

Committee: Infectious Disease

Title: Revision of the Surveillance Case Definition for Human Rabies

I. Statement of the Problem:

The purpose of the recommended revisions to the surveillance case definition of human rabies is to clarify restrictive laboratory criteria statements and to improve case classification for reporting. Current laboratory criteria recognize only the type-species *rabies virus* as opposed to the broader genus *Lyssavirus* as the etiologic agent that causes the disease rabies. In addition the indication of rabies neutralizing antibodies as opposed to binding antibody has recently been recognized as restrictive in defining a rabies case under certain rare situations. Examination of historic diagnostic testing has identified human rabies cases for which rabies specific antibody (IgM and IgG) was detected in serum and CSF but rabies-virus neutralizing antibody was absent. These cases have had additional diagnostic samples that confirmed rabies. However, a recent case of presumed abortive rabies has suggested there may be extremely rare instances in which detection of viral antigen or RNA is not possible and rabies-neutralizing antibody does not develop. This revised case definition updates laboratory criteria to include this information.

II. Background and Justification:

Lyssaviruses infect the central nervous system, causing encephalitis and ultimately death. Early symptoms of rabies in humans are nonspecific, consisting of fever, headache, and general malaise. As the disease progresses, neurological symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hypersalivation, difficulty swallowing, and hydrophobia (fear of water). Death usually occurs within days of the onset of symptoms, although treatment may increase the length of survival and very rarely even result in recovery (CDC 2004). Under extremely rare occasions, abortive infection with rabies may occur (CDC 2010). In addition to diagnostic testing for rabies, these cases require extensive medical investigation to rule-out other possible etiologies responsible for the patient's illness.

The number of rabies-related human deaths in the United States declined from more than 100 annually in 1900 to an average of two to three a year in the past decade (2000–2009). The administration of a standard regimen of postexposure prophylaxis (PEP) to persons exposed to rabies has proven extremely successful in preventing the disease. In the United States, human fatalities from rabies occur in people who fail to seek medical assistance and PEP, usually because they were unaware of the need to seek medical attention, or occasionally, not aware that an exposure may have occurred. Human rabies meets the definition of a nationally and **immediately** notifiable condition—as specified in CSTE position statement 08-EC-02—for the following reason(s):

- A majority of state and territorial jurisdictions—or jurisdictions comprising a majority of the US population—have laws or regulations requiring **immediate (urgent)** reporting of human rabies to public health authorities;

- The Centers for Disease Control and Prevention (CDC) requests **immediate (urgent)** notification of human rabies to federal authorities; and
- The CDC has condition-specific policies and practices concerning its response to, and use of, notifications.

III. Statement of the desired action(s) to be taken:

CSTE requests that CDC adopt this standardized reporting definition for human rabies to facilitate timely, complete, and standardized local and national reporting of this condition.

IV. Goals of Surveillance:

To provide information on the temporal, geographic, and demographic occurrence of human rabies to facilitate its prevention and control.

V. Methods for Surveillance:

Surveillance for human rabies should use the following recommended sources of data and the extent of coverage listed in Table V.

Table V. Recommended sources of data for case identification and extent of coverage for ascertaining cases of human rabies.

Source of data for case identification	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	X	
Laboratory reporting	X	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies)	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Extracts from electronic medical records	X	
Telephone survey		
School-based survey		
Other _____		

VI. Criteria for case identification

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

Report any illness to public health authorities that meets any of the following criteria:

- A person with one or more of the following clinical findings: encephalitis, myelitis, dysphagia, hydrophobia, anxiety, agitation, *or* paresthesias or pain at the wound site; AND one or more of the following laboratory findings:
 - detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test
 - isolation (in cell culture or in a laboratory animal) of a Lyssavirus from saliva or central nervous system tissue

- detection of Lyssavirus RNA (using reverse transcriptase-polymerase chain reaction [RT-PCR]) in saliva, CSF, or tissue
 - identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF
- A person with one or more of the following clinical findings: encephalitis, myelitis, dysphagia, hydrophobia, anxiety, agitation, *or* paresthesias or pain at the wound site; AND no previous vaccination for rabies; AND identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the person’s serum.
 - A person whose healthcare record contains a diagnosis of rabies.
 - A person whose death certificate lists rabies as a cause of death or a significant condition contributing to death.

Other recommended reporting procedures

- All cases of human rabies should be reported.
- Reporting should be ongoing and routine.
- Reporting should be immediate.

B. Table of criteria to determine whether a case should be reported to public health authorities:

Table VI-B. Table of criteria to determine whether a case should be reported to public health authorities. Requirements for reporting are established under State and Territorial laws and/or regulations and may differ from jurisdiction to jurisdiction. These criteria are suggested as a standard approach to identifying cases of this condition for purposes of reporting, but reporting should follow State and Territorial law/regulation if any conflicts occur between these criteria and those laws/regulations.

Criterion	Rabies		
<i>Clinical Evidence</i>			
Encephalitis		O	O
Myelitis		O	O
Dysphagia		O	O
Hydrophobia		O	O
Anxiety		O	O
Agitation		O	O
Paresthesias or pain at the wound site		O	O
Ascending flaccid paralysis		O	O
Healthcare record contains a diagnosis of rabies	S		
Death certificate list rabies as a cause of death or a significant contributing condition	S		
<i>Laboratory evidence</i>			
detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test		O	
isolation (in cell culture or in a laboratory animal) of a		O	

Lyssavirus from saliva or central nervous system tissue			
identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF		O	
identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the serum of an unvaccinated person			N
detection of Lyssavirus RNA (using reverse transcriptase–polymerase chain reaction [RT-PCR]) in saliva, CSF, or tissue		O	

S = This criterion alone is Sufficient to classify a case.

O = At least one of these “O” (Optional) criteria in each category (i.e., clinical evidence and laboratory evidence) in the same column—is required to classify a case.

C. Disease-specific data elements:

Patient Information

- Occupation
- Date of Illness Onset
- Outpatient Visit Date
- Date Hospitalized
- Outpatient Diagnosis
- Admitting Diagnosis
- Is/was the patient in a coma
- Date of coma onset
- Date of death

Laboratory Findings

- See CDC form
- Rabies variant identified

Symptoms

- see CDC form

Epi Information

- Travel history
- Animal exposure(s)
- Date of exposure
- Type of exposure
 - # of persons receiving PEP related to this case
 - # Healthcare workers
 - # Household contacts
 - # Other (specify)

VII. Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

Clinical evidence

Rabies is an acute encephalomyelitis that almost always progresses to coma or death within 10 days after the first symptom.

Laboratory evidence

- detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test, or
- isolation (in cell culture or in a laboratory animal) of a Lyssavirus from saliva or central nervous system tissue, or
- identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF, or
- identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the serum of an unvaccinated person, or
- detection of Lyssavirus viral RNA (using reverse transcriptase-polymerase chain reaction [RT-PCR]) in saliva, CSF, or tissue.

Case classification

Confirmed: a clinically compatible case that is laboratory confirmed by testing at a state or federal public health laboratory.

Comment

Laboratory confirmation by all of the above methods is strongly recommended.

B. Classification Tables:

Table VIIB. Criteria for case classification for a case of human rabies.

Criterion	Confirmed
<i>Clinical Evidence</i>	
Encephalitis	O
Myelitis	O
Dysphagia	O
Hydrophobia	O
Anxiety	O
Agitation	O
Paresthesias or pain at the wound site	O
Ascending flaccid paralysis	O
Healthcare record contains a diagnosis of rabies	O
Death certificate list rabies as a cause of death or a significant contributing condition	O

<i>Laboratory evidence</i>	
detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test	O
isolation (in cell culture or in a laboratory animal) of a Lyssavirus from saliva or central nervous system tissue	O
identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF	O
identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the serum of an unvaccinated person	O
detection of Lyssavirus RNA (using reverse transcriptase–polymerase chain reaction [RT-PCR]) in saliva, CSF, or tissue	O

O = At least one of these “O” (Optional) criteria in each category (i.e., clinical evidence and laboratory evidence) in the same column—is required to identify a case for reporting.

VIII. Period of Surveillance:

Indicate whether surveillance is expected to be on-going or limited to a specific time period.

Surveillance should be ongoing.

IX. Data sharing/release and Print criteria:

As appropriate, describe:

- Notification to CDC for confirmed cases is recommended.
- Expectations for sharing of case data (dataflow/notification from state/territorial health agency to CDC) and limitations on data sharing (e.g., states and territories will send CDC data for selected cases based on case classification; states and territories will send core/generic data or supplemental/extended data)
- Limitations on data re-release by CDC (e.g., only fully de-identified case data will be released by CDC to the general public, other releases by CDC require signed data sharing agreements using a format pre-approved by the state/territorial health agency) [refer to *CDC-CSTE Intergovernmental Data Release Guidelines Working Group (DRGWG) Report: CDC-ATSDR Data Release Guidelines and Procedures for Re-release of State-Provided Data (available at <http://www.cste.org/pdffiles/2005/drgwgreport.pdf> or <http://www.cdc.gov/od/foia/policies/drgwg.pdf>) as necessary]*
- Restrictions on the printing of counts of case data (e.g., CDC publication criteria will exclude selected cases from final printed counts based on case classification; provisional case report data will not be used by CDC until verification procedures are complete).

Restrictions on publishing case data

- CDC will only publish data on **confirmed** cases of human rabies. Provisional data will not be used until verification procedures are complete.

Rabies in humans in the United States is a rare event. Reported cases of rabies in humans have dropped since the 1940s as canine rabies has been controlled and ultimately

eliminated in the United States. However, during this time period the number of wildlife associated cases of rabies reported in animals has increased. Subsequently potential human exposure to rabies and postexposure prophylaxis (PEP) remains a relatively common event in the United States (35,000 to 45,000 PEP's annually). In addition, over the past 2 decades human cases of rabies have increasingly implicated bats as the primary source of human infection. Information regarding the demographic, temporal, and geographic nature of human rabies is required to facilitate its prevention and control.

Data reported through the National Notifiable Diseases Surveillance System (NNDSS) is summarized weekly in the MMWR Tables and yearly in the MMWR Summary of Notifiable Diseases. Brief case reports are generated annually in the annual rabies surveillance summary report published in September of each year. In addition, ad hoc publication of more detailed case reports are submitted to MMWR or other peer reviewed journals. Cumulative reports of human rabies cases examining characteristics and trends are produced approximately every 10 years.

A majority of state and territorial jurisdictions—or jurisdictions comprising a majority of the US population—have laws or regulations requiring immediate reporting of human rabies to public health authorities. Response and laboratory assistance may be required/requested from state for potential contact/exposure assessment. CDC provides laboratory assistance for ante-mortem testing of rabies in humans, provides ongoing laboratory support in human cases under experimental treatment protocol for rabies, provides support to state health departments for contact tracing and exposure assessment in hospital and community setting and assists with interstate communications when necessary and potentially internationally for imported cases.

X. References:

1. Bleck TP, Rupprecht CE. Chapter 160 – Rhabdoviruses. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases, 6th edition. Philadelphia: Churchill Livingstone; 2005.
2. Centers for Disease Control and Prevention (CDC). Case definitions for infectious conditions under public health surveillance. MMWR 1997;46(No. RR-10):1–57. Available from: <http://www.cdc.gov/mmwr/>
3. Centers for Disease Control and Prevention (CDC). Human Rabies Prevention — United States, 2008: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2008;57(RR03):1–26,28. Available from: <http://www.cdc.gov/mmwr/>
4. Centers for Disease Control and Prevention (CDC). Possible human rabies — patient information form. Atlanta: CDC; no date, pages 1–3. Available from: <http://www.cdc.gov/rabies/healthcare.html>. Accessed: 2008 Aug 9.
5. Centers for Disease Control and Prevention (CDC). Presumptive Abortive Human Rabies – Texas, 2009. MMWR 2010;59(7): 185-190. Available from: <http://www.cdc.gov/mmwr/>

6. Centers for Disease Control and Prevention (CDC). Recovery of a Patient from Clinical Rabies — Wisconsin, 2004. MMWR 2004;53(50):1171–1173. Available from: <http://www.cdc.gov/mmwr/>
7. Centers for Disease Control and Prevention [Internet]. National notifiable diseases surveillance system: case definitions. Atlanta: CDC. Available from: <http://www.cdc.gov/ncphi/diss/nndss/casedef/index.htm> Last updated: 2008 Jan 9. Accessed: 2008 Aug 9.
8. Centers for Disease Control and Prevention [Internet]. Rabies. Atlanta: CDC. Available from: <http://www.cdc.gov/rabies/> Last updated: 2008 Jul 31. Accessed: 2008 Aug 9.

XI. Coordination:

Agencies for Response:

- (1) Tom Frieden, MD, MPH
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333
404-639-7000
tfrieden@cdc.gov

XII. Submitting Author:

- (1) Catherine M. Brown
State Public Health Veterinarian
Massachusetts Department of Public Health
State Laboratory Institute
305 South St
Jamaica Plain, MA 02130
617-983-6804
catherine.brown@state.ma.us

Co-Authors:

- (1) Jesse D. Blanton
Epidemiologist
Centers for Disease Control and Prevention
1600 Clifton Rd., NE
Atlanta, GA 30333
(404) 639-2289
JBlanton@cdc.gov
- (2) Richard Franka
Microbiologist
1600 Clifton Rd. NE
Atlanta, GA 30333
404-639-0857
RFranka@cdc.gov