Persistence of Zika virus in semen and urine of adult men with confirmed Zika virus infection

Request for OMB approval of a New ICR

Supporting Statement B
January 23, 2021

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1. Respondent Universe and Sampling Methods

This is a descriptive study conducted in the setting of an emerging public health threat. It is impossible to predict or ensure enrollment of a specific number of participants. Given the dearth of existing information on viral shedding, enrollment of even a few participants will substantially increase knowledge of the topic and lead to improved public health recommendations. If possible, enrollment of a larger number of participants is desirable as it will allow more precise estimates of the frequency, consistency, and duration of viral shedding. For practical purposes, study enrollment will be capped at 250 participants. Assuming full enrollment and participation, this sample size would detect a prevalence of viral shedding of 5% with a 95% confidence interval of +/- 3% at any specific time point in the study.

During the 6 month Emergency clearance ICR period for this study, we reached over 50% of our target enrollment. As of September 28, 2016, we have enrolled 170 participants from 21 states plus New York City. At this pace, we anticipate meeting our enrollment goal by December 2016. Given this enrollment timeline and the fact that participants may provide data and specimens for up to 6 months after onset of their Zika virus illness, data collection for this study is anticipated to continue through June 2017.

The study population will include adult males who were symptomatic with a confirmed Zika virus infection within the past 6 months, and who reside within the continental United States.

A laboratory-confirmed case of Zika virus infection is defined as Zika virus RNA detected in any body fluid by reverse transcription-polymerase chain reaction (RT-PCR), or Zika immunoglobulin (Ig) M antibodies in serum by enzyme-linked immunosorbent assay (ELISA) with ≥4-fold difference between Zika and dengue virus neutralizing antibody titers by plaque reduction neutralization testing (PRNT).

In addition, for this study, a confirmed case of Zika virus infection can also have Zika immunoglobulin (Ig) M antibodies in serum by enzyme-linked immunosorbent assay (ELISA) and an epidemiologic link, defined as having had:

- Travel to a country or region with known ZIKV transmission, OR
- Sexual contact with a laboratory-confirmed case of ZIKV infection, OR
- Receipt of blood or blood products within 30 days of symptom onset; OR
- Organ transplant recipient within 30 days of symptom onset; OR
- Association in time and place with another laboratory-confirmed case.

Inclusion criteria: Adult males 18 years and older with confirmed Zika virus disease (onset within the past 6 months).

Exclusion criteria: Incarcerated individuals.

Zika virus disease is a nationally notifiable condition. CDC study staff will identify eligible potential participants through Zika surveillance efforts (Zikatracker or ArboNET) or through diagnostic testing services performed at CDC Fort Collins. For each case, they will work with the appropriate state (or jurisdiction) health department to reach out to potential participants. Health department staff may make contact with eligible men in their state/jurisdiction by sending a letter (Attachment K) to them that briefly describes the study and asks the man to contact CDC directly if interested in participating. Alternately, health department staff may call the eligible man using a phone script (Attachment L) where they will briefly explain the study and ask the man if they would be OK having their contact information (name and telephone number) shared with CDC study staff. The study staff will then contact the patient directly to explain the study and seek their consent to participate. Staff will call the case up to 6 times at the phone number provided. They will leave a voicemail on the 3rd and 4th attempts. Calls will occur at different times of the day on different days of the week, to increase the likelihood of contact. If state or local health officials feel that they must be engaged with the research, appropriate IRB amendments and approval will be sought.

Upon contact with the potential participant, CDC study staff will read a phone script (Attachment C) to explain the study. The men will be told to ask any questions they may have regarding the study, and they will be told they can withdraw from the study at any time. For men expressing interest in the study, staff will read the consent form and obtain verbal informed consent (Attachment C) over the phone. After verbal consent is obtained from the participant, a brief baseline questionnaire (Attachment C) that includes questions on other contact means (phone and email) and initial symptoms will be administered.

2. Data and Specimen Collection

As soon as possible after enrollment, the participant will be assigned an individual study ID number and mailed the first study kit. This kit will contain all collection and shipping materials (including cold packs and return postage-paid labels/stickers), and a copy of the consent form (Attachment F), general instructions (Attachment E), urine and semen collection instructions, a brief questionnaire (Attachments D1 or D2), and an FAQ sheet (Attachment H). The two follow-up surveys are identical aside from slight wording differences. For example, the first follow-up survey (Attachment D1) reads “Since you became ill…” while the regular follow-up survey (Attachment D2) reads “Since the last survey…”

All collection materials will be pre-labeled with the participant’s study ID number. The participant will provide the date of self-collection for each specimen on the self-administered questionnaire (Attachments D1 or D2). If they have any questions, the information sheets (consent and FAQs) will direct them to a CDC study phone number and email address. In the general instructions (Attachment E), they will be told how to simply repackage their specimens and questionnaire for return to CDC Fort Collins. They will be instructed to call a courier phone number (or Hawaii Department of Health, for interested Hawaii participants) after the package is sealed to schedule a home pickup. They can then leave the package by their front door (or in a common mail area) and the package will be retrieved by the courier (or Hawaii Department of Health, for Hawaii participants) that day, at no charge to the participant.

Participants will be asked to provide their first urine and semen specimens as soon as possible (Table 1) after receiving the sample collection kit at their home. Subsequent sample collections are meant to occur

every 2 weeks thereafter during the 6 months post illness onset, up to a maximum of 12 submitted specimens.

The participant will be asked to complete a brief (7 question) self-administered questionnaire (Attachments D1 or D2) to return with each specimen collection kit. The questionnaire will pertain to current urogenital symptoms (blood or pain), as well as frequency of ejaculations in the previous week, and time since last ejaculation.

Subsequent sample collection kits will contain the all the same materials as the first kit (except a consent form copy). In addition, these kits will contain a $50 gift card to compensate the participant for the time and effort spent on their previous sample collection and questionnaire.

A thank you letter (Attachment I) containing test results for all specimens submitted and final $50 gift card will be mailed as soon as possible after the last specimen is submitted.

Table 1. Timing of specimen collection and laboratory analysis

Collection Date	Specimen	Volume	Collection container	Storage, Procedures and Transportation for Samples
once every two weeks up to 6 months post-onset	Urine	20 ml	Screw-top urine container (clean catch)	Ship from home, overnight, on cold packs, to CDC Laboratory in Fort Collins
	Semen	Ejaculate	Screw-top urine container	Perform testing in Brault laboratory

Test results will be shared with the study participant after all of his specimens are analyzed, as communicated at the time of enrollment. Results will not be provided routinely during the course of participation due to the potential for intermittent shedding of virus in semen. A negative test result may cause the participant to discontinue precautions prematurely, leading to risk for their sexual partner, should shedding resume. In addition, participants with negative results may be more likely to drop out of the study, biasing the results and compromising the scientific value of the investigation. If test results indicate that Zika virus RNA is present in urine and/or semen specimens intermittently during the study or at 6 months post-onset of illness, we may ask participants to continue being in the study. If this is the case, we will re-consent participants into an extended study.

Spanish-speaking participants

All attachments have been translated into Spanish (Attachments C-L). A fluent Spanish speaker will call to explain the study and to verbally consent any Spanish-speaking individuals.

3. Methods to Maximize Response Rates and Deal with No Response

If participants are not prompt (i.e. 7 days after receipt of package) with returning data/specimens, they will be contacted by CDC study staff via email or text to remind them. If data/specimens are not mailed within 2 more days, they will be contacted by study staff via phone up to 3 times to remind them. Study staff may leave voicemails as a reminder on the 2nd and 3rd phone call attempts.

4. Tests of Procedures or Methods to be Undertaken

No pilot testing will be done.

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

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