

## Rabies– Human

*Note: For guidance and information on animal bites and rabies and Pre- and Post-exposure prophylaxis, consult the protocol on “Animal Rabies Epidemiology”.*

Cases of human rabies in the United States are rare, with only 1 to 3 cases reported annually. From 1960 to 2018, 127 human rabies cases were reported in the U.S., with roughly a quarter resulting from dog bites received during international travel. Of the infections acquired in the U.S., 70% were attributed to bat exposures.<sup>1</sup> Regardless, the number of human deaths in the U.S. due to rabies has steadily declined since the 1970’s as a result of several factors, including animal control and vaccination programs, modern rabies biologics following exposure, and successful outreach campaigns.<sup>1</sup> Rabies vaccination programs in fact have all but eliminated domestic dogs as reservoirs of rabies in the United States. This had the effect of likewise decreasing the level of rabies in domestic cats. Currently, the CDC reports that nationwide between 80–100 dogs and around 300 cats are confirmed rabid each year nationwide, and these are usually infected by wildlife when the former are not vaccinated against rabies. Interactions with wildlife are also the leading cause for the 30,000–60,000 Americans who receive post-exposure prophylaxis (PEP) each year.<sup>1</sup>

Since 1943, five cases of human rabies have been confirmed in Arizona.<sup>2-6</sup> As illustrated in Table 1, the cases occurring since 1940 are well dispersed chronologically exemplifying the rarity of human infections in the state.

A 1967 Public Health Service publication concerning the incidence of human and animal rabies for the period 1946–1965 illustrates this point further.<sup>7</sup> Just a single case of human rabies was recorded for Arizona (Yuma case, Table 1) during this period as opposed to 8 in neighboring California and 37 in Texas. Contrast this further with the 13-24 cases that occurred in several central and eastern states during the time, one can appreciate how fortunate Arizona is to have had so few cases.<sup>7</sup>

Table 1. Human Rabies Cases, Arizona, 1943–1981.<sup>2-6</sup>

| Year | County   | Location  | Victim                       | Animal Source |
|------|----------|---|------------------------------|---------------|
| 1943 | Pima     | Tucson  | Male, 12 yrs.                | Dog           |
| 1944 | Maricopa | Phoenix   | Male, 10 yrs.                | Dog           |
| 1950 | Yuma     | Yuma  | Child, 3 yrs.                | Unknown       |
| 1970 | Pima     | Tucson; bitten in White Mts. near McNary, Apache Co., AZ. | Male, 11 yrs.                | Skunk         |
| 1981 | Pima     | Tucson; bitten at home in Enpalme, Sonora, Mexico.        | Male, 40 yrs. (U.S. citizen) | Dog           |

### **A. Agent:**

The rabies virus belongs to the order Mononegavirales, viruses with a nonsegmented, negative-stranded RNA genome. Within this group are viruses with a distinct "bullet" shape classified as the Rhabdoviridae family. This family includes at least three genera of animal viruses, Lyssavirus, Ephemerovirus, and Vesiculovirus.<sup>1</sup>

The genus Lyssavirus includes the rabies virus, Lagos bat virus, Mokola virus, Duvenhage virus, European bat virus 1 & 2 and Australian bat virus. Lyssavirus viruses are antigenically related, but monoclonal antibody and nucleotide sequencing has revealed differences (i.e., variants) according to animal species.<sup>1</sup>

### **B. Clinical Description**

Rabies is an acute encephalomyelitis that almost always progresses to coma or death within 10 days of the first symptom onset. Initial symptoms of rabies often include general weakness or discomfort, fever, and/or headache. There may also be discomfort or a tingling/itching sensation at the site of the bite or wound. This will progress within days to symptoms of cerebral dysfunction, anxiety, confusion, and/or agitation. As the disease progresses, the person may experience delirium, abnormal behavior, hallucinations, and insomnia.<sup>8</sup>

The acute period of disease typically ends after 2 to 10 days. Once clinical signs of rabies appear, the disease is nearly always fatal, and treatment is typically supportive.

Once a person begins to exhibit signs of the disease, survival is rare. To date less than 10 documented cases of human survival from clinical rabies have been reported and only two have not had a history of pre- or post-exposure prophylaxis.<sup>8</sup>

### **C. Reservoirs**

The principal rabies hosts today are wild carnivores and bats.<sup>4,7</sup> In the U.S. and its territories, distinct reservoir rabies virus strains have been identified in insectivorous bats, foxes, raccoons, skunks, and mongoose (Puerto Rico).<sup>9</sup>

In Arizona, the greatest rabies risk to humans are three wild animal reservoir species: bats, skunks, and foxes (gray).<sup>9</sup> These wildlife contain their own rabies virus variant, and rabies occurs "naturally" in these species. Spillover of rabies to other species such as coyotes, bobcats, javelina, coatimundi, raccoons, livestock, and cats does occur and serve as a potential source of exposure to people.

### **D. Mode of Transmission**

Transmission is through the introduction of virus-containing saliva via the bite of an infected host. However, infectious saliva may also be introduced through cuts and abrasion in the skin. Similarly, transmission has occasionally been documented via other routes such as contamination of mucous membranes (i.e., eyes, nose, mouth), aerosol transmission, and corneal and organ transplantations.<sup>10</sup>

## E. Incubation Period

The incubation period for rabies is typically 2–3 months but may vary from 1 week to 1 year, dependent upon factors such as the location of virus entry and viral load.<sup>11</sup>

## F. Period of Communicability

Humans may shed rabies virus in saliva for up to 14 days prior to the onset of clinical signs, and the virus can be transmitted throughout the symptomatic period.<sup>12</sup>

Rabies virus becomes noninfectious when it dries out and when it is exposed to sunlight. Different environmental conditions affect the rate at which the virus becomes inactive, but in general, if the material containing the virus is dry, the virus can be considered noninfectious.<sup>10</sup>

## G. Susceptibility and Resistance

All mammals are susceptible to infection with rabies virus. Humans of any age and health status are susceptible.

## H. Treatment

There is no definitive treatment for rabies once a person starts showing symptoms. However, disease prevention through postexposure prophylaxis includes administration of both passive antibody, through an injection of human rabies immune globulin (HRIG) and 4 doses of rabies vaccine (on days 0, 3, 7, and 14).<sup>13</sup> Immunocompromised individuals should receive a 5<sup>th</sup> vaccine dose on day 28. Patients who have previously received either pre or post-exposure rabies prophylaxis should receive only two rabies vaccine boosters following an exposure, given on days 0 and 3. Patients who have been previously vaccinated SHOULD NOT receive HRIG, even if the pre- or post-exposure rabies prophylaxis regimen was given many years prior. Prophylaxis is recommended for any person exposed to a confirmed human rabies case.

Clinicians faced with treating clinical rabies patients can either offer supportive therapy or an aggressive treatment plan. There is no single effective treatment for rabies once clinical signs are evident. The following resources provide current research and thoughts regarding treatment options. These are not intended to serve as recommendations for rabies treatment.<sup>14</sup>

Disease Management

## I. Clinical Case Classification<sup>15</sup>

### ***Confirmed***

A clinically compatible illness that is laboratory confirmed.

### **Comment**

- Laboratory confirmation using all of the above methods is strongly recommended.

- All confirmatory testing must be performed by the Centers for Disease Control and Prevention. Contact the Arizona Department of Health Services (602) 364-4562 to consult on suspected rabies cases.
- Serology performed by a commercial laboratory **is not** recognized for diagnosis of rabies.

#### **J. Laboratory Criteria for Diagnosis**

- Detection by direct fluorescent antibody of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck), OR
- Isolation (in cell culture or in a laboratory animal) of rabies virus from saliva, CSF (cerebrospinal fluid) 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 cerebrospinal fluid (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.

#### **K. Classification of Import Status**

An imported case is defined as a person who contracted rabies while traveling outside of their country of residence.

#### **L. Laboratory Testing<sup>16, 17</sup>**

The Arizona State Public Health Laboratory does not have the ability to test for human rabies. Prior approval by CDC is needed prior to submission to ASPHL to forward to CDC for testing. CDC approval will be obtained by the Arizona Department of Health Services (ADHS) in consultation with the local health department and physician.

Criteria to test include: clinically-compatible symptoms, rapid worsening/progression of symptoms without improvement, ruling out other common causes of the patient's symptoms, and known or potential for exposure to a rabid animal or rabies virus in a laboratory setting.

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans including testing of "samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. However, it should be noted that no single test is sufficient.

Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

ADHS should always be contacted (602-364-3676; [vbzd@azdhs.gov](mailto:vbzd@azdhs.gov)) before collecting and submitting samples to the Rabies Laboratory at the CDC. Specimens should be routed through the Arizona State Public Health Laboratory. After consulting with the state health department, any remaining questions can be directed to the Rabies Duty Officer at CDC by calling 404-639-1050.

For more information about how to submit specimens to CDC, see [Rabies Specimen Submission Guidelines\(https://www.cdc.gov/rabies/resources/specimen-submission-guidelines.html\)](https://www.cdc.gov/rabies/resources/specimen-submission-guidelines.html). The following instructions will guide you in collecting samples for rabies testing.

### **Ante mortem Samples**

Antemortem samples consist of saliva, neck biopsy, serum and cerebrospinal fluid (CSF). All four are required to provide an ante mortem rule out of rabies. A rule out cannot be provided if all samples are not collected.

#### **Saliva**

Collect a saliva sample from the patient using a sterile eye dropper pipette. Place in a small sterile container which can be sealed securely. No preservatives or additional material should be added. Laboratory tests to be performed include detection of rabies RNA (by reverse transcription and polymerase chain reaction, RT-PCR, of extracted nucleic acids) and isolation of infectious virus in cell culture. Tracheal aspirates and sputum are not suitable for rabies tests.

#### **Neck Biopsy**

A section of skin 5 to 6 mm in diameter should be taken from the posterior region of the neck at the hairline. The biopsy specimen should contain a minimum of 10 hair follicles and be of sufficient depth to include the cutaneous nerves at the base of the follicle. Place the specimen on a piece of sterile gauze moistened with sterile water and place in a sealed container. Do not add preservatives or additional fluids. Laboratory tests to be performed include RT-PCR and immunofluorescent staining for viral antigen in frozen sections of the biopsy.

#### **Serum and Cerebrospinal Fluid (CSF)**

At least 0.5 ml each of serum and CSF should be collected; no preservatives should be added. Do not send whole blood. Laboratory tests for antibodies include indirect immunofluorescence and virus neutralization.

#### **Brain Biopsy**

The rarity of rabies and the lack of an effective treatment make the collection of a brain biopsy for antemortem testing unwarranted; however, biopsy samples negative for herpes encephalitis should be tested for evidence of rabies infection. The biopsy is placed in a sterile sealed container; do not add preservatives or additional fluids. Laboratory tests to be performed include RT-PCR and immunofluorescent staining for viral antigen in touch impressions.

## Postmortem Samples

In certain cases, human samples may need to be tested for rabies postmortem. Consult with the state health department before shipping any samples to the Rabies Laboratory at the CDC. Fresh tissue samples from the central nervous system (brain) should be submitted.

Postmortem diagnosis of rabies is made by immunofluorescent staining of viral antigen in touch impressions of brain tissue. Portions of the medulla (brain stem), the cerebellum, and the hippocampus should be frozen and shipped on dry ice to a public health laboratory or the CDC laboratory. Preservation of tissues by fixation in formalin is not recommended if rabies diagnosis is desired.

## M. Assessing Laboratory Results

If no vaccine or rabies immune serum has been given, the presence of antibody to rabies virus in the serum is diagnostic. Antibody to rabies virus in the CSF, regardless of the immunization history, suggests a rabies virus infection. Detection of Lyssavirus viral RNA using RT-PCR in saliva, CSF, or tissue is diagnostic for rabies.

## N. Outbreak Definition

An outbreak of human rabies would be defined as 1 or more cases of rabies linked epidemiologically with exposure, place, and/or time.

## Investigation Guidelines

## O. Time Frame

Rabies virus from a human must be reported by laboratories to ADHS within one working day after obtaining a positive test result, and they must submit a specimen for each positive test result to the Arizona State Laboratory within one working day.<sup>18</sup>

Per A.A.C. R9-6-202, health care providers must report human rabies to the local health department by telephone or through an electronic reporting system authorized by the Department within 24 hours after a case or suspect case is diagnosed, treated, or detected or an occurrence is detected.<sup>19</sup>

## P. Forms

Laboratory reporting form<sup>20</sup>: <https://azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/lab-report-form.pdf>

Health care provider communicable disease reporting form<sup>21</sup>:  
<https://azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/communicable-disease-report-form.pdf>

## Q. Investigation Steps<sup>9</sup>

1. Notify ADHS within 24 hours regarding a human rabies case or suspect case.
2. Conduct an epidemiologic investigation of each reported human rabies case or suspect case. Refer to the Animal Rabies Epidemiology {<http://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/rabies/az-rabies-manual.pdf>} for guidance on animal bites and exposure prophylaxis.
3. Evaluate the level of risk of transmission from each contact's exposure to a human rabies case and, if indicated, provide or arrange for each contact to receive prophylaxis.
4. ADHS will notify animal health partners as appropriate (AZ Dept of Agriculture, AZ Game and Fish Dept, National Park Service, Animal Control, etc.) and help coordinate public messaging and healthcare provider alerts.

## Mass Exposure Events<sup>9</sup>

In the event of a large number of people being potentially exposed to a source of rabies (example: bats in a cabin used for a summer camp with new attendees on a weekly basis, university campus dormitories, school auditoriums), the determination will be made to categorize the risk of those potentially exposed to no, low, and high risk. Post-exposure prophylaxis will likely not be recommended for all individuals in the event of a mass exposure, therefore risk assessments will be performed by public health for each person. Additionally, testing of animals may or may not be performed depending on the timeframe of exposure to prevent over- or under-estimation of rabies risk. Recent U.S. reports include a mass bat exposure at a university sorority house and at a research facility in a national park.

## R. Outbreak Guidelines

A single case of rabies in a person constitutes an outbreak and should be managed with urgency to identify other persons exposed to the same source or that came into contact with infected body fluids belonging to the case.

## References

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