Risk factors, clinical course, presence and persistence of virus in various bodily fluids, and risk of sexual transmission among U.S. adults with Oropouche virus disease

Reinstatement with change of a previously approved collection OMB Control Number

0920-1446

June 12, 2025

Supporting Statement A

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Goal of the study: The goals of this investigation are to:

1. Assess potential risk factors for Oropouche virus (OROV) disease.
2. Describe the clinical presentation of OROV disease among U.S. travelers.
3. Assess the prevalence and duration of OROV, viral RNA, and OROV-specific neutralizing antibodies in various bodily fluids.
4. Evaluate the evidence for sexual transmission of OROV.

Intended use of the resulting data:
The intended use of the resulting data includes identifying risk factors for infection to inform prevention guidance and messaging, informing recognition, diagnosis, follow up care, and counseling of patients with OROV disease, and understanding risks of sexual transmission to inform prevention recommendations, especially for pregnant women and their partners, or those considering pregnancy.

Methods to be used to collect: This data will be collected through serial interviews and specimen collection.

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- **The subpopulation to be studied:**

- The investigation population includes U.S. adults diagnosed with OROV disease according to the interim case definitions for confirmed and probable cases of OROV disease (https://www.cdc.gov/oropouche/php/reporting/index.html) within 4 months of their symptom onset and their sexual partners in the 6 weeks after symptom onset.

- **How data will be analyzed:**

- Descriptive analysis of all variables will be performed to examine the frequency and distribution of the data. The frequency of symptoms and specimens with detectable OROV virus RNA will be calculated for each time point. Viral persistence will be measured in days from time after symptom onset and persistence in body fluids will be modeled using the Weibull distribution. Association between outcomes including symptom recurrence, disease severity, duration of viral persistence, and patient characteristics will be examined using logistic regression or Weibull distribution (for duration of viral persistence).

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1. Circumstances Making the Collection of Information Necessary

Data collection for this project was originally approved through an Emergency ICR (for six months [180 days]). This is a request to extend the ICR three years.

From late 2023–2024, outbreaks of Oropouche virus (OROV) disease have been reported in several countries it had not been previously reported. More than 11,000 cases have been reported from Barbados, Brazil, Bolivia, Colombia, Cuba, Ecuador, Guyana, Panama, and Peru. While OROV does not currently circulate in the United States, disease cases in returning international travelers have been reported and there is a low risk of local transmission given the presence of vectors.

OROV is transmitted to humans primarily from the bite of infected midges (including *Culicioides paraensis*) but can also be transmitted through the bite of some mosquitoes. Symptoms of OROV disease typically include fever, headache, chills, muscle aches, and joint pain. However, OROV can cause severe disease including neurologic and hemorrhagic manifestations. Recently Brazil reported the first confirmed deaths in patients with OROV disease and found evidence of vertical transmission associated with adverse pregnancy outcomes such as stillbirths and birth defects. The geographic range expansion, in conjunction with the identification of vertical transmission and reports of deaths, has raised concerns about the broader threat this virus represents.

There are numerous gaps in our understanding of this emerging virus, such as clinical features, risk factors for infection and severe disease, and the potential for person-to-person transmission. Limited data suggest that OROV can be shed in bodily fluids with OROV RNA identified in whole blood, serum, urine, and saliva. Additionally, researchers in Italy reported culturing OROV in semen samples obtained from a returning traveler, suggesting the possibility of sexual transmission. Given the risk of vertical transmission, understanding viral shedding and potential routes of human-to-human transmission is essential. Furthermore, understanding the utility of different body fluids to allow for a molecular detection of recent OROV infection will help guide diagnostic testing considerations.

This investigation seeks to better define the risk factors, clinical course, viral shedding, and potential for sexual transmission among patients with OROV disease. This is a quickly evolving situation, and the need for data to inform response activities and prevention guidance is critical. Furthermore, as time lapses from their initial travel, recall bias can prevent CDC from receiving the most accurate information to understand the broader transmission risk.

Authorizing legislation is Section 301 of the Public Health Service Act (42 U.S.C. 241) (Attachment 1).

2. Purpose and Use of Information Collection

The results of this investigation will assist in the response to this emerging virus by:

- Identifying risk factors for infection to inform prevention guidance and messaging.
- Informing recognition, diagnosis, follow up care, and counseling of patients with OROV disease.

- Understanding risks of sexual transmission to inform prevention recommendations, especially for pregnant women and their partners, or those considering pregnancy.

CDC will work with state health departments to determine if any individuals who either are reported as OROV disease cases to ArboNET (approved under OMB Control Number 0920-0728), the national surveillance system for arboviral diseases, or have samples submitted to CDC that test positive for OROV infection meet the inclusion criteria.

For all individuals diagnosed with OROV disease who meet the inclusion criteria, investigation staff from either a state, territorial, local, or tribal (STLT) health department or CDC will contact cases. If CDC staff will be contacting cases, CDC will ask STLT health departments to distribute information (email informational flyer or read aloud: Attachment 8) explaining the investigation and notifying patients to expect contact from CDC.

Enrollment:
Patients will be enrolled to participate in investigation activities based on the duration since initial symptom onset and which activities they consent to. We will attempt to enroll eligible patients with confirmed or probable Oropouche virus disease and symptom onset ≤4 months prior.

The following activities will be completed as soon as possible after enrollment:

1. Interview participant using the initial clinical and risk factors survey (Attachment 3) and, if applicable, provide them with a symptom diary (Attachment 5) to record details on symptoms daily.
2. Initial specimen collection (see "Specimen Collection" section below)
3. Interview participants to identify sexual partners between their illness onset and time of interview (maximum of 6 weeks post symptom onset) using Attachment 6 and obtain permission to reach out to those sexual contacts.
4. Interview sexual contacts of patients using Attachment 7 to determine if they had a clinically compatible illness after sexual contact with an OROV disease patient and when their symptoms occurred relative to any travel.
    a. Obtain consent to collect a serum sample from sexual contacts who reported being symptomatic to test for the presence of RNA or neutralizing antibodies to OROV, depending on time from symptom onset to sample collection.
        i. If, after testing, contact meets case definition for confirmed or probable OROV disease, attempt to enroll in symptom and specimen collection components of investigation.

Follow-up:
The following activities will be completed weekly for the first four weeks after symptom onset, and then every two weeks until 12 weeks after symptom onset, and then at 16 weeks after symptom onset:
1. Complete abbreviated clinical survey (Attachment 4) until participant reports no symptoms for 4 weeks
2. Complete specimen collection (see "Specimen Collection" section below)

Time points for data and specimen collection will allow for 4 days on either side of the collection date. For example, if 8 weeks post onset is November 20, week 8 samples and/or symptoms could be

collected from November 16 through November 24. The one exception is if an individual is enrolled >12 weeks after their symptom onset. Individuals can be enrolled between 13-16 weeks and will only have the one visit without follow-up visits conducted.

If participants miss a time point, we will still attempt to collect specimens and symptoms at the next scheduled time point, but they will not be included in calculating frequencies of symptoms or viral RNA positivity for the missed time point.

Specimen Collection

Participants in the sample collection investigation will be asked to donate blood, semen or vaginal secretions, urine, and saliva. All sample types will be collected weekly through 4 weeks post symptom onset. Then, all specimen types except for blood will be collected every two weeks until 12 weeks after symptom onset and at 16 weeks after symptom onset. If a case patient reports breastfeeding during initial interview, they will be asked if they consent to submit a sample of breast milk for OROV testing, but breast milk will not be collected repeatedly. Participants can refuse to submit any of the specimen types.

Blood (whole blood and serum) will be collected at local or state health department clinics. If the patient does not live near a health department clinic or the health department does not have capacity to collect blood, alternative blood collection sites include the patient's physician's office or using a contracted phlebotomy service. Blood will be spun down and serum removed and placed into a separate tube. Sample can be kept refrigerated (4°C) until it is sent to CDC for testing. If the sample cannot be sent within one week, it should frozen at -20°C to -80°C until it be sent. Other specimens are to be collected by the participant at home, with plain language instructions on sample collection, all equipment needed to collect samples, and box with prepaid shipping labels and ice packs provided to the participants via mail. Urine will be collected prior to semen or vaginal secretion samples.

Specimens will be shipped to CDC's Arboviral Diseases Branch in Fort Collins, CO. Surveillance testing using real-time reverse transcription-polymerase chain reaction (rRT-PCR) will be performed on whole blood, semen, vaginal secretions, urine, saliva, and breast milk specimens to detect OROV viral RNA. Viral culture will be attempted on specimens that are positive on rRT-PCR and have a cycle threshold (CT) value that indicates the potential for intact virus (e.g., CT value <32). Serum specimens will undergo diagnostic testing by either rRT-PCR or plaque reduction neutralization testing (PRNT), depending on the timing of specimen collection in relation to symptom onset.

Data Collection Tools

Initial Clinical and Social Survey (Attachment 3): this tool collects information including demographics, signs and symptoms experienced up until that time (e.g., onset, what symptoms were experienced, severity of disease, recurrence of symptoms), underlying conditions/medical history, travel history, and potential risk factors for infection during travel (e.g., outdoor activities, time spent outdoors, insect repellent use).

Follow-up Clinical Survey (Attachment 4): this tool will collect information on symptoms experienced since the participant's most recent clinical survey, including onset, recurrence and duration, and specific signs and symptoms. This tool will help determine if specific symptoms are ongoing or have recurred since previous surveys.

Symptom Diary (Attachment 5): in order to reduce recall bias in follow-up clinical surveys, this tool will be distributed to participants so they can record details on specific symptoms they experience on a daily basis. This tool will be used to complete the Follow-up Clinical Survey.

Contact Tracing Survey (Attachment 6): this tool will collect the number of sexual partners (who did not travel) between returning from travel and 6 weeks post symptom onset and then for each sexual partner will collect information on the timing and type of sexual contact, use of condoms or other barrier contraception, and contact information for eligible sexual partners.

Sexual Contact Interview (Attachment 7): this tool will be used to interview sexual contacts to confirm that they had no recent travel history to places with local transmission of OROV, and to see if they had any symptoms consistent with OROV disease within 2 weeks after any sexual contact with the case patient. This information will identify possible instances of sexual transmission of OROV so we can ask sexual contacts to submit a blood specimen for OROV testing.

Experience to Date

Since the initiation of this protocol, one Oropouche patient has been successfully enrolled. We anticipate that more travel-associated cases in the United States will be detected February- October because of seasonal transmission patterns.

3. Use of Improved Information Technology and Burden Reduction

Information will be collected via telephone interviews and recorded on paper forms or fillable PDFs. Participants will not be able to enter their responses via an electronic form. Survey data will be entered into an electronic database regularly. Data will be organized in a REDCap database stored on a secure server at CDC. Data files will be restricted to investigation staff via a secure share folder. Paper forms and electronic devices will be kept locked when not in use.

4. Efforts to Identify Duplication and Use of Similar Information

CDC is not aware of the availability of any similar information. There are existing case reports and case series describing the symptoms experienced and specimens that contained OROV viral RNA, but these have been reports of individual or small numbers of cases. CDC engages across the US government, particularly with NIH, to ensure coordination of efforts and avoid duplication of information collection.

5. Impact on Small Businesses or Other Small Entities

This data collection will not involve small businesses. 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 Oropouche virus response 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 Oropouche virus transmission and to do everything possible to limit, if not stop, mortality and adverse pregnancy outcomes because of this disease.

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

This request fully complies with the regulation 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 11/04/24 (Vol. 89, No. 213, p. 87585) (Attachment 2). CDC did not receive any comments related to the notice.

B) Based on state and local health department input, CDC was better able to inform data collection across multiple jurisdictions to meet critical emergency response needs while also ensuring state and local health departments were not overly burdened with this collection.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift will be given to respondents in this investigation.

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 (Attachment 12). The applicable System of Records Notice is 09-20-0136.

All participant information contained on investigation forms, in laboratory records and reports, and in electronic files will be kept confidential. Specimens and investigation forms will be linked through a unique participant number only.

Only the investigation staff will have access to the participants' information. Physical documents containing investigation data will be stored in a locked file cabinet in the CDC investigation coordinator's office. These data collection forms will be destroyed at the time the investigation is completed. At that same time, all PII will be deleted from the investigation database and any separate

specimen data will be de-identified. All electronic files will subsequently be stored in a password protected database on a CDC secure network. The results from this investigation will be published or presented for scientific purposes in aggregate form only so that individuals cannot be identified.

Data will be kept private to the extent allowed by law.

Verbal informed consent will be sought over the telephone using a standardized forms that include all required consent elements (Attachments 9–11). A copy of the consent form will be mailed or emailed to participants for their reference. Participants will consent to clinical interview, specimen collection, and sexual partner contact tracing separately and can choose which they would consent to participate in.

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

Institutional Review Board (IRB)

NCEZID's Human Subjects Advisor has determined that information collection is not research involving human subjects (Attachment 13). IRB approval is not required.

Justification for Sensitive Questions

There is some risk of embarrassment or anxiety for the participant associated with recent sexual history interview and provision of semen or vaginal secretion samples. However, investigation staff will be trained in collecting sensitive information and will assure the participant that they can stop or withdraw from the investigation at any time. Semen and vaginal secretion samples will be collected by the participant in their own home, with clear instructions to minimize any discomfort.

This information is important to collect given the isolation of viable virus from semen and evidence of vertical transmission resulting in fetal developmental abnormalities and fetal loss. Collecting this sensitive information is essential to identify if there is evidence of sexual transmission which will inform prevention recommendations, especially for pregnant women and their partners, or those considering pregnancy.

12. Estimates of Annualized Burden Hours and Costs

A. Estimated Annualized Burden Hours

The total estimated burden is 663 hours. This represents the time it will take 200 respondents to each complete the 30-minute baseline survey (Attachment 3) once and the 10-minute symptom diary (Attachment 5) and 15-minute follow-up survey (Attachment 4) an average of six times. This also represents the time it will take 100 respondents to complete the 15-minute interview to identify sexual

contacts (Attachment 6), that they will identify an average of 1.5 sexual contacts, and time for the 150 sexual contacts to complete the 15-minute sexual contact interview (Attachment 7)

Type of Respondent	Form Name	No. of Respondents	No. Responses per Respondent	Avg. Burden per response (in hrs.)	Total Burden (in hrs.)
General public	Baseline survey (Attachment 3)	200	1	30/60	100
	Follow-up clinical survey (Attachment 4)	200	6	15/60	300
	Symptom Diary (Attachment 5)	200	6	10/60	200
	Contact Tracing Survey (Attachment 6)	100	1	15/60	25
	Sexual Contact Interview form (Attachment 7)	150	1	15/60	38
Total					663

B. Estimated Annualized Burden Costs

The 2023 mean hourly wage for all occupations in the United States ($31.48) from the Department of Labor website was used to calculate these costs. The total annual burden is estimated to be $20,997

Type of Respondent	Form Name	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
General public	Baseline survey (Attachment 3)	100	$31.48	$3,148
	Follow-up clinical survey (Attachment 4)	300	$31.48	$9,444
	Symptom Diary (Attachment 5)	200	$31.48	$6,422
	Contact Tracing Survey (Attachment 6)	25	$31.48	$787

	Sexual Contact Interview form (Attachment 7)	38	$31.48	$1,196
Total				$20,997

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 total estimated cost to the government is $34,887.93. The table below breaks down how many CDC employees will be working on this project, what percentage of their time will be devoted to this project, how much they will make during this time; the estimated cost of supplies is also listed below. Information collection is expected to last three years. Hourly wages were based on Step 1 employees for Denver-Aurora, CO locality available here: https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/24Tables/html/DEN_h.aspx .

Grade	# of FTEs	Hourly Wage	% Time Devoted to Project	Total Hours	Cost
GS-12	2	$41.02	2	42	$1,722.84
GS-13	2	$48.78	25	522	$25,460.55
O-6	1	$60.64	10	105	$6,367.54
Total Cost					33,550.93

The total estimated costs for specimen collection supplies is $1,337.

Item	Estimated Cost	Quantity	Total Cost
Thermosafe insulated shipping boxes (12 boxes/box)	$120	5	$600
RD plastics reclosable bags (1000/case)	$84	2	$168
Fisherbrand Sterile Alcohol Prep Pads (200/pack)	$6	6	$36
Sonoco™ ThermoSafe PolarPack™ Gel Packs(72/case)	$43	3	$129
Specimen containers (500/case)	$202	2	$404
Total			$1,337

15. Explanation for Program Changes or Adjustments

Change request (November 2024):

A Change Request was submitted on November 29, 2024 to make non-substantive changes to the protocol in response to feedback from state partners. Enrollment criterion was changed from 3 months to

4 months (16 weeks) for collection of bodily fluids to capture an additional timepoint to measure Oropouche viral persistence among symptomatic patients. Additionally, enrollment criteria were modified to allow for participation among people who had sexual contact with the case, and who also may have traveled with the case. Other minor changes included clarification of terms, timelines (e.g., when a patient got sick), travel dates, areas of transmission risk, and the addition of a question about use of screens or air conditioning.

Recent adjustments to data collection forms:

Gender questions and terms were adjusted to comply with recent Executive Orders. Minor edits were also made to the data collection forms including the addition of "unknown" response options for certain questions (e.g., in case the patient could not recall the hospital admission date), listing fatigue and malaise as separate symptoms, and corrections to skip patterns.

16. Plans for Tabulation and Publication and Project Time Schedule

	Project Timeline in Months											
Activities	1	2	3	4	5	6	7	8	9	10	11	12
Human Subjects and PRA determination		**x**										
Investigator Coordination Meeting	**x**	**x**	**x**	**x**								
Questionnaire Development	**x**	**x**										
Staff Training		**x**	**x**									
Recruitment		**x**	**x**	**x**								
Data Collection		**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**
Summarize Preliminary Results		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Dissemination of Project Outcomes		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

Month 1 is September 2024.

Will analyze data from initial data collection and contact tracing and disseminate relevant results to inform response activities, as well as analyze and disseminate results of longitudinal data regarding symptoms and presence of virus and viral RNA in bodily fluids once data collection is complete.

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

The display of the OMB Expiration date is not inappropriate.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

Attachments

1. Authorizing Legislation: Section 301 of the Public Health Service Act (42 U.S.C. 241)
2. 60-Day FRN

3. Initial Clinical and Social Survey
4. Follow-up Clinical Survey
5. Symptom Diary
6. Contact Tracing Survey
7. Sexual Contact Interview
8. Background information and frequently asked questions for participants
9. Consent for medical and social information
10. Consent for sample collection
11. Script and consent for sexual partner interview and OROV testing
12. Privacy Impact Assessment
13. Human Subjects Determination Memo