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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[30Day-18-17AZX]

Agency Forms Undergoing Paperwork Reduction Act Review

In accordance with the Paperwork Reduction Act of 1995, the Centers for Disease Control and Prevention (CDC) has submitted the information collection request titled Zika Puerto Rico Study: Zika Virus RNA Persistence in Pregnant Women and Congenitally Exposed Infants in Puerto Rico to the Office of Management and Budget (OMB) for review and approval. CDC previously published a "Proposed Data Collection Submitted for Public Comment and Recommendations" notice on April 19, 2017 to obtain comments from the public and affected agencies. CDC did not receive comments related to the previous notice. This notice serves to allow an additional 30 days for public and affected agency comments.

CDC will accept all comments for this proposed information collection project. The Office of Management and Budget is particularly interested in comments that:

(a) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of

the agency, including whether the information will have practical utility;

(b) Evaluate the accuracy of the agencies estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used;

(c) Enhance the quality, utility, and clarity of the information to be collected;

(d) Minimize the burden of the collection of information on those who are to respond, including, through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses; and

(e) Assess information collection costs.

To request additional information on the proposed project or to obtain a copy of the information collection plan and instruments, call (404) 639-7570 or send an email to omb@cdc.gov. Direct written comments and/or suggestions regarding the items contained in this notice to the Attention: CDC Desk Officer, Office of Management and Budget, 725 17th Street, NW, Washington, DC 20503 or by fax to (202) 395-5806. Provide written comments within 30 days of notice publication.

Proposed Project

Zika Puerto Rico Study: Zika Virus RNA Persistence in Pregnant Women and Congenitally Exposed Infants in Puerto Rico – New – National Center of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC).

Background and Brief Description

The Puerto Rico Department of Health (PRDH) reported the first case of autochthonous transmission of Zika virus (ZIKV) in December 2015. As of December 16, 2016, Puerto Rico reported 35,648 ZIKV cases, more than any other location in the U.S., and health officials expect the number of cases to continue to rise. Among the cases, 2,864 have been among pregnant women, and the PRDH announced the first case of microcephaly in a fetus with confirmed ZIKV infection on May 13, 2016. Currently, testing for ZIKV infection can be done by either using rRT-PCR to detect the presence of ZIKV RNA or by serologic testing to detect IgM and neutralizing antibodies. rRT-PCR testing is the preferred and suggested method for diagnosing ZIKV infection because it provides a definitive diagnosis and is not subject to the limitations (e.g., cross-reactivity) associated with serology testing. However because level of viremia is generally low and RNA concentrations decline over time, ZIKV rRT-PCR has generally only been considered for a short testing window (2 weeks).

Currently, the CDC and the PRDH recommend ZIKV testing of all pregnant women living in areas with active ZIKV

transmission, such as Puerto Rico. Symptomatic pregnant women should have serum and urine tested for the presence of ZIKV RNA by rRT-PCR within two weeks of symptom onset. Symptomatic pregnant women tested more than two weeks after symptom onset and symptomatic women with negative rRT-PCR test results should have serologic testing. CDC recommends serologic testing of asymptomatic pregnant women at the initiation of prenatal care and again during their second and third trimesters as a part of routine care; CDC recommends serum and urine rRT-PCR testing after a positive or equivocal serological test result to identify persistent RNA and to provide a definitive diagnosis. For infants, CDC currently recommends ZIKV testing within two days of life for infants born to women with laboratory evidence of possible ZIKV and for infants who have abnormal clinical or neuroimaging findings suggestive of congenital ZIKV syndrome, regardless of maternal ZIKV test results.

Limited data suggest that ZIKV RNA might be detectable for a much longer period in whole blood than in serum or urine; however, researchers have primarily seen these results in non-pregnant adults. While ZIKV RNA typically only persists in serum for 3-7 days and is thought to clear by 10 days, animal data suggest that pregnancy may be associated with prolonged detection of ZIKV RNA. An ongoing study of pregnant Rhesus macaques found ZIKV RNA in plasma up to 36 and 71 days post

first trimester infection, and up to 9 and 36 days after third trimester infection. Preliminary results from a first trimester-infected macaque with detectable virus for 71 days indicate that the fetus had no clinical signs of microcephaly but fetal necropsy showed ZIKV RNA in the axillary lymph nodes, bone marrow, and optic nerve (although not in brain tissue). By comparison, two non-pregnant female animals no longer had detectable RNA at 17 days post-infection.

Limited data from human studies also suggest that pregnant women have persistent detection of ZIKV RNA in serum. Symptomatic women had detectable virus at 17, 23, 44, and 46 days post symptom onset and one asymptomatic woman was still rRT-PCR positive 53 days after returning from travel. In one symptomatic pregnant woman with prolonged detection of ZIKV RNA, the pregnancy ended as a fetal loss and researchers found ZIKV RNA in the fetus. Findings from these case reports and series led to the hypothesis that persistent detection of RNA in pregnant women may be a marker of fetal infection and thus, potentially a marker of adverse fetal outcomes including microcephaly and brain abnormalities. However, researchers need more data including whether the detection of IgM influences the risk of adverse infant outcomes.

Researchers know even less about persistent detection of ZIKV RNA and IgM in infants. One case study reported persistent

ZIKV RNA detection in a male child born in Brazil at 40 weeks gestation with brain abnormalities. Fifty-four days after birth, the infant's serum, saliva, and urine all tested positive for ZIKV RNA; the detection of ZIKV RNA continued in the infant's serum on day 67 and had cleared by day 216. The infant exhibited no obvious illness or evidence of being immunocompromised when examined on day 54. However, he demonstrated neuropsychomotor developmental delay, with global hypertonia and spastic hemiplegia, by 6 months of age. The duration of IgM detection in infants is also important to determine the window of diagnostic utility of this test for infants not tested at birth.

Due to the short window of time during which ZIKV RNA is typically detectable in serum, expanding rRT-PCR testing to asymptomatic women and women outside of the two-week window may provide more information than serologic testing alone. This is because positive serology does not allow for definitive diagnosis of infection as false positives and cross-reactivity with other flaviviruses complicates diagnosis. The rRT-PCR, per standard, requires a blood sample obtained by venipuncture for ZIKV RNA detection. However, recent unpublished data from the Institute Pasteur have demonstrated that in 57% of patients there was a significantly longer ZIKV RNA detection in capillary blood samples collected from Zika positive pregnant women tested

with rRT-PCR than in venous samples. Similar findings from a study conducted during the Ebola outbreak showed that capillary blood samples can be used as an alternative to venous blood samples, and may be a more accurate method for monitoring viral load.

If prolonged ZIKV RNA persistence is, in fact, a marker of fetal infection and adverse outcomes, determining the prevalence of prolonged detection of ZIKV RNA is essential for clinical management of pregnant women with ZIKV infection and public health planning for the outbreak. Further, understanding persistent ZIKV RNA in congenitally-exposed infants is also important for clinical management of infants and identifying adverse outcomes that may present several months after birth. Finally, understanding the relationship between persistence and viral load may inform clinical guidance and management of pregnant women and their families.

In this study, we will estimate the prevalence and duration of persistent ZIKV RNA in pregnant women and congenitally exposed infants. We will also evaluate the diagnostic utility of PCR testing for ZIKV RNA on capillary blood and determine if persistent ZIKV RNA in pregnant women is associated with adverse outcomes or infection in infants. Finally, we will examine the association of different factors that are associated with

persistent detection of ZIKV RNA in pregnant women and congenitally exposed infants.

This study will provide critical data in establishing guidance for testing in pregnant women and congenitally exposed infants. There are no costs to the respondents other than their time. The total estimated annual burden hours are 785.

Estimated Annualized Burden Hours

Type of Respondents	Form Name	Number of Respondents	Number of Responses per Respondent	Average Burden per Response (in hours)
ZIKV positive Pregnant women	Pregnant women screening form	150	1	2/60
ZIKV positive Pregnant women	Pregnant women enrollment questionnaire	150	1	8/60
ZIKV positive Pregnant women	Pregnant women symptom questionnaire	150	1	8/60
ZIKV positive Pregnant women	Pregnant women follow-up questionnaire	150	30	8/60
ZIKV positive Pregnant women	Infant enrollment and delivery questionnaire	150	1	8/60
ZIKV positive Pregnant women	Infant follow-up questionnaire	150	6	8/60

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