratifying by age and comparing the rates that participants with current or recent ZIKV infection reported recent onset rash, fever, arthralgia, or conjunctivitis. Demographic and clinical characteristics of symptomatically ZIKV-infected individuals identified through household investigations will be compared to those of laboratory-positive ZIKV cases reported to PRDH to identify characteristics associated with seeking care, hospitalization, or diagnosis as ZIKV disease. These findings will then be used to develop or refine messaging to the public and medical communities to improve case-seeking behavior and case reporting, respectively.

3. Methods to Maximize Response Rates and Deal with Nonresponse

To maximize response rate, the purpose and importance of the investigation will be thoroughly explained to heads of household and household members. All questions from potential participants will be answered to ensure that they are adequately informed about the purposes and importance of the investigation. Using the household tracking form (Attachment I), households that do not participate will be designated as

either vacant homes, no response, or refused participation. The age and sex of all household residents will be recorded for participating households, as will the potential participants that are either not home at the time of the visit or refuse participation. Data will then be analyzed taking into account the rates of non-participation by households and household residents to identify potential biases in participation.

4. Tests of Procedures or Methods to be Undertaken

Testing of the questionnaires will be done among CDC employees. Furthermore, the questionnaires are modified from similar CHIKV cluster investigations, so the majority of the proposed questionnaires have been pre-tested, in effect.

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

Brad Biggerstaff is the lead biostatistician for this analysis, and will be assisted by Mark DeLorey and potentially others on the Division of Vector-borne Diseases statistical analysis team. All other CDC co-investigators are expected to be involved in data collection and/or analysis.

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[i] Ruktanonchai DJ, Stonecipher S, Lindsey N, McAllister J, Pillai SK, Horiuchi K, et al. Effect of aerial insecticide spraying on West Nile virus disease--north-central Texas, 2012. The American journal of tropical medicine and hygiene. 2014;91(2):240-5. doi: 10.4269/ajtmh.14-0072. PubMed PMID: 24778196; PubMed Central PMCID: PMCPMC4125243.