Zika virus persistence in body fluids of patients with Zika virus infection in Puerto Rico (ZIPER Study)

Request for OMB approval of a New ICR

Supporting Statement A

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- **Goals:** The objectives of this study are to assess among Zika Virus (ZIKV) PCR-positive cases the:
    - Presence and duration of ZIKV RNA in body fluids including blood, semen or vaginal secretions, urine, saliva and breastmilk among lactating women;;
    - Presence and duration of anti-ZIKV IgM antibodies and presence of anti-ZIKV IgG in

duration of persistence of anti-ZIKV IgM antibodies is unknown as well as the timing from infection to the development of IgG antibodies. The prevalence of ZIKV RNA in various body fluids among patients with acute ZIKV infection and the length of time that ZIKV RNA might persist in these body fluids is not well understood, nor the frequency with which it is infectious. Characterizing these parameters has implications both for diagnosis of ZIKV infection using specimens other than blood that may be more convenient to collect, as well as for potential human-to-human transmission.

Our knowledge of the presence of ZIKV in semen is based on few previous case reports. In one report, of suspected sexual transmission of ZIKV, the wife of a returning traveler was believed to become infected with ZIKV after having sexual intercourse with the traveler. The wife had no other known exposures to ZIKV, and had serologic and clinically compatible ZIKV illness. Because the wife had not traveled outside of the United States, and the couple reported sexual intercourse one day after the traveler returned, transmission of virus through semen has been suggested. The returning traveler experienced symptoms of dysuria, and prostatitis, though the presence of ZIKV RNA in the semen is not known. In a second case, a patient in Tahiti sought care for hematospermia. The patient experienced two Zika-like illnesses, the first 77 days prior to the onset of hematospermia, and the second 21 days prior to the onset of hematospermia. A sample collected 80 days post first illness onset and 24 days post second illness onset was found to contain infectious ZIKV. Based on these cases and case reports in additional body fluids of infected individuals we have reason to believe that ZIKV can be found in the semen of infected men. Virus in semen could be shed intermittently as it has been suggested for other viruses, like Ebola and HIV. More recently, as part of the current outbreak of ZIKV in the Americas, there have been several reports of potential ZIKV sexual transmission. The prevalence of ZIKV RNA and antibodies (IgM and IgG) in body fluids among patients with ZIKV infection and the length of time that ZIKV RNA persists in these body fluids is not well understood.

It is also not known if individuals with asymptomatic ZIKV infection contribute to mosquito-borne virus transmission. Learning about the presence and viral load of ZIKV RNA in the blood of asymptomatic persons would help us determine if mosquitoes can potentially be infected from asymptomatic individuals and thereby contribute to virus transmission and spread. In Puerto Rico, vector control activities are focusing in the geographic areas where symptomatic cases are reported. Determining if asymptomatic individuals can potentially infect mosquitoes would greatly inform strategies for vector control. Moreover, if asymptomatic ZIKV infection does contribute to virus transmission, messaging to household contacts of individuals with ZIKV infection regarding need for use of mosquito avoidance measures would be of public health importance. Measuring the prevalence of shedding among individuals with asymptomatic ZIKV infection in body fluids other than blood could also inform the use of different specimens for screening and diagnosis of Zika, particularly in pregnant women.

Authorizing Legislation comes from Section 301 of the Public Health Service Act (42 U.S.C. 241) (Attachment A).

2. Purpose and Use of Information Collection

The Zika PERsistence (ZIPER) study will help inform the presence and duration of ZIKV shedding in several body fluids among RT-PCR-positive ZIKV cases from Puerto Rico. It will also provide information regarding the duration of detection of anti-ZIKV IgM antibodies and the time for development of IgG antibodies among the same population. In addition, this study will determine the prevalence of anti-ZIKV IgM and IgG, and virus shedding in body fluids among household contacts of ZIKV cases.

We propose to investigate the persistence (shedding) of ZIKV in different body fluids and its relation to immune response to provide a basis for development of non-blood-based diagnostic tools, and target and refine public health interventions to arrest ongoing spread of infection. To do so, we will conduct a prospective cohort study of individuals with reverse transcription-polymerase chain reaction (RT-PCR) positive ZIKV infection and a cross-sectional study of their household contacts. Results and analyses will be used to update relevant counseling messages and recommendations from the CDC.

The study will include baseline and follow-up questionnaires and the collection of the following specimens: blood, saliva, urine from participants of all ages, and semen/vaginal secretions from adults (ages 21 years or older) and legally emancipated minors (support themselves financially, live independent of their parents, are pregnant, or have children). Individuals with RT-PCR positive ZIKV infection will be recruited through the Sentinel Enhanced Dengue Surveillance System (SEDSS) at Saint Luke’s Episcopal Hospital in Ponce, Puerto Rico and through passive surveillance in selected municipalities in Puerto Rico. SEDSS was established in 2012 through a cooperative agreement between the hospital in Consortium with the Ponce School of Medicine and Ponce Research Institute from the Ponce Health Sciences University and the Centers for Disease Control and Prevention (CDC) (Protocol # 6214). Specimens will be tested for the presence of ZIKV RNA by RT-PCR at the CDC Dengue Branch Laboratory in San Juan, and positive specimens will be further tested for virus isolation to evaluate infectivity. Each body fluid will be collected on a weekly basis for 4 weeks and biweekly thereafter until two consecutive negative RT-PCR results are obtained from all specimens. Irrespective

of RNA detection, body fluids will also be collected for RT-PCT at 2, 4, and 6 months to investigate intermittent shedding. Analyses of antibody response through titers of IgM and IgG will be performed at baseline and repeated at 2, 4, and 6months. Among symptomatic participants seven milliliters of blood will be drawn at each study visit split into a tiger top tube (5ml) and a purple top tube (2ml) for a total not to exceed 50 ml during any given 8-week period. At enrollment healthy non-pregnant adults will have 20 ml of blood collected following standard procedures. Two tiger top tubes of 8.5 ml and one 3ml purple top tubes will be collected. These procedures will be repeated at each follow-up visit, see below. RT-PCR-positive participants will be asked to refer up to 5 household members to establish the percentage of household members with detectable and potentially infectious Zika virus RNA in body fluids. Household members who are found to be ZIKV RT-PCR-positive in any body fluid will be invited to participate in the cohort study. A second study visit will be scheduled with household contact at 2 or 4 months, to detect new infections and estimate incidence. Because the original study consent forms do not include this visit, household contacts will be contacted by study staff and will be consented again using the same consent form.

Since gaining emergency clearance on March 18, 2016, the study has made the following progress: staff have been hired and trained on study procedures. Recruitment of participants started on May 2, 2016 using mobile teams. Through September 22, 2016, a total of 316 participants have been recruited in the Ponce health region, including 141 cohort patients and 175 household contacts, of which 23 were positive by RT-PCR in one or multiple specimens and hence were recruited into the cohort arm of the study. A study site has been operating in Ponce since July and a second study site is operating in San Juan. . No analyses of study outcomes has been conducted at the time of this OMB application. We need to continue the study for an additional year in order to complete enrolment of cohort participants to meet the estimated sample size of 350 participants and complete follow-up for all of them.

3. Use of Improved Information Technology and Burden Reduction

Collected data will be directly recorded on computers or tablets to minimize data recording and entry errors and minimize delays in data availability. If paper forms must be used, interview responses will be entered into the database either daily or as a group at the close of data collection.

4. Efforts to Identify Duplication and Use of Similar Information

CDC is leading a study in the United States on the persistence of Zika virus RNA in semen and urine of adult men. The purpose of this study is to determine the frequency, duration, and pattern of Zika virus shedding in semen and urine of infected men. Eligible participants are adult men living in the continental United States or Hawaii who have laboratory-confirmed Zika virus infection. Background health information and specimens from consenting men are self-collected at home once every two weeks for up to 6 months after symptom onset. Specimens are tested for Zika virus RNA by RT-PCR at CDC; those testing positive are further evaluated by virus isolation techniques. As of September 22, 2016, 96 men have consented to participate. We are closely coordinating with the study principal investigator and

may conduct joint analyses for the semen outcomes. The main differences are that the Ziper study in Puerto Rico includes males and females and participants of all ages. It also collects blood, saliva and vaginal secretions in addition to semen and urine.

5. Impact on Small Businesses or Other Small Entities

The collection of information does not primarily involve small entities. However, for the small entities involved, the burdens imposed by CDC's information collection requirements have been reduced to the minimum necessary for CDC to meet its regulatory and public health responsibilities.

6. Consequences of Collecting the Information Less Frequently

It is necessary to collect multiple samples from each participant to increase the robustness of the scientific conclusions of the collection.

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

The activities outlined in this package fully comply with all guidelines of 5 CFR 1320.5.

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

A. A 60-day Federal Register Notice was published in the Federal Register on Monday, May 2, 2016, Volume 81, No. 84, p. 26231 (Attachment B). One non-substantive public comment was received (Attachment B1).

B. There was no consultation outside of the Agency.

9. Explanation of Any Payment or Gift to Respondents

Participants will be provided a token of appreciation for their time. The token of appreciation will be provided to participants in consideration for their time off work to attend the study visit or complete procedures and transportation. In the past, SEDSS participants received an incentive of $20 to return for a convalescent study visit; however, only 30% returned for the follow-up visit. Informal conversations with participants suggested that increasing incentives could help with attrition. Thus, participants will receive $50 dollars for each study visit. All participants older than 7 years of age will receive the same incentive amount. For participants under 7 years of age, the parent will receive the full incentive. Participants will receive this token of appreciation for attending the study visit even if there is incomplete specimen collection. In this study, subjects are paid an amount that is commensurate with time and effort. Whether a subject successfully provides all four samples or just some, he/she is still being inconvenienced, had to miss time from work or school, and had to find transportation. It would be unjust to withhold payment for time and effort based on an inability or unwillingness to provide all samples, and it would constitute a penalty for the voluntary refusal of study procedures, which is prohibited by the regulation. Therefore, incentives will be provided to all participants who attend study visits irrespective of the number of specimens collected. The incentive is based on what other CDC supported projects are using in Puerto Rico. One example is the CDC National HIV Behavioral Surveillance, a cross-sectional study of populations at risk for HIV infection that pays $75 for

participation. The minimum wage in Puerto Rico is $7.25. Public transportation is not readily available in the study areas, and participants usually pay for taxis to attend follow-up visits. Participants travel distance ranges from 5km tin neighborhoods close to downtown Ponce as El Tuque to 40km from neighboring municipalities such as Yauco. Baseline visits take on average one hour , while follow-up visits take about 20 minutes. The incentive used in ZiPer, has contributed to greater retention. Of the 141 cohort participants enrolled so far, two have been administratively discontinued, and only one has been lost to follow-up. Visit attendance is 88% for the second study visits and from 97% to 100% attendance for the other study visits. The incentive amount is appropriate in order to compensate for time lost, travel and meals and has contributed to prevent attrition in the Ziper project. Because we do not yet know how long Zika virus persists in body fluids, we do not have a set time frame or a maximum number of visits for the study. At present, the study is designed to obtain body fluids at 2, 4, and 6 months for all subjects, even if they no longer have detectable virus in their samples. The minimum number of visits will be 8, and there could be as many as 14 or more, if subjects still have detectable virus at 6 months.

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

This information collection request has been reviewed by the CDC National Center for Emerging and Zoonotic Diseases (NCEZID). NCEZID has determined that the Privacy Act applies to this information collection request. The applicable System of Records Notice is 09-20-0136.

Only interviewers and staff trained in specimen collection will be used in the proposed study. A private environment will be used for study procedures to ensure confidentially of participant data. All participant information contained on study forms, in laboratory records and reports, and in electronic files will be kept confidential. Specimens and study forms will be linked through a unique study number only. Personally identifying information (e.g., names) will not be transmitted with specimens.

Only the Site Coordinator and authorized hospital staff will have access to the patient's information. The study forms will be faxed or sent courier in a sealed envelope marked as confidential to the CDC Dengue Branch for data entry after the forms are reviewed and completed. Physical documents containing study data will be stored in a locked file cabinet at the CDC Site Coordinator's Office. Questionnaires will be destroyed within one year after all data are entered and verified. Consent forms will be kept in locked cabinets for 3 years after data collection is complete. All electronic files will subsequently be stored in a password protected database on a secure network at the Dengue Branch. Only individuals with security codes will have access to electronically stored data. Additionally, only the CDC Site Coordinator, primary investigator, and co-investigators will have access to data with identifying information; collaborators will only be provided de-identified data with codes. The results from this study will be published or presented for scientific purposes in aggregate form only so that individuals cannot be identified.

Informed consent

If the person agrees to participate, the nurse will give the person the consent form to read and asked to provide written consent (Attachment E). Informed consent will be administered in Spanish. If the patient agrees to participate and cannot read, the nurse or CDC staff will read the consent form as the participant looks at the form being read to them. Illiterate participants will be asked to consent with their name or to write a letter "x," which is accepted as legally effective signature. The consent will also be available in audio/video format that will be administered in a tablet/computer. A paper copy will still be signed and a copy of the consent provided to the participant.

Parents/legal guardians will be asked to provide permission for children to participate. In Puerto Rico the legal age for consenting for medical treatments is 21 years old. However, emancipated minors are not considered children under the law and may give legal informed consent. Patients 14 to 20 years old who fulfill one or more of the following criteria are considered emancipated and will provide independent consent to participate in the study as adults and parental permission will not be sought: 1) legally emancipated, 2) support themselves financially, 3) live independent of their parents, 4) are pregnant, or 5) have children. (Article 13, Section 13 of Regulation 7617 of the Office of Patient Ombudsman, Act #194 of August 25, 2000). All non-emancipated minors between 14 and 20 years old, will complete an assent form (Attachment E) and if accompanied by a parent, the parent will complete the consent form. For all non-emancipated minors 16 to 20 years old who wish to participate and are **not** accompanied by their parents, we will request a waiver of documentation for parental permission in accordance with the provision of law (Article 13, Section 13 of Regulation 7617 of the Office of Patient Ombudsman, Act #194 of August 25, 2000) that allows for them to receive medical care without written consent under emergency situations. This will be recorded in the consent form and the parents will be called by phone to request their authorization for enrollment in the study. Written assent will be sought from non-emancipated minors age 14-20. Verbal assent will be sought for those from 7 to 13 years old. Recruiter will use a script to obtain verbal assent among this group (Attachment E). Written informed consent will be obtained from all adult subjects. If the patient is undecided and/or has questions about study participation, they will be encouraged to discuss any questions with study staff.

After the consent form is signed, a copy of the consent/assent form will be provided to the participant for their records. All consent and assent forms will be placed in a locked box in the triage area during the day and they will be brought by the study coordinator to a locked office and placed in a locked cabinet at the end of each day. All consent and assent forms will be destroyed 3 years after the study has been closed.

Waiver for documentation of parental permission.

The Puerto Rico law (Article 13, Section 13 of Regulation 7617 of the Office of Patient Ombudsman, Act #194 of August 25, 2000) states that a non-emancipated minor 14 to 20 years old may request medical treatment for emergency situations without parent present if the physician determines that the minor has the maturity and capacity to consent for him or herself. The physician providing medical care to this minor is responsible for the proper documentation in the medical record of how he/she determined the minor's capacity to consent for treatment. Given that this study presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context, we are requesting to have the parental permission

documentation waived for non-emancipated minors age 16 (legal driving age) to 20 who are not accompanied by a parent. The nursing staff will document in the inform consent form (Attachment E) that the parent was contacted by phone and authorized the study procedures. The physician in care of the minor will attest that the patient was determined to be capable of providing informed consent by documenting this fact in the patient's medical record.

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

Institutional Review Board (IRB)

The protocols and tools used to conduct the shedding study were reviewed and approved by NCEZID's Human Subjects Advisor who determined that the data collection meets the definition of research under 45 CFR 46.102(d). The protocols and tools were approved (Attachment L).

Justification for Sensitive Questions

Sensitive questions are essential to meeting the goals of these information collections.

12. Estimates of Annualized Burden Hours and Costs

Estimated Annualized Burden Hours

The total number of estimated annualized burden hours for this projects is 374. The breakdown of how this estimate was reached is in the following table.

Type of Respondent	Form Name	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Burden Hours
Public health personnel	Shedding Questionnaire (Symptomatics)	200	8	10/60	267
	Shedding Questionnaire (Cross-Sectional Asymptomatics)	600	1	10/60	100
General public	Shedding Eligibility Form	1,000	1	2/60	33
	Contact Information Form	200	1	2/60	7
Total					407

Estimated Annualized Burden Costs to Respondents

The average annual response burden cost is estimated to be $12,114.10. The hourly wage estimates are based on the Bureau of Labor Statistics May 2014 National Occupational Employment and Wage

Estimates (http://www.bls.gov/oes/current/oes_pr.htm#00-0000). Registered nurses are often the persons interviewed at hospitals, so their mean hourly wage ($33.55) is used to represent the public health personnel wages.

Type of Respondent	Form Name	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Public health personnel	Questionnaire (Symptomatics)	267	$33.55	$8,957.85
	Questionnaire (Cross-Sectional Asymptomatics)	100	$33.55	$3,355.00
General public	Shedding Eligibility Form	33	$22.71	$749.43
	Contact Information Form	7	$22.71	$158.97
Total				$13,221.25

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

There are no costs to respondents other than their time to participate.

14. Annualized Cost to the Government

The cost to the federal government is estimated at $109,521.60. The study will require one doctoral level epidemiologist for six months (50% of the time), two MPH-level contractors full-time for six months, and two nurse contractors part-time for six months. For the CDC employees, hourly wage rates were used for step-1 FTEs for the Atlanta locality. These numbers are available at https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/pdf/2015/ATL.pdf. The hourly wage for the nurse contractors comes from the mean national hourly wage for registered nurses.

Position	**Hours**	**Hourly Wage**	**Total**
Epidemiologist	480	$42.31	$20,308.80
MPH-level contractors (x2)	1,920	$29.69	$57,004.80
Nurse contractors (x2)	960	$33.55	$32,208.00
Total			$109,521.60

15. Explanation for Program Changes or Adjustments

This is a new information collection request, therefore program changes and adjustments do not apply at this time.

16. Plans for Tabulation and Publication and Project Time Schedule

Estimated dates for implementing and completing key activities are demonstrated in the table below. The shaded sections are the activities that will be completed before the expiration of the emergency

clearance on September 30, 2016.

Activities	Study Timeline in Months													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Local Ethics Committee Review	x													
Investigator Coordination Meeting	x													
Questionnaire Development	x													
Study Training		x												
Recruitment		x	x	x										
Data Collection		x	x	x	x	x	x	x	x	x	x	x		
Data Management		x	x	x	x	x	x	x	x	x	x	x		
Data Analysis		x	x	x	x	x	x	x	x	x	x	x		
Laboratory Analysis		x	x	x	x	x	x	x	x	x	x	x		
Results					x	x	x	x	x	x	x	x		
Interim Project Report				x	x									
Final Project Reports												x	x	x
Final Project Review Process												x	x	x
Dissemination of Project Outcomes												x	x	x

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

The OMB Expiration Date will be displayed.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

Attachments

A. Public Health Service Act (42 USC 241)
B. 60-day FRN
    B1. Public comment
C. Model Coupon
D. Eligibility Form
E. Consent Forms for Zika Persistence Study (English and Spanish versions)
F. ZIPER Phone recruitment script (English and Spanish versions)
G. Contact Information Form
H. Baseline and follow-up questionnaires (English and Spanish versions)
I. Protocol for zika virus specimen collection (English and Spanish versions)
J. Laboratory Form
K. Counseling messages for study participants
L. IRB Approval
M. Additional pregnancy questions for baseline and follow-up questionnaire (English and Spanish versions)

N. Informational Flyer