

# Zika Virus Associated Neurologic Illness Case Control Study

Request for Emergency OMB approval of a new ICR

## **Supporting Statement A**

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- The objectives are to:
  - o Define the historic incidence of SEVERE NEUROLOGIC ILLNESS at participating hospitals;
  - o Describe demographic, epidemiologic, and clinical characteristics of patients with SEVERE NEUROLOGIC ILLNESS

### **1. Circumstances Making the Collection of Information Necessary**

This is an emergency request for a new information collection for 3 months.

The emergence of Zika Virus (ZIKV) in the Americas may be associated with increased rates of SEVERE NEUROLOGIC ILLNESS including Guillain-Barre syndrome (GBS). During the current ZIKV outbreak in Brazil, the Brazilian Ministry of Health reported a marked increase in the number of GBS cases and other cases of severe neurologic illness following suspected ZIKV infection. Similar reports have been made

from French Polynesia, El Salvador, and Colombia.

In the Commonwealth of Puerto Rico, the first confirmed case of locally-acquired ZIKV infection was identified in early December 2015. In January 2016, the first case-patient with ZIKV-associated GBS was hospitalized, and several dozen additional GBS cases were hospitalized thereafter. More than a dozen additional SEVERE NEUROLOGIC ILLNESS cases have been reported to the Puerto Rico Department of Health (PRDH) in 2016 that had evidence of current or recent ZIKV infection. Co-circulation of other arboviruses, high prevalence of HIV, and an ongoing influenza epidemic may complicate association of ZIKV infection with GBS and SEVERE NEUROLOGIC ILLNESS.

There is an urgent public health need to understand the potential association between SEVERE NEUROLOGIC ILLNESS and ZIKV infection. Currently, increased numbers of SEVERE NEUROLOGIC ILLNESS cases have been reported in ZIKV-affected contexts, but it is not known if this is due to ZIKV, another etiologic agent, or some combination/interaction thereof. PRDH is establishing SEVERE NEUROLOGIC ILLNESS surveillance and defining baseline incidence toward investigating the association between SEVERE NEUROLOGIC ILLNESS and ZIKV infection in Puerto Rico. More broadly, the results of this investigation would be relevant to other ZIKV-affected contexts, serving toward enabling clinical and/or public health action to manage and prevent additional cases.

A case-control investigation will be conducted to identify potential risk factors for the development of SEVERE NEUROLOGIC ILLNESS. As part of the investigation, blood specimens will be collected from SEVERE NEUROLOGIC ILLNESS cases and matched controls to evaluate for antibodies against several pathogens known to cause SEVERE NEUROLOGIC ILLNESS (e.g., influenza) or pathogens hypothesized to contribute to this illness cluster (e.g., ZIKV, dengue virus, chikungunya virus, HIV, *Campylobacter jejuni*, *Leptospira* species bacteria).

CDC and Puerto Rico Department of Health recently collaborated on collection of very similar data for a Guillain-Barre syndrome case-control investigation, (OMB 0920-1106). After clinical reports and field observation of a broader range of health endpoints, this larger investigations is now being undertaken to expand the exploration of the association of Zika virus infection with not only Guillain-Barre syndrome but also other SEVERE NEUROLOGIC ILLNESSES.

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 objectives of the case-control study are to:

- Describe demographic, epidemiologic, and clinical characteristics of patients with SEVERE NEUROLOGIC ILLNESS identified at participating hospitals in 2016;
- Collect clinical specimens from SEVERE NEUROLOGIC ILLNESS patients to define potential infectious etiologic agents; and,
- Conduct a case-control investigation to define demographic characteristics, environmental exposures, or infectious agents associated with the development of SEVERE NEUROLOGIC ILLNESS.

SEVERE NEUROLOGIC ILLNESS patients at participating hospitals are being identified prospectively

through surveillance conducted by PRDH. Case reporting requires submission of a serum specimen and a case report form that collects descriptive demographic, epidemiologic, and clinical data. SEVERE NEUROLOGIC ILLNESS patients will be contacted by project field epidemiologists, who explain the purpose of the investigation. For those that give written consent to participate in the investigation (Attachment D), remaining clinical specimens (e.g., cerebrospinal fluid (CSF), urine, stool or rectal swabs) will be collected, and retrospective medical chart review will be performed to collect detailed information on clinical characteristics (Attachment F).

#### *Data collection and analysis*

Case and control interviews will be conducted using the questionnaire developed by the investigation team (Attachment C). All cases and controls will be asked questions about activities, antecedent signs and symptoms of illness, and exposures in the two months prior to onset of neurologic illness for cases and the same time period for their matched controls. A calendar will be used to orient cases and controls to the time period of interest.

Also during the time of the interview, sera, urine, and saliva will be collected from cases and controls using standard techniques. The sera will be tested for antibodies against suspected infectious pathogens, such as ZIKV, dengue virus, chikungunya virus, influenza virus, human immunodeficiency virus, and *Leptospira* species bacteria. Urine specimens will be tested by rRT-PCR to identify ZIKV, dengue virus, or chikungunya virus. Serum will also be tested for anti-GM1 antibodies that have been previously associated with specific sub-types of SEVERE NEUROLOGIC ILLNESS.

If any residual specimens are available from cases, those will also be obtained and undergo testing for infectious pathogens. It is not expected that matched controls will have any previously collected clinical specimens; however, in cases where controls had specimens collected while seeking medical care for an acute illness experienced within two months of SEVERE NEUROLOGIC ILLNESS symptom onset of the matching case, these specimens will also be collected and tested for evidence of infection with the aforementioned pathogens. Residual samples will be stored after infectious testing is complete at the U.S. CDC with an identification number for possible additional testing for SEVERE NEUROLOGIC ILLNESS-associated biological markers or other infectious pathogens as clinically indicated. If a participant does not provide consent to store the specimens, all specimens for that participant will be destroyed once testing for infectious disease pathogens has been completed. As with cases, written consent will also be obtained to review controls' medical records, where applicable and available, using a standardized chart abstraction form (Attachment F). Diagnostic test results will be securely transmitted from CDC to PRDH, which will then transmit diagnostic test results to participants by telephone or mail, as they prefer.

Data analysis will focus on potential demographic, environmental, and/or medical risk factors for developing SEVERE NEUROLOGIC ILLNESS, as well as laboratory evidence for infection with the aforementioned pathogens.

It is not expected that this investigation will need more than six months, but if it does, then an ICR extension will be formally submitted to OMB for non-emergency review following the publication of broad 60- and 30-day FRNs.

### **3. Use of Improved Information Technology and Burden Reduction**

Household interviews will be done in-person and on paper. Data will be entered into an electronic database. Abstraction of medical records will be done via tablet and stored on an electronic database.

#### **4. Efforts to Identify Duplication and Use of Similar Information**

CDC and Puerto Rico Department of Health recently collaborated on collection of very similar data for a Guillain-Barre syndrome case-control investigation. After clinical reports and field observation of a broader range of health endpoints, this larger investigations is now being undertaken to expand the exploration of the association of Zika virus infection with not only Guillain-Barre syndrome but also other SEVERE NEUROLOGIC ILLNESSES. As such, this collection builds on OMB 0920-1106 (exp 9/30/16), but does not duplicate it.

#### **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**

CDC activities pertaining to the zika virus response in Puerto Rico would be significantly hindered if it were not able to collect the information at the frequency necessary to prohibit the spread of this disease. Collecting information less frequently than the CDC recommendations would interfere with the public health actions required to contain and respond to zika virus transmission and to do everything possible to limit, if not stop, deaths and associated illnesses due to this disease.

#### **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), To continue this work past the 90 days being allotted for this emergency, a 60-day notice will publish in the Federal Register to notify the public of CDC's activities and in order for standard review of this ICR to take place.

B) There was no consultation outside of the Agency.

#### **9. Explanation of Any Payment or Gift to Respondents**

There is no payment or gift to respondents. Blood, urine, and saliva from consenting participants (i.e., case-patients and randomly selected controls) will be collected on a single occasion only. In our experience from past similar investigations, this has not required incentives. For SEVERE NEUROLOGIC ILLNESS patients, CDC will use clinical specimens (e.g., CSF) collected during hospitalization.

## 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 does apply to this information collection request. The applicable System of Records Notice is 09-20-0136.

Paper copies of data collection instruments will be stored in a locked, secured filing cabinet at PRDH. Only investigators directly involved in the investigation will have access to case report forms. Photocopies of data collection instruments with only case identification numbers and no personal identifying information will be securely transported to San Juan for data entry into a RedCap database. Information about sensitive topics, such as sexual behavior or drug use, will not be collected. Names will not be included in electronic databases. Any reports related to the findings of this investigation will not include personal identifying information.

Potential participants will be introduced to the investigation following a script that explains the reasons the investigation is being conducted, the activities involved in the evaluation, and the risks and benefits of participation (Attachment D). Written consent will be obtained from all participants for the following: 1) participation in the survey and collection of blood specimen on the day of the survey; 2) storage of specimens for future diagnostic testing; 3) retrieval of clinical specimens and review of medical records from any illness for which the individual sought medical care in the previous two months; and 4) willingness to be contacted in the future depending on test results or if additional studies are proposed. If a second specimen is needed one month after the initial investigation visit, a second consent form will be obtained (Attachment E). For participants meeting the definition of a minor in Puerto Rico (i.e., individuals <21 years of age, unmarried, without children, and living with their parents), written permission to participate will be obtained from a parent or guardian. Verbal assent will be obtained from participants 8–12 years of age.

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

### IRB Approval

The protocols and tools used to conduct the case-control investigation was reviewed and approved by NCEZID’s Human Subjects Advisor who determined that the data collection does not meet the definition of research under 45 CFR 46.102(d). IRB review is not required (Attachment G).

### 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 project is 90. This includes the burden associated with our information collection instruments. Specimen collection will be done during the administration of the SEVERE NEUROLOGIC ILLNESS Questionnaire for cases and controls.

Type of Respondent	Form Name	No. of Respondents	No. of Responses per	Average Burden per	Total Burden
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			Respondent	Response (in hours)	Hours
	SEVERE NEUROLOGIC ILLNESS Chart abstraction questionnaire	10	6	1	60
General public	SEVERE NEUROLOGIC ILLNESS Questionnaire for cases and controls and specimen collection	120	1	15/60	30
<b>Total</b>					90

#### Estimated Annualized Burden Costs to Respondents

The average annual response burden cost is estimated to be \$2694.30. 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\\_nat.htm](http://www.bls.gov/oes/current/oes_nat.htm)). 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
	SEVERE NEUROLOGIC ILLNESS Chart abstraction questionnaire	60	\$33.55	\$2,013.00
General public	SEVERE NEUROLOGIC ILLNESS Questionnaire for cases and controls and specimen collection	30	\$22.71	\$681.30
<b>Total</b>				\$2694.30

### **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 \$26,030.40. The investigation requires four CDC employees—two EIS officers and two PHAP trainees—for three months at an average of 20 hours per week. 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.

<b>Project</b>	<b>Position</b>	<b>Hours</b>	<b>Hourly Wage</b>	<b>Total</b>
SEVERE NEUROLOGIC ILLNESS case- control investigation	EIS Officers (x2)	480	\$29.69	\$14,251.20
	PHAP Trainees (x2)	480	\$24.54	\$11,779.20
<b>Total</b>				\$26,030.40

### **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**

Once OMB approval is obtained, patients will be identified in real-time. Patients and their matched controls will be interviewed within 30 days of patient illness onset. Following the completion of case and control interviews, diagnostic testing and data analysis will require an additional two to three months to complete. This project is not expected to exceed three months.

### **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. Draft 60-day FRN
- C. Case-control investigation questionnaire for the investigation of SEVERE NEUROLOGIC ILLNESS in relation to arboviral infections
- D. Case-control investigation consent/parental permission form
- E. Case-control investigation consent/assent form follow-up
- F. Case-control investigation chart abstraction questionnaire for the investigation of SEVERE NEUROLOGIC ILLNESS in relation to arboviral infections
- G. IRB Approval for Case-Control Investigation